Endovascular treatment of acute ischemic stroke

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ABSTRACT

Early recanalization of the occluded artery leads to better clinical outcomes in patients with acute ischemic stroke (AIS) through protection of the time-sensitive penumbra. Intravenous administration of pharmacologic thrombolytic agents has been a standard treatment for AIS. To get better rates of recanalization, enhance the time window, and diminish the possibility of intracranial hemorrhage, endovascular thrombectomy was launched, with first authorization of the Merci clot retriever, a corkscrew-like apparatus, followed by approval of the Penumbra thromboaspiration system. Both devices lead to a high rate of recanalization. On the other hand, time to recanalization was on an average of 45 minutes, with most of the patients attaining only partial recanalization. More lately, retrievable stents have shown promise in decreasing the time to recanalization, and attaining a superior rate of complete clot resolution. The retrievable stent can be released within the clot to engage it within the struts of the stent, and afterwards it is taken back by pulling it under flow arrest. Neurointerventional techniques have a persistently ever-increasing and stimulating role in the management of AIS, as indicated by the advent of several important techniques. Stent retrievers have the capability to be ascertained as the most important approach to endovascular stroke treatment.

Key words: Endovascular, merci, penumbra, stent retrievers, stroke, thrombectomy

Introduction

Stroke remains a main source of morbidity and mortality around the world, with approximately 800,000 people being affected annually in United States. Of all strokes, 85% are ischemic in nature. Intracranial artery occlusions account for 80% of all acute ischemic strokes (AISs), for which reperfusion therapy is the mainstay of treatment, with the clot being the target.¹⁻³ Thrombolysis with intravenous administration of recombinant tissue plasminogen activator (rt-PA) is only useful within a period of fewer than 3 or 4.5 hours. Moreover, the recanalization rate is less than 50%. Indications for endovascular therapy in AIS by intra-arterial thrombolysis or mechanical thrombectomy include patients with large-vessel occlusions and patients in the early postoperative phase when the systemic effects of IV rt-PA are not desirable. Intra-arterial thrombolysis (IAT) by recombinant pro-urokinase offers many advantages over the intravenous rt-PA by permitting a direct infusion of the thrombolytic agent into the thrombus, a longer time window of administration, and a superior recanalization rate. However, brain hemorrhage after administration of fibrinolytic agent, long recanalization times, and poor recanalization rates in proximal large vessel occlusion with high thrombus burden, such as the ICA or M1 segment, can worsen the outcome of patients.⁴⁻⁶ Therefore, importance of mechanical thrombectomy has noticeably increased, and many devices have been used in recent years for endovascular stroke treatment. Endovascular thrombectomy presents many benefits over endovascular application of pharmacologic fibrinolytic agents. Mechanical therapies characteristically work more speedily, attaining recanalization within a span of few minutes, when compared to 120 minutes taken by IA fibrinolytics; are linked with lesser intracerebral and systemic hemorrhage likelihood; and are more efficient in treatment of large clot volumes in proximal vessels (Carotid T).⁴
Of all endovascular mechanical treatment devices, the “stent retrievers” seem particularly promising in decreasing the time to recanalization and attaining a higher rate of complete clot resolution with better feasibility.\cite{7} A recent review of literature by Koh et al. showed that Solitaire stent retriever appeared to have more favorable clinical outcomes when compared with the results of other mechanical thrombectomy devices evaluated in Penumbra and MERCI trials.\cite{8} The SWIFT trial\cite{9} also showed significantly better clinical outcome in Solitaire FR group than MERCI retriever group. However, withdrawing the unfolded stent by mechanical force to perform thrombectomy may increase the risk of vascular intimal injury and also the incidence of vasospasm.\cite{10} In this fast-growing field, we intend to review important current advances linked to the endovascular treatment of stroke.

**Endovascular thrombectomy in acute stroke therapy**

Mechanical thrombectomy devices take out occluding thrombi from the target vessel by a catheter. Subgroups comprise (1) suction thrombectomy devices that remove occlusive stuff from the cerebral vessels by aspiration (Proximal Thrombectomy) and (2) clot removal devices that physically seize cerebral thrombi and drag them out of the cerebral vessels (Distal Thrombectomy).\cite{11,12}

**Proximal endovascular thrombectomy**

Manual suction thrombectomy is done by moving forward an aspiration catheter at the proximal surface of the thrombus. Manual aspiration is then carried out and the aspiration catheter is taken back under continuous negative pressure. The Penumbra System (Penumbra, Almeda, USA) is a variation of the manual proximal aspiration method which comprises a dedicated reperfusion catheter attached to a pumping system applying constant aspiration. A second retriever device is similar to a stent and is utilized to take out resistant clot. The time window for neuroradiological intervention is 8 hours after stroke onset in patients not eligible for i.v thrombolysis or in whom intravenous thrombolysis is unsuccessful.

