Thrombectomy for Acute Ischemic Stroke Treatment: A Review

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Abstract

Mechanical treatment approaches for acute ischemic stroke treatment aim for fast and efficient reperfusion with short procedure times and high recanalisation rates, thus extending the treatment window. We review the current literature on mechanical thrombectomy for the treatment of acute ischemic stroke.

Keywords: endovascular, stroke treatment, mechanical thrombectomy, stent retriever

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>IAT</td>
<td>intra-arterial thrombolysis</td>
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<tr>
<td>IV rtPA</td>
<td>intra-venous administration of tissue plasminogen activator</td>
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<td>IMS III</td>
<td>Interventional Management of Stroke III Trial</td>
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<td>MERCI Trial</td>
<td>Mechanical Embolus Removal in Cerebral Ischemia</td>
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<td>TREVO 2 study</td>
<td>Thrombectomy REvascularisation of Large Vessel Occlusions in acute ischemic stroke</td>
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<td>STAR Trial</td>
<td>Solitaire FR Thrombectomy for Acute Revascularisation</td>
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<td>SWIFT study</td>
<td>Solitaire FR with the Intention for Thrombectomy</td>
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<td>siICH</td>
<td>symptomatic intracranial haemorrhage</td>
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Introduction

Acute ischemic stroke is a major cause of death or disability in industrialised countries. Significant modifiable factors influencing the clinical outcome are the time span between symptom onset and revascularisation, recanalisation rate and the occurrence of symptomatic intracranial haemorrhage (siICH) [1]. Recanalisation has been shown to be the most important modifiable prognostic factor for favorable outcome in ischemic stroke treatment. Successful recanalisation overall increases the chance of favourable outcome 4-fold compared to patients without recanalisation, and decreases the mortality rate 4-fold [1]. The importance of recanalisation is even more pronounced in basilar artery occlusion, where the chance of an independent life is only 2% in patients without recanalisation [2].

Systemic thrombolysis with intra-venous administration of tissue plasminogen activator (IV rtPA) and local intra-arterial thrombolysis (IAT) have been shown to be effective and to improve patients’ outcome compared to placebo [3-5]. However, pharmacological thrombolysis with both methods has limitations and disadvantages. First, the time window for treatment and therefore recanalisation is limited [5-7]. Second, the administration of thrombolytic drugs might increase the risk of siICH [8]. Third, recanalisation success depends on the site of vessel occlusion: proximal large vessel occlusion such as the ICA or M1 segment have a limited recanalisation rate after IAT and especially after IV rtPA [7-8].
Therefore, the key aims of mechanical treatment approaches for acute ischemic stroke treatment are achieving rapid and efficient reperfusion with short procedure times and high recanalisation rates while extending the treatment window. Furthermore, possible reduction or waiver of thrombolytic drugs may lower the risk of sICH [8].

**Mechanical thrombectomy in acute stroke treatment**

Various thrombectomy approaches have been advocated alone or in combination with adjuvant IV rtPA or IAT. Mechanical recanalisation techniques can be divided by their working principle into two major approaches: proximal and distal thrombectomy.

**Proximal thrombectomy**

Manual suction thrombectomy is performed by advancing an aspiration catheter at the proximal surface of the thrombus. Manual aspiration is then applied and the aspiration catheter is retrieved under constant negative pressure. Although this approach is widely used in proximal vessel occlusion such as the distal cervical internal carotid artery, the carotid terminus or the basilar artery [9-10], only a few systematic studies have been published on this approach with one recent study reporting recanalisation rates of 81.9 % and good clinical outcome in 45.5 % of patients [11].

The Penumbra System (Penumbra, Almeda, USA) is a modification of the manual proximal aspiration technique and consists of a dedicated reperfusion catheter connected to a pumping system applying continuous aspiration. A microwire with an olive shaped tip - the separator - is used to clean the tip of the reperfusion catheter of clot fragments in order to avoid obstruction. The system was FDA approved for acute stroke treatment in 2007. The Penumbra System has been investigated in several trials. The Penumbra Pivotal Stroke Trial [12] prospectively recruited 125 stroke patients (mean NIHSS 18) within 8 h of symptom onset. Recanalisation of the target vessel was successful in 81.6 % of patients. Nevertheless, good clinical outcome was achieved in only 25 % of all patients and in 29 % of patients with recanalisation of the target vessel. Mortality was comparably high (32.8 %) and sICH occurred in 11.2 %. The poor clinical outcome despite the relatively high recanalisation rate in this trial prompted discussion of the impact of recanalisation using mechanical thrombectomy. Subsequent single-centre studies showed better clinical results using the Penumbra System. Kulcsar et al. [13] reported successful recanalisation in 93 % of 27 patients with large vessel occlusion (mean NIHSS 14) and good clinical outcome in 48 % with a mortality rate of 11 %. Mean procedure time was 1.6 h. The Penumbra System was one of the approved devices used in the Interventional Management of Stroke III Trial (IMS III).

