REPERFUSION STRATEGIES FOR ACUTE ISCHAEMIC STROKE FROM PAST TO PRESENT: AN OVERVIEW TOWARDS FUTURE PERSPECTIVES

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ABSTRACT

Timely reperfusion of brain ischaemic tissue is the main therapeutic target for acute stroke. In the last few decades many recanalisation strategies have been studied by randomised controlled trials (RCTs), including intravenous (IV), intra-arterial (IA), and combined approaches. Clinical research is addressed to identify the drug associated with the better reperfusion properties and the lower rate of side-effects. To date, according to current evidence-based guidelines, IV tissue plasminogen activator (tPA) is the only approved treatment for acute ischaemic stroke (AIS) within 4.5 hours from onset. Other IV thrombolytics, such as tenecteplase and desmoteplase, have shown promising results in preliminary RCTs and are currently being investigated to produce further evidence. Endovascular catheter-based treatments (including IA administration of thrombolytics or mechanical thrombectomy) have quite inferior feasibility, being performed only by stroke-trained interventional neuroradiologists. Until a few months ago, many trials had investigated the safety and efficacy of endovascular techniques compared with IV tPA without consistent results, limiting their application to patients with contraindications or poor response to IV tPA. More recently, the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN), Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times (ESCAPE), and Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-arterial (EXTEND-IA) trial results have demonstrated the superiority of endovascular procedures associated with standard care in AIS due to proximal arterial occlusion in the anterior cerebral circulation. These data are going to change the current decision-making process and the care pathway in AIS patients.

Keywords: Reperfusion, stroke, thrombolysis, intravenous, intra-arterial, endovascular.

INTRODUCTION

Stroke represents a heavy social burden in terms of mortality, morbidity, and costs.[1] Ischaemic stroke accounts for approximately 80% of all strokes[2] and its severity is directly linked to the size and location of the lesion.[3] The main therapeutic target in ischaemic stroke is a rapid vessel recanalisation and the subsequent restoration of blood perfusion into the ischaemic area. It has been highlighted that patients who underwent revascularisation strategies have lower mortality rates and better functional outcome at 3 months than untreated patients.[4] Since underperfusion damage is time-dependent, timeliness is one of the critical issues in disease management. According to the well-known aphorism 'time is brain', the earlier the reperfusion, the better the outcome for the patient. It has been estimated that each spared minute in establishing therapy increases the chances of functional improvement.[5]

To avoid delays, implementation of stroke care systems has been set up[6] to reach the goal of the fastest assessment and treatment for acute stroke patients. Hyperacute stroke management starts in the community: an increased public awareness about stroke symptoms and needs has enhanced the rapid emergency system alert and consequently allows faster transfers to appropriate emergency departments. To enhance access to care considering the available resources, the current goal would be a 'hub-and-spoke' model in which resources are centralised and patients tend to flow from peripheral facilities ('spokes') to larger clinical centres ('hubs'). The subsequent in-hospital phase includes a focussed clinical assessment and appropriate imaging in order to evaluate and put into practice the best therapeutic options according to the patients' needs. The therapeutic strategies for revascularisation include both intravenous (IV) and endovascular approaches, with different features in terms of feasibility, safety, and efficacy.[7-9] In this paper we will review the options that are currently available.

SYSTEMIC REPERFUSION THERAPIES

Systemic reperfusion therapies consist of IV administration of thrombolytic agents. The most well-known drug of this category is tissue plasminogen activator (tPA). To date, alteplase (recombinant tPA) is the only approved treatment for acute ischaemic stroke (AIS) within 4.5 hours from onset of symptoms. Dose of administration is based on the patient's weight (0.9 mg/kg, with a maximum dose of 90 mg; 10% in bolus, the remaining 90% in 1-hour IV infusion). The first study that reported a safe benefit from tPA treatment was conducted by the National Institute of Neurological Disorders and Stroke (NINDS),[10] which considered patients treated within 3 hours from symptom onset. The narrow therapeutic window, which limits the eligible patients to those who arrive in time at the emergency room, has always been considered to be the main disadvantage of IV tPA; the subsequent randomised controlled trial (RCT) research has addressed trying to widen this window. This timeframe has been extended after European Cooperative AcuteStroke Study III (ECASS 3) trial results: better outcome without higher mortality rate for patients treated within 4.5 hours, compared with placebo.[11,12]

