Endovascular treatment of acute stroke[1]

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Key points

What data are available on the clinical outcome of stroke patients after intravenous or intra-arterial thrombolysis?

The acute ischaemic cerebrovascular stroke is characterised by neurological deterioration caused by the sudden occlusion of a brain perfusing artery either by an embolic occlusion with thrombotic material or less often due to a locally formed thrombus.

After initial occlusion of a cerebral vessel, the full extent of the infarction does not become apparent until days after the initial event. By this time the surrounding watershed zone, or penumbra, either survives or succumbs to necrosis over time. The effect of treatment is therefore time dependent and the neurological outcome is a function of the time span between onset of symptoms and recanalisation as well as the recanalisation rate.

The intravenous administration of thrombolytic drugs (intravenous thrombolysis, IVT) has been evaluated in various randomised studies applying recombinant tissue plasminogen activator (rt-PA) to acute ischaemic stroke patients. The NINDS study [1] was able to demonstrate the efficacy of systemic intravenous thrombolysis therapy when initiated within three hours from onset of stroke symptoms if haemorrhage is previously ruled out.

The IVT has been permitted in the USA since 1996. All thrombolytic therapies heighten the risk of bleeding. In 6.4% (NINDS) to 8.8% (ECASS) of patients with IVT a symptomatic intracranial haemorrhage (sICH) occurred.

The intra-arterial thrombolysis (IAT) was evaluated in the large scale, multicentre, randomised trial PROACT II [2]. The study included 180 patients with angiographically confirmed M1- or M2-occlusion within the first six hours after onset of symptoms. 121 patients (NIHSS 17) received low dose intravenous heparin and intra-arterial pro-urokinase proximally to the thrombus. No mechanical disruption of the thrombus was allowed. 59 patients in the control group received only low dose intravenous heparin.

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The intra-arterially treated group showed a significantly ($P < 0.001$) higher rate of partial or complete recanalisation in 66% compared to 18% in the heparin only group. Excellent neurological outcome was achieved in 40% of the treated patients compared to 25% in the control group ($P = 0.04$). The rate of sICH within 24 hours was elevated to 10% in the pro-urokinase group compared to 2% in the control group ($P = 0.06$) but no significant difference in the 90 day mortality was found (25% in the treated and 27% in the control group).

Although both approaches have proven to be effective there is still large room for improvement in the treatment of acute ischaemic stroke.

What is the rational for endovascular treatment in acute ischaemic stroke?

Due to the narrow time window for IVT and various exclusion criteria, only 9% to 22% of ischaemic stroke patients admitted to stroke centres are treated intravenously within a three hour time window. The ECASS III study has recently proven that the application of thrombolytic drugs beyond the time window of three hours after onset of neurological symptoms is safe. However, the efficacy of IVT within the time window of 3 to 4.5 hours is low. In addition, a reanalysis of the NINDS study revealed the limited effect of IVT in patients with severe stroke (national institute of health stroke scale (NIHSS): >16). The NIHSS increases with the size of the vessel occluded. Whether IVT or IAT is superior in central vessel occlusions is still subject to debate.

The local intra-arterial techniques expand the time window for treatment and may increase the recanalisation rate compared to the systemic IVT. In IAT a microcatheter is placed proximal to or directly into the thrombus. In theory, this route of application offers several advantages. The angiographic evaluation reveals the precise occlusion site and the extent of collaterals and assesses the grade of recanalisation during treatment. A higher effective dosage of thrombolytic agent is delivered directly to the thrombus and reduces the systemic exposure. In fact, in open clinical series IAT has achieved a higher early recanalisation rate compared to IVT. Furthermore, the approach facilitates

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the combination with mechanical recanalisation techniques but is generally more time consuming compared to IVT. It involves manipulation of cervical and cranial vessels with the risk of peri-interventional complications and demands highly specialised centres and can be considered as a labour and capital intensive treatment. Furthermore, the direct endovascular access to the distal intracranial vasculature e.g. distal M2- and M3-segments of the medial cerebral artery (MCA) is limited.

A recent publication compared the outcome and morbidity of patients treated with IVT and IAT in two different stroke units [3]. The patients were selected by the presence of a hyperdense middle cerebral artery sign on computed tomography (CT), indicating an M1-occlusion. 55 patients were treated with IAT using urokinase, 59 patients underwent IVT. Although the time to treatment was significantly ($P = 0.0001$) longer in the IAT group (mean 244 min) than in the IVT group (mean 156 minutes), the study revealed a more frequent favourable outcome for the patients treated with urokinase (53%) compared to the patients treated with IVT (23%, $P = 0.001$). In addition, the mortality rate was reduced (4.7%) in the IAT group compared to the IVT group (23%, $P = 0.001$).

Studies indicate a benefit for IAT over IVT especially for large vessel occlusions in the anterior circulation. There is a need for more data on both approaches. Other possibilities for improving ischaemic stroke therapy are expansion of the time window using magnetic resonance imaging selection criteria for treatment and the use of combined intravenous and intra-arterial thrombolysis, the so-called bridging concept [4].

Intra-arterial mechanical thrombectomy – which approaches are available?

Although thrombolysis is effective in some patients, the limited recanalisation rate and the increase of complications gives room for further improvement in the strategy of stroke treatment. Recent developments focused on the possibilities of a mechanical recanalisation in order to reduce revascularisation time and to increase revascularisation rate. Furthermore, the waiving of thrombolytic drugs is considered to reduce the occurrence of sICH and might prolong the time window for treatment, especially in the ICA territory.