**Distal thrombectomy**

Compared to proximal thrombectomy approaches, distal thrombectomy is technically more challenging. In the first step, the occlusion site has to be passed with a microcatheter in order to deliver the device distally to the thrombus. The distal approach has been shown to be more effective in in-vivo experimental studies compared to proximal manual aspiration [14-15]. Proximal balloon occlusion using a balloon guide catheter placed in the cervical internal cerebral artery and aspiration during device retrieval is recommended for most devices to avoid thromboembolic complications.
Several distal thrombectomy devices have been introduced into clinical practice (e.g. Catch, BALT, Montmorency, France; Phenox pCR/CRC, Phenox GmbH, Bochum, Germany). Large clinical studies have been performed and published using the Merci device (Concentric Medical, Mountain View, USA), which was the first distal thrombectomy device that received FDA approval in 2004.

The Merci Retrieval system has been investigated in the MERCI trial (Mechanical Embolus Removal in Cerebral Ischemia) [16]. The trial included 151 patients with large vessel occlusion of the anterior (90 %) and posterior (10 %) circulation ineligible for IAT within 8 h of symptom onset (mean NIHSS 20). Successful recanalisation was achieved in 46 % with good clinical outcome in 27.7 % of patients. Mean procedure time was 2.1 h and clinically significant procedural complications occurred in 7.1 % with a rate of sICH of 7.8 %. The subsequent Multi-MERCI trial [17] was an international single-arm trial including 164 patients (mean NIHSS 19), again within 8h of symptom onset. In contrast to the MERCI trial, IV rtPA, IAT or other mechanical treatment approaches were allowed in addition to the Merci device, and new modified versions of the Merci device were included. Successful recanalisation was achieved in 57.3 % using the Merci retriever alone and in 69.5 % using additional recanalisation modalities. Overall, favorable clinical outcome was achieved in 36 %. Mean procedure time was 1.6 h, with clinically significant procedural complications in 5.5 % and sICH in 9.8 %.

The MERCI and Multi-MERCI trials promoted the introduction of the Merci device into wider clinical practice by providing clinical data from an early phase of the device introduction. Furthermore, both trials demonstrated a significant improvement in favourable clinical outcome in patients with recanalisation compared to those without successful recanalisation. The Merci devices were approved for the IMS III.

**Stent retriever**

The most recently introduced mechanical treatment approaches are “stent retrievers”. Stent retrievers are self-expandable, re-sheathable and re-constrainable stent-like thrombectomy devices. Mechanical thrombectomy using stent retrievers is an emerging treatment approach for acute ischemic stroke. The concept of stent retrievers combines the advantages of intracranial stent deployment with immediate flow restoration and a thrombectomy device with definitive clot removal from the occluded artery. The complete removal of the device avoids the major disadvantages associated with permanent stent implantation, such as the need for double anti-platelet medication which potentially increases the risk of hemorrhagic complications [18-19] and the risk of in-stent thrombosis or stenosis [20].

Application is comparable to that of intracranial stents. Initially, the occlusion site is passed with a microcatheter (0.0165-0.027 in inner diameter) and the stent retriever is deployed by retrieving the microcatheter and un-sheathing the device covering the entire thrombus. The radial force of the stent retriever is able to immediately generate a channel by compressing the thrombus and to partially restore blood flow to the distal territory in most cases, creating a channel for a temporary bypass. Adjuvant intra-arterial thrombolysis can be applied and the temporary bypass effect can be used to facilitate clot dissolution by increasing the thrombus surface in contact with thrombolytic drugs. However, the device is typically left in place for an embedding time up to 10 min allowing engagement of the thrombus within the stent struts [21-23]. During retrieval of the stent retriever into the guide catheter, proximal balloon occlusion and flow reversal by additional aspiration at the guide catheter is again recommended. In-vivo
experimental studies have illustrated incorporation of the thrombus within the stent struts. During mobilisation and retrieval of the device, the thrombus-device complex remains in a straight position without obvious compression or elongation of the clot material [21, 23]. This might result in an increased retrieval force required to mobilise the thrombus and lower retrieval success rate [14-15, 21]. Therefore, straight thrombus position during retrieval and firm clot engagement appear to be key features of stent retrievers compared to the mechanical principle of action of other thrombectomy devices and may explain their high success rates [21, 23]. However, since the optimal design of stent retrievers needed to maximise clot engagement remains unclear, variations of retriever designs have been developed. The different designs vary in terms of radial force, stent cell design, material, design of the proximal and distal stent opening (e.g. closed basket-like ends) and additional intraluminal struts. Distinctive features of currently available stent retrievers are summarised in Table 1.