The method was approved for AIS treatment in 2007.\cite{13-15} The Penumbra System has been examined in many trials. The Penumbra Pivotal Stroke Trial\cite{16} was a prospective, single-arm, multicenter study that recruited 125 stroke patients (mean NIHSS 18) within 8 hours of symptom onset and was successful (TIMI grade 2 or 3) in 81.6% of treated vessels. However, a good clinical outcome at 90 days was attained in only 25% of patients and in 29% of patients with successful recanalization of the target vessel. There were poor clinical results in spite of the comparatively better recanalization rates with mortality rate of 32.8% and symptomatic ICH occurred in 11.2%. The Penumbra System was one of the devices to be employed in the Interventional Management of Stroke III Trial (IMS III).

**Distal endovascular thrombectomy**

In contrast to proximal thrombectomy technique, distal thrombectomy is technically more difficult.\cite{11} Many clinical studies have been carried out using the Merci device (Concentric Medical, Mountain View, USA), which was the earliest distal thrombectomy device that got FDA authorization in 2004. In the initial stage, the occlusion site has to be traversed with a microcatheter so as to deploy the device beyond the thrombus. The device is pulled back into the thrombus and positioned within the clot. Then, the Merci Retriever and the trapped clot are withdrawn, initially into the positioning catheter and then out of the patient’s body. Proximal balloon occlusion by means of a balloon guide catheter and aspiration during retrieval of the device is done for the majority of cases to prevent thromboembolic complications.\cite{17,18} During in vivo experimental studies, the distal technique has been shown to be more efficient as compared to proximal manual aspiration.\cite{11} The Merci Retrieval devices were experienced in the MERCI trial (Mechanical Embolus Removal in Cerebral Ischemia)\cite{19} which was a 25-site, uncontrolled, technical efficacy trial. The trial incorporated 151 patients with occlusion of the internal carotid artery, M1 or M2 MCA, or vertebral and basilar arteries, who did not qualify for IAT within 8 hours of symptom onset (mean NIHSS 20). Successful recanalization was accomplished in 46%, with excellent clinical outcome in 27.7% of patients. Successful recanalization was linked with distinctly better clinical outcomes. Average procedure time was 2.1 hours, with clinically noteworthy procedural complications occurring in 7.1% and a rate of symptomatic ICH occurring in 7.8% of patients. The heartening outcomes of the MERCI trial led the FDA in August 2004 to approve the Merci Retriever as the earliest device reperfusion therapy labeled exclusively for use in AIS. A second generation Merci device is the Merci Retriever LX (Concentric Medical) which has already been tested in human beings in the Multi-MERCI clinical trial. The Merci Retriever LX is made of concentric helical loops with polymer filaments appended, augmenting clot traction, and accomplished superior recanalization rates than the first generation devices (X5/X6 retrievers) in preclinical studies. The succeeding Multi-MERCI trial\cite{20} was an international, multicenter, prospective, single-arm trial including 164 patients with large vessel stroke treated within 8 hours of symptom onset (mean NIHSS 19). In distinction to the MERCI trial, IV
rtPA, IAT, or other mechanical treatment techniques were permitted besides the Merci device, and recent modified versions of the Merci device were also included. Successful recanalization of target vessel was accomplished in 57.3% using the Merci retriever only and in 69.5% by means of supplementary recanalization modalities. On the whole, good clinical result was attained in 36%. Average procedure period was 1.6 hours, with clinically important procedural complications in 5.5% of patients and symptomatic ICH in 9.8%. The MERCI and Multi-MERCI trials endorsed the induction of the Merci device into wider clinical practice by signifying a noteworthy improvement in clinical outcome in patients with recanalization in contrast to those without successful recanalization.

Self-expanding stents
Until recent times, intracranial stenting was restricted to off-label use of balloon-mounted stents intended for cardiac circulation. These stents are not good equipments for treating intracranial disease because they are stiff, making navigation in the convoluted intracranial vessels difficult. The currently offered self-expanding intracranial stents permit acute stenting as an alternative in AIS that is unmanageable with conventional management. The clot occluding the vessel is quickly displaced outwardly by the side of the vessel wall and becomes trapped in the interstices of a self-expanding stent (SES). Wingsan, Neuroform, and Enterprise self-expanding stenting systems appear to have improved steering, cause a reduced amount of vasospasm, and side-branch occlusions than balloon-inflated stents. Potential drawbacks of this method comprise delayed in-stent thrombosis necessitating future follow-up, the use of platelet inhibitors which may cause ICH and perforator occlusion from relocation of the thrombus after stent placement.[21‑24]

