Endovascular approaches for acute ischaemic stroke: the current evidence and organizational issues

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Abstract

Stroke is a leading cause of death and the most frequent cause of disability in adults. The specific evidence-based treatments include intravenous thrombolysis, aspirin and stroke unit care. They are associated with a reduction in mortality and increase in the chance of being independent. Endovascular approaches have been emerging as a new option in the management of stroke. They are associated with a higher recanalization rate of intracranial arteries. Several smaller trials have shown that intra-arterial thrombolysis with pro-urokinase can be effective in acute stroke with large artery occlusion, but the drug has been withdrawn from the market. Currently recombinant tissue plasminogen activator (rt-PA) is most widely used for this purpose. Mechanical thrombectomy is a very promising new method with a high recanalization rate. Still its efficacy has not been proven in the settings of randomized controlled trials, which are currently under way. There are several devices commercially available that have been introduced and some of them already approved for use by regulatory authorities. The most frequently used are the MERCI, Penumbra and Solitaire FR devices. The procedures should be performed in a setting of a comprehensive stroke unit. There is an urgent need for creating training systems in neuroendovascular medicine in Europe similar to the American system to provide appropriate care. There is also a great need for randomized clinical trials which will confirm the efficacy of the endovascular strategies for ischaemic stroke.

Key words: stroke, intra-arterial thrombolysis, mechanical recanalization

Introduction

Stroke affects 183 to 349 per 100,000 population annually [1]. In Poland ca. 70,000 patients are hospitalized because of it each year. It is one of the leading causes of death in the population and the number one cause of permanent disability in adults. In the aging population of Europe we should expect that the impact of stroke will increase.

The last three decades have granted us effective evidence-based treatments for acute ischaemic stroke. Aspirin, intravenous thrombolysis and stroke unit care are accessible for almost every patient in the developed world, including Poland [2-5]. All of them are associated with better outcome (reduction in death or death or disability or both of them combined). In a very limited number of patients with malignant middle cerebral artery (MCA) syndrome, decompressive hemicraniectomy has proved to be associated with much better survival rates and lower disability [6].

Nevertheless, despite a statistically significant improvement in outcome measures, the current treatments might not be available for every patient. Although stroke unit care should be accessible to almost every patient in the developed world and aspirin is widely available, thrombolysis is limited by a strict time window and is still underused, and even despite an undoubted statistical effect it is not expected to cure every patient. The number needed to treat is 7 for thrombolysis within the 3-hour time window and rises to 14 up to 4.5 hours after stroke [4, 5].

The endovascular approach

An occlusion or severe stenosis of the cerebral arteries can be found in up to 70% to 80% of all ischaemic strokes [7, 8]. Because lack of patency correlates closely with poor clinical outcome, it is crucial to achieve recanalization in hyperacute stroke. Spontaneous recanalization occurs in 24% of patients within 24 h of symptom onset and even 53% beyond this time limit. Usually it happens too late and

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that is why no or little clinical benefit is observed. The recanalization rate increases up to 43% with intravenous recombinant tissue plasminogen activator (rt-PA) and 63% with intra-arterial thrombolysis. A combination of the two leads to 68% success. The chance of recanalization after the use of mechanical devices can be as high as 84% [9].

Intra-arterial thrombolysis

The whole concept of intra-arterial lysis started with the use of pro-urokinase within 6 h of stroke onset. The PROACT (Prolyse in Acute Cerebral Thromboembolism) study showed a significantly higher recanalization rate (58% vs. 14%, $p = 0.02$) with a trend towards no disability (modified Rankin Score – mRS 0-1) at 90 days (31% vs. 21%, $p = 0.72$) [10]. This implied the conduction of a second trial – PROACT II [11]. The difference in recanalization rates between patients undergoing treatment and controls was even higher (66% vs. 18%, $p < 0.01$) and the good clinical outcome was statistically significantly higher (40% vs. 25%, $p = 0.04$). It needs to be mentioned that the risk of symptomatic intracranial haemorrhage (sICH) did not differ between the 2 groups. Nevertheless, pro-urokinase is no longer commercially available and therefore other fibrinolytics are in use right now.