The first dedicated combined flow restoration and thrombectomy device for acute stroke treatment was the Solitaire FR (Covidien/eV3, Irvine, USA), receiving the CE mark in 2009 and FDA approval in 2012. The device is based on the Solitaire AB Neurovascular Remodeling Device, originally developed 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 [22, 24-26].

The first clinical case series published by Castano et al. [24] included 20 patients with M1 and carotid terminus occlusions and showed the ability for fast and efficient clot retrieval using the Solitaire AB with successful recanalisation (TICI 3 or 2b) in 90% of patients and good clinical outcome (mRS ≤2) in 45% of patients. Subsequent single-centre studies have demonstrated the potential to reduce the procedure time (42-55 min) and to increase recanalisation rates to over 80-90% in large cerebral arteries, with favorable clinical outcome in a large percentage of patients (42-54%) [22, 24-27], indicating the potential of this technique to be established as a major approach to endovascular stroke treatment.

The largest retrospective study reported results from 6 large European stroke centres [28] treating 141 patients (median NIHSS 18) for large vessel occlusion with the Solitaire FR as first choice mechanical thrombectomy device. In 52%, IV rtPA was administered prior to mechanical thrombectomy. Median recanalisation time was 40 min, and successful recanalisation was achieved in 85% of target vessels with favorable clinical outcome in 55%. sICH occurred in 6% with an overall mortality of 20.5%. Subgroup analysis demonstrated a significantly lower rate of collateral infarcts using proximal balloon occlusion compared to procedures without proximal balloon occlusion of 6% versus 32%.

The SWIFT study (Solitaire FR with the Intention for Thrombectomy) [29] was a prospective multi-centre trial comparing the efficacy and safety of the Solitaire FR with the Merci device. The trial recruited 113 patients with ischemic stroke randomly assigned to undergo endovascular treatment with the Solitaire FR or the Merci device within 8 h of symptom onset. The trial was halted a year sooner than anticipated on the advice of the safety monitoring committee due to a significantly better clinical outcome in the Solitaire FR patient group. Successful recanalisation was achieved in 83.3% with the Solitaire FR compared with 48.1% with the Merci retriever, with good clinical outcome of 58.2% versus 33.3% respectively. Overall, 40% of patients had already been treated with IV rtPA but failed to improve. sICH occurred in 2% of the Solitaire FR group and in 11% of the Merci device group with mortality rates of 17% and 38% respectively.
The TREVO 2 study (Thrombectomy REvascularisation of Large Vessel Occlusions in acute ischemic stroke) [30] was a randomised multi-centre trial comparing the Trevo Pro retriever (Stryker Neurovascular, Fremont, USA) with the Merci device. 178 patients were randomised (median NIHSS 18) within 8 h of symptom onset. Successful recanalisation was achieved in 89.7% in the Trevo group compared to 63.3% in the Merci group with good clinical outcome in 55% and in 40%, respectively. sICH occurred in 6.8% in the Trevo group and in 8.9% of the Merci group with mortality rates of 33% versus 24% respectively. The results of these trials support the assumption that there are distinctive mechanical mechanisms of action and therefore different success and efficacy rates depending on the thrombectomy approaches applied. This has to be taken into consideration in planning future studies investigating the efficacy of mechanical thrombectomy.

The effect of stent retrievers in acute stroke treatment is currently being investigated in several ongoing prospective, multi-centre trials such as the STAR Trial (Solitaire FR Thrombectomy for Acute Revascularisation), the EXTEND-IA, the THRACE trial and the RIVER II trial.