Stent retrievers (retrievable thrombectomy stents)
To get rid of the potential drawbacks of SES, the “stent retrievers” have been developed which are most newly launched mechanical treatment approaches. These are self-expandable, re-sheathable, and re-constrainable stent-like thrombectomy devices which combine the advantages of intracranial stent deployment with immediate reperfusion and subsequent retrieval with definitive clot removal from the occluded artery. Since it can be retrieved, it does not become a permanent implant and while being recovered, it functions as a thrombectomy device in addition. Mechanical thrombectomy by means of stent retrievers is a promising treatment approach for AIS.[19] The entire removal of the device circumvents the most important drawbacks linked with permanent stent implantation, for example the requirement for double anti-platelet medication which potentially adds to the risk of hemorrhagic complications and the risk of in-stent thrombosis or stenosis. Application is analogous to that of intracranial stents. Under general anesthesia, using a transfemoral approach, a guide catheter is positioned in the proximal internal carotid artery. A guide wire is advanced coaxially over a microcatheter within the blocked intracranial vessel and navigated past the thrombus. The microcatheter is then advanced over the wire through the clot, and the guide wire is substituted for the embolectomy device. The revascularization device is placed with the middle third of the device residing within the thrombus formation. The radial force of the stent retriever is capable to instantly create a channel by squeezing the thrombus and to partially restore blood flow to the distal territory in the majority of cases, producing a channel for a temporary bypass. The subsequent angiogram is done to confirm flow restoration of the affected artery. The device is usually left in place for an embedding time up to 10 minutes, permitting entrapment of the thrombus within the stent struts. To extract the thrombus, the unfolded stent and the microcatheter are slowly dragged into the guide catheter with flow reversal by continuous aspiration with a 50-ml syringe from the guide catheter. Post-procedural angiography is done to confirm recanalization and reperfusion. Nevertheless, given that the most favorable design of stent retrievers required to maximize clot engagement remains uncertain, variations of retriever designs have been made. The diverse designs differ in terms of radial strength, design of the proximal and distal stent aperture, stent cell design, material and supplementary intraluminal struts.[25‑27] The safety and effectiveness of Stent Retrievers in animal models gave significant technical data with clinical inferences. Jahan[28] carried out mechanical thrombectomy in Swine with the Solitaire device (ev3 Inc., Irvine, CA) in six cases and successful recanalization was achieved in all the cases. None of the cases had distal embolization, vessel damage, or thrombosis. Reversible vasospasm was encountered in all the cases. Follow-up angiography at 30 days demonstrated no evidence of vessel injury. Microscopic assessment of the treated vessels at 30 and 90 days illustrated mild intimal thickening with roughly 1% to 5% reduction of the vessel lumen. The initial dedicated collective flow restoration and thrombectomy device for acute stroke management was the Solitaire FR (Covidien/ev3, Irvine, USA), receiving the CE mark in 2009 and FDA endorsement in 2012. The apparatus is derived from the Solitaire AB Neurovascular Remodelling Device, firstly manufactured for stent-assisted treatment of wide-neck intracranial aneurysms. Within a short period of time, numerous studies have reported the in vivo and clinical application of the Solitaire FR for
stroke treatment. Many single-center studies with stent retrievers have confirmed the potential to diminish the procedure time (42-55 minutes) and to improve the recanalization rates in large cerebral arteries more than 80 to 90%, with good clinical results in a large percentage of patients (42-54%).[28-31] The largest retrospective study[32] from Europe compiled results from six large stroke centers of 141 patients treated for large vessel occlusion, with the Solitaire FR as an initial choice mechanical thrombectomy device. Successful recanalization was attained in 85% of target vessels with median recanalization time of 40 minutes, and favorable clinical results in 55% of patients. ICH happened in 6% with on the whole mortality of 20.5%. The SWIFT study[33] (Solitaire FR with the Intention for Thrombectomy) was a prospective, open label, randomized, multi-center trial comparing the efficacy and safety of the Solitaire FR with the Merci device. The trial included patients with ischemic stroke randomly allocated to go through endovascular treatment with the Solitaire FR or the Merci device within 8 hours of symptom onset. The primary result was recanalization rate of an occluded target vessel to TIMI 2 or 3. Secondary results were time to first recanalization, NIHSS score, Barthel index, and mRS score at 30 and 90 days after the procedure. Morbidity and mortality rates and the occurrence of symptomatic ICH were also documented at these time points. Successful (TIMI 2 or 3) recanalization was attained in 83.3% with the Solitaire FR in contrast to 48.1% with the Merci retriever, with excellent clinical outcome of 58.2% vs 33.3%, respectively. Symptomatic ICH happened in 2% of the Solitaire FR group and in 11% of the Merci device group with mortality rates of 17% and 38% correspondingly. The trial was stopped a year earlier (in early 2011) than expected on the recommendation of the safety monitoring team due to a considerably superior clinical outcome in the Solitaire FR patient group. The TREVO 2 study (Thrombectomy REvascularisation of Large Vessel Occlusions in AIS)[33] was an open label, multi-center trial evaluating the efficacy of the Trevo Pro retriever (Stryker Neurovascular, Fremont, USA) with the Merci device in patients with large vessel ischemic stroke. The most important outcome was revascularization, characterized as no less than TICI 2a in the target vessel. The secondary results were mRS score, NIHSS score, and mortality at 90 days. Device-related severe undesirable events and symptomatic ICH rates were also documented. A total of 178 patients were included within 8 hours of symptom onset. Successful recanalization was realized in 89.7% in the Trevo group in contrast to 63.3% in the Merci group, with excellent clinical outcome in 55% and in 40%, correspondingly. Symptomatic ICH happened in 6.8% in the Trevo group and in 8.9% of the Merci group, with mortality rates of 33% vs 24% in that order.