Further extension of the therapeutic window has not been firmly supported by recent RCTs. The third International Stroke Trial (IST-3) considered patients treated within 6 hours from onset, and reported higher rates of intracranial bleeding and mortality rates without consistent benefit to outcome.[13] The main selection criteria that weigh on tPA treatment are represented by bleeding exclusion and determining time of symptom onset (however, some studies suggest that even wake-up strokes - without early ischaemic signs on imaging - could be safely treated with tPA thrombolysis).[14] Other important contraindications are: seizures at onset, unmanageable hypertension, international normalised ratio >1.7, and blood glucose <50 or >400 mg/dl. Complications of tPA treatment can result from the thrombolytic effect itself (intracerebral and/or systemic haemorrhage, reperfusion injury with cerebral oedema, and seizures), its ineffectiveness (reocclusion), or secondary embolisation due to redistribution of the lysed clot.[15]

A combined administration of tPA with antiplatelet or low-molecular-weight heparin has been proposed to avoid early vessel reocclusion. These therapeutic schemes[16,17] are burdened with a higher risk of symptomatic cerebral haemorrhage, which overrides the clinical benefit. The combination of a glycoprotein IIb/IIIa antagonist, eptifibatide, with IV tPA (0.6 mg/kg) has been investigated in the Study of the Combination Therapy of Rt-PA and Eptifibatide to Treat Acute Ischemic Stroke (CLEAR-ER), with promising results in terms of lower rate of symptomatic intracranial haemorrhage compared with standard IV tPA alone; a trend has also been observed towards a better functional outcome,[18] but further studies are needed to confirm efficacy. Other glycoprotein IIb/IIIa antagonists have been tested in AIS treatment, but with unconvincing results: in the Safety of Tirofiban in acute Ischemic Stroke (SaTIS) trial, IV tirofiban has been given to AIS patients within 22 hours from symptoms onset, with good safety and lower mortality but no significant clinical benefit in the treated group compared with placebo;[19] abciximab has been tested in only one RCT (Abciximab in Emergency Treatment of Stroke Trial [AbESTT-II]), which was prematurely stopped because of the high number of intracranial bleeds.[20] A direct thrombin inhibitor, argatroban, has been studied in the Argatroban in Ischemic Stroke (ARGIS-I) trial; patients treated with argatroban showed neither significant clinical benefit nor higher bleeding rate.[21] In the Argatroban tPA Stroke Study

(ARTTS) trial argatroban has been combined with IV tPA, reporting a good rate of complete recanalisation at 24 hours.[22]

The other thrombolytic agents (streptokinase, ancrod, tenecteplase [TNK], desmoteplase), which work by converting plasminogen into active plasmin and are currently used for thromboembolic disease such as acute myocardial infarction or pulmonary embolism, have not yet demonstrated sufficient evidence to deserve their promotion among treatments recommended for AIS. This is generally due to a higher risk of bleeding not counterbalanced by better outcome, or to complex methods of administration. Streptokinase administered intravenously within 6 hours from symptom onset showed a high mortality rate compared with 300 mg aspirin in two studies (the Multicenter Acute Stroke Trial [MAST-I] and [MAST-E]);[23,24] a safer and more effective profile was found from the Australian Streptokinase Trial, but only if treating patients within 3 hours from onset.[25]

Ancrod, a serine protease with fibrinogen-depleting properties extracted from Malayan pit viper venom, has been tested in the Stenting in Aneurysm Treatments (STAT) trial by administering a 72-hour infusion of ancrod versus placebo within 3 hours from stroke onset followed by a 1-hour infusion at 96 and 120 hours. Better clinical outcome and insignificantly higher rate of haemorrhage have been observed in the treated arm, thus the complexity of administration has to be considered.[26] TNK is a semi-synthetic tPA with longer half-life and higher fibrin affinity. It is administered as a bolus and is able to induce faster thrombolysis with fewer bleeds and reocclusions. Safe doses (0.1-0.25 mg/kg) have been identified in a Phase IIB trial, prematurely interrupted due to slow enrolment.[27] The following Tenecteplase versus Alteplase for Acute Ischemic Stroke (TAAIS) trial (TNK 0.1/0.25 mg/kg versus tPA in patients with perfusion >20% ischaemic core and computed tomography angiography occlusion) found that TNK 0.25 mg/kg had the better benefit-to-risk ratio for all efficacy outcomes[28] (probably thanks to the inclusion criteria that favoured patients most likely to benefit from the treatment[9]).

Desmoteplase is extracted from vampire bat saliva and has a longer half-life and higher fibrin affinity than tPA. The Desmoteplase In Acute Ischemic Stroke (DIAS) trial had the aim of finding the dose with better safety and efficacy in patients with perfusion—diffusion mismatch within 3-9 hours from onset: after reporting a high number of symptomatic bleeds the dose had been weight-adjusted, with subsequent clinical benefit for treated patients compared with placebo.[29] The following trials, Dose Escalation of Desmoteplase in Acute Ischemic Stroke (DEDAS) and DIAS-2, had inconclusive results due to the low number of patients recruited and the study design.[16] Desmoteplase is currently being investigated in two ongoing trials, DIAS-3 and DIAS-4, considering patients within 9 hours from onset.[30]

