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Recent Advances in Thrombolysis and Thrombectomy in Acute Ischemic Stroke Treatment: Neurologist's and Interventional Neuroradiologist's Perspective

Pinar Gelener and Süha Halil Akpınar

Abstract

As stroke is still the leading cause of disability and mortality worldwide, it is promising that there has been a significant change in the acute treatment options for the patients presenting with acute ischemic stroke over the last 23 years after the approval of alteplase. Vascular recanalization of the occluded artery by endovascular methods with or without thrombolysis has shown improved clinical outcomes, particularly after randomized control trials (RCTs), which were conducted between December 2010, and December 2014. These trials will be discussed in more detail the below following sections of this chapter. Successful emergency reperfusion conducted on time still remains the most important determinant of good clinical outcome.

Keywords: thrombectomy, advances, acute ischemic stroke

1. Introduction - Neurologist's perspective

1.1 Choices for intravenous thrombolysis

Vascular recanalization of the occluded artery by endovascular methods with or without thrombolysis has shown improved clinical outcomes, particularly after randomized control trials which were conducted between December 2010, and December 2014. These trials will be discussed in more detail the below following sections of this chapter. Successful emergency reperfusion conducted on time still remains the most important determinant of good clinical outcome [1].

Another choice for rtPA is tenecteplase, which is a variant of rtPA with a longer half-life and greater fibrin specificity. The Norwegian Tenecteplase Stroke Trial 2 (NOR-TEST 2) is still continuing, but the NOR-TEST 1 trial showed that tenecteplase has a similar safety profile to alteplase but it is not superior [2].

According to the Tenecteplase versus Alteplase, before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trial that included patients with acute proximal intracranial artery occlusion eligible for mechanical thrombectomy, tenecteplase has a higher reperfusion incidence and better functional outcomes when compared to alteplase [3].

1.2 Patients exceeding time-limit: presenting from very-late to unknown “last-seen-well” time

There is a group of patients in the extended time window for whom acute reperfusion therapies may still be effective. Perfusion brain imaging is crucial in this group of patients [4].

1.3 Intravenous rtPA across 4.5–9 hours

A recent meta-analysis of the EXTEND and EPITHET Randomized Clinical Trials revealed that reperfusion with IV alteplase reduced disability in patients with acute ischemic stroke (AIS) within 4.5–9 hours after symptom onset or wake-up onset, who were selected by perfusion imaging mismatch, without increasing the risk of symptomatic intracerebral hemorrhage [5].

The efficacy and safety of MRI-Based Thrombolysis in the Wake-Up Stroke (WAKE-UP) trial including patients beyond 4.5 hours who woke up with a stroke or could not identify the onset and had a diffusion and flair mismatch, also showed receiving IV rtPA was beneficial [6].

The ongoing “Tenecteplase in wake-up ischemic stroke” (TWIST) trial will answer further questions about the superiority of tenecteplase over standard treatments for acute ischemic stroke patients in the extended time window [7].

1.4 Time limit for endovascular therapies

The first two trials DAWN (the DWI or CTP Assessment with clinical mismatch in the triage of wake-up and late presenting strokes undergoing neurointervention) and DEFUSE 3 (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 3) showed dramatic benefit with regard to thrombectomy in patients who had been last well within previous 6–24 hours with radiologic criteria indicating a mismatch between ischemic core and penumbra by perfusion or diffusion-weighted images [8, 9].

The aim of the diffusion/perfusion images is to identify the ischemic penumbra which is the salvageable hypoperfused (but not yet infarcted) region [4].

It is known that in patients with AIS due to large vessel occlusion (LVO) who present very late or who’s last seen well period unknown, this may persist beyond 16 hours according to baseline ischemic core, collateral situation status, and perfusion parameters. It is also suggested that the target mismatch pattern may persist up to several days after symptom onset in AIS with large vessel occlusion. In another series of patients with anterior LVO who were evaluated 16 hours after onset, one-third of them had salvageable tissues [10–12].

According to a recent study, patients with acute anterior circulation last vessel occlusion presenting beyond 16 hours up to 10 days from the time they were last seen well, in whom the symptoms slowly progressed, benefited from endovascular treatment. According to the protocol of this study, collateral circulation and perfusion images were evaluated and patients were selected based on core-penumbra mismatch. Good collateral circulation was defined as filling 50% or more middle cerebral artery pial arterial circulation in computed tomography (CT) scan or Magnetic Resonance (MR) angiography [10, 13].

1.5 The role of collateral flow

The primary collaterals refer to the circle of Willis whereas secondary refers to ophthalmic and leptomeningeal arteries and tertiary collaterals to newly developed vessels due to angiogenesis [14, 15].

Leptomeningeal collateral circulation develops chronologically by several compensatory metabolic, hemodynamic, and neural responses. This collateral circulation shows great variability in each individual according to age, genetics, anatomical variations, serum glucose level, and metabolic syndrome [10, 16, 17].