The outcomes of these trials sustain the supposition that there are unique mechanical mechanisms of action and consequently dissimilar success and efficacy rates depending on the thrombectomy approaches applied.

Not much data are available regarding clinical outcomes of patients treated with endovascular therapy as compared with intravenous t-PA. The recently published results of three randomized trials comparing endovascular procedures with medical treatments for AIS have provided some interesting results. The Interventional Management of Stroke III (IMS III) was a randomized, open-label international trial which involved 656 patients and compared outcomes of combined intravenous and endovascular stroke treatment with standard intravenous t-PA alone within 3 hours after onset of stroke. In spite of a superior recanalization rate in the endovascular group, clinical outcomes were alike in the two groups.[34]

Synthesis Expansion investigators compared the clinical outcomes of 362 patients within 4.5 hours after stroke onset, who were randomly assigned to endovascular therapy or intravenous t-PA. The average time from stroke onset to the commencement of treatment in the endovascular group was just 1 hour more than in the medical-therapy group; still no significant difference was found in clinical outcomes of endovascular treatment as compared with intravenous t-PA. They concluded that endovascular therapy is not superior to standard treatment with intravenous t-PA in respect to clinical outcomes.[35]

It has been shown in nonrandomized studies that patients who are beyond the 4.5-hour window after onset of stroke along with an ischemic penumbra on perfusion MRI may benefit from endovascular treatment.[36,37] In Mechanical Retrieval and Recanilization of Stroke Clots Using Embolectomy (MR RESCUE) trial, 127 patients were randomized to treatment with embolectomy devices or standard medical care within 8 hours after onset of stroke. Investigators were not able to find any evidence of superior revascularization, better tissue reperfusion, or improved clinical outcomes in the embolectomy group in contrast to the standard medical care group and were not able to demonstrate that multimodal MRI facilitates in finding the suitable patients for endovascular treatment.[38]

There are certain implications of the results of above mentioned trails for clinical practice. The IMS III and Synthesis Expansion trials demonstrated that intravenous t-PA should persist to be the first-line treatment for all patients within 4.5 hours after AIS onset and there is no
benefit from recanalization if it occurs after the brain tissue has infarcted. The MR RESCUE trial results do not show any advantage of the use of endovascular treatment in patients after 4.5 hours of onset of stroke with an ischemic penumbra of any size. [39,40]

However, there were some drawbacks of these three trials. MR RESCUE trial was restricted by the undersized sample and use of less effective thrombectomy devices. In IMS-3 and Synthesis trials, criteria for inclusion of patients were poor, since these studies also included patients with no arterial occlusion and without endovascular treatment into the endovascular arm. Moreover, the recanalization rates attained in these studies were too low to actually investigate the effect of arterial recanalization and tissue reperfusion. [39,40] Therefore, larger randomized trials will be required with the use of newer embolectomy devices such as stent retrievers to show that management of AIS can be improved if patients are vigilantly and swiftly identified for the most suitable treatment. The outcomes of stent retrievers in AIS are presently being scrutinized in a number of underway large prospective, multi-center trials, for example the STAR Trial (Solitaire FR Thrombectomy for Acute Revascularization), the THRACE trial, the RIVER II trial, and the EXTEND-IA trial.

Conclusions

Neurointerventional techniques for the treatment of AIS are fast-growing field with persistently recuperating tools and ever-developing indications. Recanalization rates emerge to be on the increase in more recent studies in contrast to earlier studies. The available data on stent retrievers show good results with improved and quicker recanalization rates, perhaps superior short-term outcomes compared with other reported endovascular devices, and mortality and ICH rates analogous with published results of earlier neurointerventional studies. Larger clinical trials are in progress to evaluate the advantages of these devices in AIS therapy.

References

Singh, et al.: Endovascular treatment of stroke


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