Sonothrombolysis could be defined as an enhanced version of systemic thrombolysis, where the mechanical pressure waves given by transcranial ultrasounds help the penetration of tPA inside the clot, improving its fibrinolytic effect.[31] The efficacy of the technique has been proven in the Combined Lysis of Thrombus in Brain Ischemia with Transcranial Ultrasound and Systemic TPA (CLOTBUST) trial, and a subsequent meta-analysis confirmed its safety and effectiveness compared with tPA treatment alone.[32] A further development of this mechanism has been obtained by combining systemic thrombolysis with ultrasound-guided gaseous microspheres, which seems able to improve tPA action.[33] Despite all of these efforts in research, the standard and recommended treatment for AIS is still IV thrombolysis with the tPA alteplase.[12]

Apart from guidelines, it has to be noted that the outcome of the treated patient is strongly influenced by multiple clinical and anatomical variables such as: age and comorbidities of the patient, with worse outcomes for older and vulnerable patients;[2] thrombus size and composition (small and fibrin-rich clots are more likely to be lysed);[2,34] site of occlusion,[35] with fewer chances of recanalisation for large calibre vessels (internal carotid artery, proximal middle cerebral artery); the presence of residual flow that enhances tPA action;[36] and the validity of collateral circulation[37] that promotes better clinical outcome.[2] Imaging diffusion—perfusion profile is another crucial item. Recent studies (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study [DEFUSE] and [DEFUSE-2]) have outlined how perfusion-mismatched patients are more likely to benefit from reperfusion. On the other hand, a 'malignant mismatch' has been identified, with diffusion-weighted imaging area >100 ml correlated to worse outcome and higher risk of haemorrhagic transformation.[38,39]

ENDOVASCULAR TREATMENT

The need for and development of endovascular catheter-based approaches derive from the limitations of systemic therapies, mainly concerning their narrow therapeutic window and poor efficacy against large vessel occlusion.[9] Proximal occlusion of the major intracranial arteries accounts for more than one-third of anterior circulation strokes[40] and only about one-third of these patients could obtain early recanalisation after IV thrombolysis.[41] Intra-arterial (IA) topical delivery of the thrombolytic agent has been the first attempt in the field: the Prolyse in Acute Cerebral Thromboembolism (PROACT) trial[42] reported a favourable 3-month outcome in patients treated with IA pro-urokinase up to 6 hours from stroke onset, although with a higher rate of symptomatic intracranial bleeding that prevented the FDA endorsement as an alternative treatment to IV tPA. A 'bridging' treatment (IV tPA followed by IA administration of tPA) has been compared with conventional systemic tPA, showing similar safety and outcome measures.[43,44]

Conceived to treat proximal large artery occlusion in particular, the most recent type of endovascular approach consists of clot retrieval or thrombectomy with mechanical devices, currently performed in centres equipped with stroke-trained interventional neuroradiologists.[9] The earliest systems were the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) retriever,[45] designed to engage, proximally withdraw, and then aspirate the clot, and the PENUMBRA device,[46] able to aspirate the clot directly from the site of occlusion. The therapeutic window was initially wider than that of systemic thrombolysis, up to 8 hours. The delayed, although complete, recanalisation obtained by thrombectomy was associated with worse clinical outcome compared with IV tPA,[47] probably due to the difference in time windows favouring systemic tPA due to starting treatment earlier.[9] Subsequently, the stent-retriever devices SOLITAIRE FR and TREVO have been endorsed by the FDA[48] for acute stroke caused by large vessel occlusion for their safer and more effective profile than the MERCI system.[49] These devices also play a crucial role in the treatment of basilar artery occlusion, with proven safety and effectiveness.[50]

The results of subsequent prospective endovascular RCTs (Interventional Management of Stroke [IMS] III, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy [MR RESCUE], and SYNTHESIS Expansion) have demonstrated that the IV and endovascular approaches have consistently similar safety profiles; thus, endovascular treatments are not superior to IV thrombolysis[51] and have to be applied only in selected conditions. The neutral results should be read considering that these studies were tarnished by some critical issues: a widespread use of old, first-generation devices and limited use of stent-retrievers, lack of pre-treatment angiographic imaging causing a number of futile interventions in patients without large vessel occlusion (nearly 47% of the study population in the IMS-III), non-consecutive inclusions, and long delays from clinical onset to achieve recanalisation. However, current American Heart Association/American Stroke Association guidelines recommend IA thrombolysis in AIS patients with contraindications to systemic approach within 6 hours from onset, and suggest that patients with large vessel occlusion and a poor response to IV tPA could benefit from a 'rescue' treatment with IA thrombolysis or thrombectomy.[48]