Collateral flow plays a very important role in ensuring that the ischemic penumbra remains viable in patients receiving reperfusion therapies consisting of chemical thrombolysis with alteplase and/or mechanical thrombectomy. The presence of collateral blood supply preserves cerebral perfusion and helps the survival of the hypoperfused ischemic penumbra [4, 18].

Collateral circulation is parallel to better clinical outcomes in AIS patients receiving acute reperfusion therapies, as well as in patients with acute intracranial large vessel occlusions and distal arterial occlusions [19, 20].

There are recent advances in neuroimaging in the evaluation of ischemic penumbra and pial collateral vessels. Vessel-encoded multi-post labeling delay arterial spin labeling (ASL) is a non-invasive, non-contrast magnetic resonance imaging (MRI) measuring collateral perfusion and delayed blood arrival in acute stroke patients [21].

1.6 Patients with mild or rapidly improving deficits and low National Institutes of Health Stroke Scale (NIHSS) scores

It is known that the National Institutes of Health Stroke Scale (NIHSS) score is weighted toward anterior circulation strokes and represents posterior circulation stroke symptoms with lower cutoff values [22].

Although the NIHSS is a predictor of overall AIS outcomes, this does not apply to patients with low NIHSS scores. There is significant variability in the outcomes of patients with AIS and low NIHSS scores, which demonstrates the limitation of NIHSS as a screening tool for treatment eligibility [23, 24].

A patient NIHSS score of 5 or less should be assessed with extra care before the decision to administer rtPA, particularly for those presenting with hemianopia. The “Potential of rtPA for Ischemic Strokes with Mild Symptoms” (PRISMS) trial suggested benefits in terms of thrombolysis in patients with minor non-disabling strokes [4, 25].

Patients with AIS and LVO who present with only mild neurological deficits (NIHSS scores equal or lower than 5) who are treated with IV thrombolysis alone are at risk of early neurological deterioration and poor 3-month outcomes. The two independent predictors of this deterioration are more proximal occlusion sites and thrombus length (according to a Youden index of 9 mm or longer). Bridging therapy, IV rtpA followed by endovascular intervention may be reasonable in this high-risk patient group [26, 27].

Two very important ongoing clinical trials are investigating endovascular thrombectomy in patients with acute large vessel occlusion strokes and low NIHSS score ≤ 5 : “Endovascular Therapy for Low NIHSS Ischemic Strokes” (ENDOW) and “Minor Stroke Therapy Evaluation” (MOSTE) [23].

1.7 Patients on anticoagulant therapies

According to current guidelines, IV rtPA can only be administered to acute ischemic patients on warfarin if the international normalized ratio (INR) is ≤ 1.7 without increasing the risk of symptomatic intracranial hemorrhage [28]. The situation in patients on direct oral anticoagulant (DOAC) treatment is more complex as there is no available standardized rapid test to measure DOAC activity (complexities). According to American Heart and Stroke Association guidelines, tPA cannot be given as a treatment in AIS patients if DOAC use is suspected within the past 48 hours [1].

Idarucizumab reverses dabigatran rapidly and irreversibly and andexanet alpha reverses most of the DOACs' anticoagulant activity but it needs a continuous infusion. There is still uncertainty surrounding the treatment of this patient group with rtPA after using reversal agents [29, 30].

In patients taking DOAC with proven AIS with large vessel occlusion, direct endovascular thrombectomy without bridging with IV thrombolysis is preferred especially when thrombectomy can be provided without delay [30].

Recent data suggests that selected patients on DOAC therapy have similar bleeding risks after IV rtPA compared to those who are not. Drug-specific coagulation assays like calibrated anti-Xa activity measure DOAC levels to identify patients with low anticoagulant activity. Thromboelastography is a novel tool used for measuring the viscoelastic properties of clotting blood and the safe threshold for thrombolysis [30–33].

1.8 Patient care after reperfusion therapies

Besides the importance of reperfusion therapies, hemodynamic management and early recognition and treatment of brain edema, infections, and cardiac arrhythmias and failure are critical. Collateral flow can be supported by avoiding sudden drops in blood pressure and the administration of intravenous fluids or vasopressors [4].

According to a recent study from Italy involving patients receiving endovascular treatment for acute stroke, general anesthesia during mechanical thrombectomy was associated with worse functional outcomes compared with conscious sedation and local anesthesia, whereas recanalization success rates did not differ [34].

Both hypoglycemia and hyperglycemia should be avoided in patients with acute ischemic stroke. According to the “Stroke Hyperglycemia Insulin Network Effort (SHINE)” randomized trial, intensive treatment of hyperglycemia (with target 80–130 mg/dl) did not improve functional outcome in patients with acute ischemic stroke when compared to standard treatment (with target 80–179 mg/dl) [35].