Initial attempts reported experience with proximal devices using a microcatheter for thrombus aspiration in combination with IAT. Since 2004 a few studies have reported on mechanical thrombectomy as a stand alone therapy in acute stroke. This development is mainly driven by the fast and innovative device improvement in a parallel field of cerebrovascular intervention, the intracranial aneurysm therapy.

The various devices can be divided into two major groups according to where they apply force on the thrombus. Proximal devices (PD) apply force to the proximal base of the thrombus (this group includes various aspiration catheters). Distal devices (DD) approach the thrombus proximally but then are advanced by guide wire and microcatheter past the thrombus to be unsheathed behind it, where force is applied to the distal base of the thrombus (this group includes snare-like, basket-like or coil-like devices). The clinical success of the different approaches has been illustrated in multiple reports and small clinical studies. However, to date no randomised clinical data is available. This limits the comparison of the clinical effectiveness between different devices and other techniques (IVT and IAT). Although some single arm trials on the clinical application of these devices (e.g., Merci, Phenox, Catch, Penumbra) have illustrated a high recanalisation rate. The clinical outcome of the patients has not yet been proven to be superior to thrombolytic therapy. Furthermore, time to recanalisation was prolonged and the studies have shown a new spectrum of peri-procedural complications such as vessel dissections, perforations and vasospasm due to the repetitive mechanical manipulation to the vasculature.

What are the novel techniques for endovascular treatment of acute ischaemic stroke?

Recent approaches adopt the angiological procedure for treatment of vessel occlusions by stent placement.

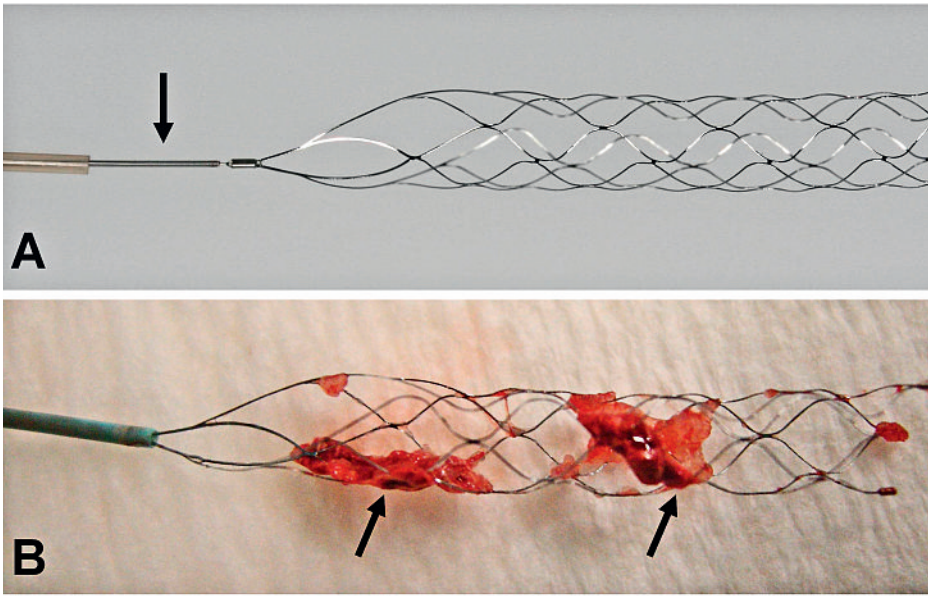

Figure 1
Solitaire FR revascularization device (A) after complete deployment. The stent device with a closed-cell honeycomb pattern, firmly molded to a nitinol pusher wire (arrow). The device (B). Encasement of the thrombus between the stent struts and the partial re-sheathing of the stent (arrows).

Instead of mechanical retrieval, this approach achieves recanalisation by compressing the thrombus to the vessel wall. The use of self-expanding intracranial stents is an emerging and promising treatment option for acute stroke. The main potential advantage of stenting is immediate recanalisation without repetitive passing and retrieval attempts combined with a high technical success rate. On the other hand permanent stent placement carries major disadvantages such as the need for immediate and long term multiple anti-platelet therapy, which might increase sICH and the risk of delayed in-stent stenosis and thrombosis.

The latest development is the introduction of self-expandable and retrievable stent systems with the concept of a temporary endovascular bypass. These devices were originally developed for stent-assisted coiling of intracranial aneurysms. Combining the advantages of temporary stenting with immediate flow restoration and thrombectomy with definitive thrombus removal is a new promising treatment concept for acute ischaemic stroke.

The Solitaire Revascularization Device (ev3, Irvine, USA, fig. 1) is a modification of an aneurysm remodelling device. First clinical series on 22 patients (mean NIHSS: 19.4) have demonstrated a high recanalisation rate (90.9%) in conjunction with a short recanalisation time [5]. The number of patients with a favourable outcome (mRS ≤2) was comparably high (50%).

So far, this approach seems to be safe and effective and is the first mechanical thrombectomy device that might also serve as a temporary endovascular bypass for IAT.

The role and future development of endovascular stroke treatment is difficult to predict. Our institutional guidelines at the University of Berne, Switzerland recommend the endovascular approach in central, large vessel occlusions as first-line treatment or after failed bridging therapy. Due to the fast, uncomplicated and efficient recanalisation using retrievable stent systems, this approach has become the treatment of choice when applicable.

Key words: intra-arterial thrombolysis; mechanical thrombectomy

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