Recent studies have promoted the acceleration of the use of endovascular approaches, to result in timely and better reperfusion of ischaemic penumbra and achieve clinical improvement, especially for large artery obstruction for which recanalisation is required to avoid a poor prognosis.[52,53] The MR CLEAN trial has recently proved that IA treatment (thrombolysis and/or mechanical procedures) associated with 'usual care' (that could include systemic thrombolysis) within 6 hours from onset of symptoms in AIS patients with a proximal intracranial occlusion of the anterior circulation (radiologically confirmed) is effective and safe; compared with usual care alone, it is associated with a better 3-month functional outcome (an absolute difference of 13.5 percentage points in the modified Rankin score) and no significant differences in terms of mortality or bleedings.[54] MR CLEAN will change perspectives about endovascular treatment; thanks to these positive results, it could be considered in patients other than those with contraindications or poor response to IV thrombolysis. The beneficial effect of endovascular treatment has been confirmed even in subgroup analysis for age, stroke severity, and ASPECTS score.[54]

Further evidence comes from the ESCAPE trial, the results of which have recently been published. The trial reported improved functional outcome

and lower mortality rates compared with standard care alone for the rapid (within 12 hours from onset) endovascular treatment added to standard care in ischaemic stroke patients with small infarct core, proximal intracranial artery occlusion, and moderate-to-good collateral circulation.[55] The study design highlights the importance of a careful patient selection to identify the subgroup of individuals who would benefit from treatment. This method has been applied also in the EXTEND-IA trial, by setting precise perfusion-imaging inclusion criteria (large vessel occlusion and an ischaemic core <70 ml on CT perfusion). This study demonstrated that such patients, treated with IV alteplase and early (within 4.5 hours from onset) thrombectomy with the SOLITAIRE FR device compared with standard systemic thrombolysis, showed better reperfusion, earlier neurological recovery, and better 3-month functional outcome.[56] Both the ESCAPE and EXTEND-IA trials were stopped after the release of the MR CLEAN results on the advice of the data safety monitoring board, because the predetermined boundary for efficacy had been reached.[55,56] These latest RCTs highlight the need for adequate vessel imaging before selecting patients for an endovascular procedure. The limited use of such techniques has probably contributed to determining the inconsistent results of previous trials. From these considerations we could infer that endovascular approaches cannot alter the natural history of AIS in the absence of large arterial occlusion.

LACUNAR SYNDROMES

Lacunar stroke is an expression of small vessel disease, for which the implementation of thrombolytic treatment is currently under debate. First of all, lacunar syndromes are not usually associated with high clinical severity and generally show a good prognosis (while in the long term, a higher incidence of recurrent stroke and dementia is reported). A mechanism of thrombosis has never been proven for lacunar strokes, hence the questions about the need for the advocacy of reperfusion for its treatment. However, a recent review states that thrombolysis can be judged to be an effective treatment in acute lacunar stroke. On the other hand, the presence of small vessel disease increases the risk of intracranial haemorrhage during thrombolysis, even if it is not considered as an absolute exclusion criterion.[57] Evaluating the extent of small vessel disease should be done with MRI and could be difficult with neuroimaging techniques that are available in the emergency setting.

CONCLUSION

Even though IV alteplase is still the recommended therapy for AIS patients, the most recent data from endovascular RCTs would probably determine a revolution in the world of stroke care, promoting interventionists to become essential, at least for every 'hub' stroke centre, and perhaps also changing the fundamental requirements, in terms of neurovascular imaging, for primary stroke centres. In this fight against the time-dependency of recanalisation and clinical efficacy, neurologists and interventionists should be activated in parallel to decrease the time to the procedure.[58]

From the aforementioned, we can conclude that the patient-selection process plays a fundamental role in acute stroke treatment, possibly causing biases that deeply influence the results of RCTs and consequently guideline recommendations. The desirable direction to take in future studies is to further refine this process, investigating AIS patients with an extensive imaging (evaluation of large vessels by angio-imaging, evaluation of brain parenchyma by the use of MRI to rule out or quantify small vessel disease) and clinical workup, to achieve the most targeted treatment according to their needs.

Key Points

- IV tPA (0.9 mg/kg, maximum dose 90 mg) is the recommended therapy for AIS patients within 4.5 hours from onset
- Endovascular procedures must not be applied as an alternative to IV tPA in patients who are eligible to systemic thrombolysis
- IA treatments (IA thrombolysis, thrombectomy, or both) associated with usual care (that could include systemic thrombolysis) are likely to be beneficial if performed in patients with AIS due to proximal arterial occlusion in the anterior cerebral circulation (intracranial internal carotid artery, proximal middle cerebral artery, proximal anterior cerebral artery) within 6 hours from onset
- IA treatments associated with usual care can be performed in patients with AIS due to arterial occlusion of posterior large vessels

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