Urokinase has been used in some countries routinely for intra-arterial thrombolysis in stroke. The MELT (Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial) showed that its intra-arterial administration in middle cerebral artery (MCA) strokes was associated with a 42% chance of achieving mRS of 0-1 compared to 23% in the control group, $p = 0.05$ [12].

Rt-PA is most widely used for intra-arterial thrombolysis due to its availability and efficacy shown in trials of intravenous thrombolysis. Only two trials of intra-arterial rt-PA have been completed, but these were only single arm trials – the IMS (Interventional Management of Stroke) and IMS II studies aiming at assessing the safety and efficacy of combined intravenous rt-PA with a bridging dose of 0.6 mg per kg and intra-arterial thrombolysis vs. sole intravenous rt-PA with a full dose of 0.9 mg per kg [13, 14]. The intravenous thrombolysis group was a historical control group for the NINDS (National Institute of Neurological Disorders and Stroke) Rt-PA Study [5]. It showed only a slight trend towards lower mortality without statistical significance. This hypothesis still needs to be verified in the settings of a randomized clinical trial (IMS III – awaiting results).

In spite of limited evidence, intra-arterial thrombolysis is still widely used. Currently it is being ousted by mechanical recanalization devices, but still it is used as an add-on therapy to the latter in cases of no reflow or in cases of distal occlusion.

Mechanical revascularization

The first device which was tested in the setting of a single-arm trial was the MERCI device [15]. It is a corkscrew-like device which needs to be deployed distally to the clot. By retrieving it the spirals engage the clot and later retract it down to the balloon catheter. Applied within the first 8 h after stroke onset it was shown to have a 48% recanalization rate. The 90-day mortality was 44% and the chance of regaining independence in activities of daily life was 28%. Symptomatic intracranial haemorrhage occurred in 8% of patients. The following Multi-MERCI study which also allowed enrollment of patients after failed intravenous thrombolysis and used newer generation devices showed a higher, 57% recanalization rate increasing to 70% with add-on intra-arterial thrombolytic treatment [16]. The mortality was 34% and the independence rate was 36%, which is a positive trend compared to the first trial, despite a slight increase in sICH rate (10%). In both studies recanalization correlated strongly with favourable outcome on follow-up. The MERCI device was the first to receive FDA (Food and Drug Administration) approval for use in acute ischaemic stroke.

The Penumbra system, also approved already by the FDA, is based on a different concept [17]. An aspiration catheter is placed below the clot and a separator is placed inside it. After engaging suction the separator is used for disrupting the clot which is being aspirated. The recanalization rate was as high as 81%. Nevertheless, the mortality rate was 33% and the chance of being independent after 3 months was 25%.

Intracranial stents have been used now for several years in endovascular treatment for intracranial aneurysms in cases of wide-neck aneurysms and also fusiform aneurysms. Their utility for mechanical recanalization was discovered by chance in acute vessel thrombosis during coil embolizations. When partly deployed beyond the clot and not released, pulled down the vessel they proved to be highly effective in recanalization. The first stent used for this case and the only one with FDA approval for ischaemic stroke is the Solitaire FR device. Recently a multicentre study on the Solitaire has been published showing an 85% recanalization rate and a surprisingly high rate of 55% of patients independent after the stroke [18]. New similar devices have been introduced and many are still in development. The Solitaire has initiated the advent of a new generation of thrombectomy devices called *stentrievers*. Another benefit of these devices is that in cases when a deployed stent causes recanalization as a temporary by-pass but the artery re-occludes after retrieval, then the stent can be released and left in the artery. Of course, dual antiplatelet therapy has to be introduced in these cases.

Many other new devices with different underlying mechanisms of action have been and still are being introduced for acute ischaemic stroke.

Angioplasty and stenting with a stent designed for atherosclerotic lesions in the cerebral vessels (Wingspan) has also been tested in single arm clinical trial [19]. The imme-

diate recanalization rate is close to 100%, which is not surprising as leaving an expandable stent in the artery should help avoid re-occlusion after the procedure. Again the radiological effect is not strictly associated with a favourable outcome. The chance of having an mRS score of 1 or less was 45%.