Implications of IMS III

IMS III is an international multi-centre randomised controlled trial which aims to determine whether an IV and IA approach is superior to standard IV rtPA alone (<3 h after stroke onset). Following enrolment of 587 of the planned 900 patients at over 50 sites worldwide, IMS III enrolment was suspended in April 2012 because of equipoise. Three thrombectomy devices were approved during the study period: MERCI (cleared 2004), Penumbra (cleared 2007) and Solitaire (cleared March 2012). Although the study has yet to be published in detail, it is unlikely that a larger number of patients treated with stent retrievers had been included prior to suspension of enrolment. Therefore, the results cannot be generalised to mechanical thrombectomy in general, and especially not for the clinical results of stent retrievers.

Conclusion

The introduction of mechanical recanalisation techniques in the treatment of acute ischemic stroke has undoubtedly broadened the spectrum of patients for treatment. By omitting thrombolytic drugs, the time window has been extended to 8 h after onset of stroke. Furthermore, in cases of proximal artery occlusion (such as carotid termination or ICA-MCA tandem occlusion) with high thrombus burden, mechanical approaches are likely to succeed in the future.

Within the time window of 4.5 h, the indication for mechanical thrombectomy in relation to IV rtPA is subject to debate and further research. Various approaches and devices have been advocated in recent years. However, the most frequently applied group of devices are the stent retrievers. Multiple smaller and larger clinical studies have found similar results; high recanalisation rates which translate into high rates of favourable clinical outcome.

The IMS III trial has found equipoise using mechanical approaches compared to IV rtPA within the 4.5 h time window. However, due to the late clearance of a stent retriever in this trial, the IMS III results most likely only reflect the clinical success of the Penumbra and MERCI thrombectomy system. In this respect, the results of the SWIFT trial are important; however, this trial was stopped due to the superior results of the stent retriever (Solitaire FR).
The role of stent retrievers within this early time window, the impact of bridging therapy on recanalisation and haemorrhage rates and peri-procedural aspects such as the impact of general anaesthesia on safety and clinical outcome are some of the additional aspects of endovascular stroke treatment that will require further attention going forward.

Conflict of interest

JG is global PI for the STAR trial (Solitaire FR in stroke) and therefore consults for Covidien.
References


### Tables

Table 1 - Distinctive features of currently available stent retrievers.

<table>
<thead>
<tr>
<th>Device</th>
<th>Company</th>
<th>Feature</th>
<th>Delivery system min ID (inch)</th>
<th>Sizes (mm)</th>
<th>Vessel diameter range (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitaire FR</td>
<td>Covidien/ ev3</td>
<td>honeycomb-like cell design, longitudinal open slit design</td>
<td>0.021</td>
<td>4 x 15/20 6 x 20/30</td>
<td>2-4 3-5.5</td>
</tr>
<tr>
<td>Trevo Pro</td>
<td>Stryker Neurovascular</td>
<td>endoluminal orientation of the broader base of stent struts to enhance clot integration, active area with higher radial force, closed distal end</td>
<td>0.021</td>
<td>4 x 20</td>
<td>1.5-4</td>
</tr>
<tr>
<td>Revive SE</td>
<td>Codman</td>
<td>decreased cell size from proximal to distal retrieval zone to enhance clot engagement, high radial force, closed distal end</td>
<td>0.021</td>
<td>4.5 x 22</td>
<td>1.5-5.5</td>
</tr>
<tr>
<td>Aperio</td>
<td>Acandis</td>
<td>hybrid open-closed cell design</td>
<td>0.027</td>
<td>4.5 x 40</td>
<td>2-4</td>
</tr>
<tr>
<td>Capture</td>
<td>Mindframe</td>
<td>constant radial force minimizing cell deformation</td>
<td>0.027</td>
<td>3 x 30 5 x 30</td>
<td>2-3 2.5-4.5</td>
</tr>
<tr>
<td>Capture LP</td>
<td>Mindframe</td>
<td>low profile delivery system</td>
<td>0.0165</td>
<td>3 x 30 5 x 30</td>
<td>2-3 2.5-4.5</td>
</tr>
<tr>
<td>pREset</td>
<td>Phenox</td>
<td>helically shaped slit design, proximal cell connector</td>
<td>0.021</td>
<td>4 x 20</td>
<td>2-4</td>
</tr>
<tr>
<td>Penumbra Separator 3D</td>
<td>Penumbra</td>
<td>4 intraluminal chambers</td>
<td>0.025</td>
<td>4.5 x 26</td>
<td>≥3</td>
</tr>
<tr>
<td>CATCH+</td>
<td>BALT</td>
<td>longitudinal open slit design</td>
<td>0.021</td>
<td>4 x 20</td>
<td>2-4</td>
</tr>
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