Why does it happen that despite effective recanalization the clinical effect is not always as we would expect? First of all, necrosis of the brain occurs already very early in the course of stroke, so despite effective reperfusion the tissue cannot be salvaged. The longer the time to recanalization, the lower the chance for a favourable outcome. During the procedure itself parts of the clot may be dislocated into the perforating arteries, causing deep structure ischaemia, or distal embolism can lead to smaller cortical strokes.

Mechanical devices of recanalization are used within up to 8 h after stroke onset in the anterior circulation and even up to 15 h in the posterior circulation. Nevertheless, it has to be remembered that, similarly to intravenous thrombolysis, the greatest effect can be expected the sooner the procedure is done.

The number of procedures is increasing rapidly, but we need to remember that there is still no hard evidence from clinical trials to justify this. Nevertheless, many healthcare providers have decided to reimburse the procedures. That is why we urgently need randomized controlled trials of mechanical thrombectomy in general versus control, but even more we need to compare the devices so we can choose the best option when treating the individual patient. The ongoing SYNTHESIS trial is comparing the intra-arterial approach to intravenous thrombolysis. In the BASICS trial all patients receive intravenous thrombolysis and thereafter in cases of no recanalization are allocated to being treated further with an endovascular procedure or not. Just recently the results of the SWIFT trial comparing the Solitaire FR with MERCI have been published [20]. The use of the first one was associated with higher recanalization rates (69% vs. 30%), more patients having an mRS 0-2 (58% vs. 33%), and lower 3-month mortality (17% vs. 38%). All these outcome measures were statistically significant in favour of the Solitaire FR.

We have to remember that due to lack of data from controlled trials the implementation of mechanical recanalization should proceed with caution and certain limitations. Currently the method cannot be used as an alternative to evidence-based treatments and cannot replace them (e.g. intravenous thrombolysis, stroke unit care). It can be used in cases when there is a large artery occlusion and there are contraindications to intravenous thrombolysis such as exceeding the 4.5-hour time window, clotting disorders (also effective treatment with heparin or vitamin K antagonists with an INR > 1.7), recent surgery or trauma, etc. Endovascular management can also be used in patients treated with thrombolysis in whom there is no recanalization.

Organizational issues

Endovascular systems for stroke in contrast to pharmacological treatment cannot be introduced without any extra work-up. Such services require extra facilities to the standard stroke unit – a comprehensive stroke unit. Apart from providing specialist care and neuroimaging in a 24/7 system (at least computed tomography – CT) they also need to have 24/7 access to interventional neuroradiology (INR), neurosurgery and also magnetic resonance imaging (MRI). Only in this setting can the patient be appropriately qualified and receive the best pre- and postoperative care.

Appropriate care in a stroke unit can be provided by trained stroke physicians (in Poland – stroke neurologists). They are capable of qualifying patients for intra-arterial thrombolysis or mechanical recanalization based on the clinical appearance of the patient and neuroimaging.

A non-invasive diagnostic workup is mandatory in the process of qualifying patients for an endovascular intervention. This should be either computed tomography angiography (CTA) or magnetic resonance angiography (MRA). An arterial occlusion should be confirmed in one of the above to procede to invasive digital subtraction angiography (DSA) with an intention to perform intra-arterial thrombolysis or mechanical recanalization.

On-site access to a neurosurgical department is required as back-up for endovascular stroke treatment, because patients with large artery occlusion are potentially at risk of developing a malignant MCA syndrome or large posterior fossa infarcts requiring decompressive surgery or eventually intraventricular drainage.

Another important issue in this new field is who should actually perform these procedures. Interventional neuroradiologists seems to be the natural choice, but the number of such specialists is far too small to cover the needs for 24/7 service. Neurologists and neurosurgeons remain an option as actually they are the ones who deal with patients with cerebrovascular disease on a day-to-day basis. The American Accreditation Council for Graduate Medical Education (ACGME) guidelines specify that 2 years of training for specialists in neurology, neurosurgery and radiology are required to perform independently a full variety of neuroendovascular procedures [21]: apart from acute stroke, aneurysm and arteriovenous malformation embolizations, carotid artery stenting, etc. The programme depends on their background, e.g. with more practical training for neurologists and more neuroscience basics for radiologists. Last year the European Union of Medical Specialists (UEMS) outlined similar guidelines allowing also other specialists to obtain training in neuroendovascular medicine. The guidelines are not very specific. In almost all European countries no such specific training has been conducted since then. Hopefully in the next few years the lack of manpower and increasing need for endovascular stroke treatments should force the decision makers to implement such programmes.

There is still low use of intra-arterial thrombolysis and mechanical thrombectomy not only in Poland, but also in the majority of European countries. In Poland 126 procedures have been done in the 3-year period from 2009 to 2011, which means that merely 0.06% of all strokes are treated in this manner. With the lack of evidence it cannot be stated whether this is high or low. Nevertheless, this means that we still have insufficient expertise in this method. This indicates that currently the only way is to create a smaller number of high volume centres rather than a lot of centres performing less than e.g. 5 procedures annually.

Conclusions

Although large artery occlusion or stenosis remains an important feature of acute ischaemic stroke, the efficacy of endovascular treatments remains uncertain. Intra-arterial thrombolysis and mechanical recanalization are an option in patients with contraindications for or failure of intravenous thrombolysis. These procedures should be performed in the setting of a stroke unit. More education is needed to increase the number of physicians performing these procedures.

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References

1. Bamford J, Sandercock P, Dennis M, et al. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project-1981-86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry 1990; 53: 16-22.
2. Chen ZM, Sandercock P, Pan HC, et al. Indications for early aspirin use in acute ischemic stroke: a combined analysis of 40 000 randomized patients from the chinese acute stroke trial and the international stroke trial. On behalf of the CAST and IST collaborative groups. Stroke 2000; 31: 1240-1249.
3. Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev 2002; CD000197.
4. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008; 359: 1317-1329.
5. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995; 333: 1581-1587.
6. Vahedi K, Hofmeijer J, Juettler E, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurol 2007; 6: 215-222.
7. Allendoerfer J, Goertler M, von Reutern GM. Prognostic relevance of ultra-early doppler sonography in acute ischaemic stroke: a prospective multicentre study. Lancet Neurol 2006; 5: 835-840.
8. Bar M, Skoloudik D, Roubec M, et al. Transcranial duplex sonography and CT angiography in acute stroke patients. J Neuroimaging 2010; 20: 240-245.
9. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome. Stroke 2007; 38: 967-973.
10. del Zoppo GJ, Higashida RT, Furlan AJ, et al. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. Prolyse in Acute Cerebral Thromboembolism. Stroke 1998; 29: 4-11.
11. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. JAMA 1999; 282: 2003-2011.
12. Ogawa A, Mori E, Minematsu K, et al.; The MELT Japan Study Group: randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke. Stroke 2007; 38: 2633-2639.
13. IMS II Trial Investigators: The Interventional Management of Stroke (IMS) II Study. Stroke 2007; 38: 2127-2135.
14. IMS Study Investigators: combined intravenous and intra-arterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study. Stroke 2004; 35: 904-911.
15. Smith WS, Sung G, Starkman S, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. Stroke 2005; 36: 1432-1438.
16. Smith WS, Sung G, Saver J, et al. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. Stroke 2008; 39: 1205-1212.
17. The Penumbra Pivotal Stroke Trial Investigators. The Penumbra Pivotal Stroke Trial. Stroke 2009; 40: 2761-2768.
18. Davalos A, Pereira VM, Chapot R, et al. Retrospective multicenter study of solitaire FR for revascularization in the treatment of acute ischemic stroke. Stroke 2012 [e-pub ahead of print].
19. Levy EI, Siddiqui AH, Crumlish A, et al. First food and drug administration-approved prospective trial of primary intracranial stenting for acute stroke. Stroke 2009; 40: 3552-3556.
20. Saver JL, Jahan R, Levy EI, et al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. Lancet 2012 [e-pub ahead of print].
21. Flodmark O, Grisold W, Richling B, et al. Training of Future Interventional Neuroradiologists. Stroke 2012 [e-pub ahead of print].