According to a collaborative pooled analysis of acute ischemic stroke patients treated by thrombectomy; a systolic blood pressure value of 157 mm Hg predicted the lowest all-cause death rate. It should also be kept in mind that baseline high SBP might reflect the autoregulative hemodynamic intracranial mechanism for the need of good collaterals in large vessel occlusion strokes [36, 37].

Although the current American Heart Association/American Stroke Association guidelines recommend SBP <180 mmHg and DBP <105 mmHg during and after mechanical thrombectomy, evidence for optimal management is limited. Among acute stroke patients with large vessel occlusion treated with mechanical thrombectomy, elevated blood pressure is associated with adverse outcomes before, during, and after the procedure [38].

In some trials, in AIS patients within 6 hours of symptom onset, blood pressure was maintained ≤ 180 –105 mm Hg for the first 24 hours after reperfusion therapies whereas systolic blood pressure was recommended to be <140 mmHg for the first 24 hours in patients with complete recanalization [8, 13].

1.9 Recent news

According to a newly conducted trial involving 41 centers in China, endovascular thrombectomy alone was non-inferior on functional outcome compared to IV alteplase administered within 4.5 hours in AIS from LVO in anterior circulation [39].

2. Interventional radiologist's perspective

2.1 Introduction

Thrombus aspiration and Stent Assisted Thrombectomy (SAT) used either in combination or alone are today the most accepted interventional methods in acute ischemic stroke treatment in large vessel occlusions [40, 41].

The efficacy of the endovascular stroke treatment (EVT) is dependent on the time last seen well and the patient's admittance, imaging methods used to decide whether the patient is eligible for stroke treatment, the technique of thrombectomy with or without bridging, the number of passes during stent retrieval and also the clot type.

2.2 Stroke time and patient's admittance

Admittance of stroke patients to stroke centers was initially made according to two methods. These were, "drip and ship"; putting the patient on a thrombolysis drip after excluding the intracranial hemorrhage mostly by non-contrast CT scan at the closest stroke center and then transferring them to an endovascular center where the endovascular stroke treatment (EVT) is performed. On the other hand, the patient can be admitted directly to an endovascular stroke center to receive the EVT from an experienced stroke team, which is referred to as "direct to mother-ship" [42].

Today, alternative methods are suggested for the transportation of stroke patients.

Mobile stroke units consist of an ambulance equipped with a Computed Tomography (CT) scanner so that suspected stroke patients can have their initial noncontrast CT taken to exclude other causes to allow thrombolysis to be started on the way to the endovascular center [43].

The other option is for a mobile stroke team to evaluate the patient's scans and travel to the hospital with appropriate equipment to conduct an EVT without a neuro interventional team. When the decision is made to intervene, the contact hospital prepares the patient at the local hospital according to the clinical and imaging findings and will also call the anesthesiology team to the angio suite, thus reducing the unwanted delays caused by transfers while the neuro interventional team travels to the hospital to perform the EVT [44].

2.3 Imaging methods

Endovascular stroke treatment was applied within 6 hours in the initial RCTs which resulted in the implementation of the EVT according to AHA/ASA guidelines [45]. However, it was subsequently identified that some patients could still have good results with EVT, even after the 6-hour time limit was exceeded. New imaging-based new trials were introduced to identify why some patients still benefit from EVT even after the eligible time period. According to the latest DAWN and DEFUSE 3 trials, which focused on wake-up and late presenting strokes, the role of multimodal imaging has led to EVT being extended to 24 hours [8, 9].

Most centers apply Computed Tomography (CT) based imaging, which as a start noncontrast CT imaging is frequently used to estimate the ischemic core according to the Alberta Stroke Programme Early CT score (ASPECTS) and to exclude the presence of cerebral hemorrhage. This is followed by CT angiography to identify the level of occlusion as well as the anatomical challenges for procedural planning.

Computed tomography perfusion (CTP) and Diffusion weighted imaging (DWI) are used to identify the core, ischemic penumbra, degree of collaterals, and information of occluded vessels. These data obtained from advanced imaging show that the effectiveness of EVT is not only time-dependent, resulting in “Imaging is Brain” concept instead of “Time is Brain”, especially at late attended cases. The 2018 AHA/ASA guidelines recommend the inclusion of CTP, DWI, or Perfusion imaging for the standard evaluation of patients admitted within 6–24 hours. According to imaging cerebral blood flow (CBF) below 30% is defined as infarct core and in DEFUSE 3 T-max more than 6 seconds or apparent diffusion coefficient (ADC) image less than $620 \text{ Ym}^2/\text{s}$ is used to define the penumbra. Patients with a clinical mismatch (mismatch between the size of infarction and the clinical defect) or patients with target perfusion mismatch (mismatch between the size of infarction and the perfusion lesion) concept were used to define the penumbra and calculate with imaging measurements its ratio to core infarction [46]. Multiphase CTP is also used to define the collateral supply at the risked parenchyma as good collaterals have a reduced rate of infarct growth [47, 48].

2.4 The technique of thrombectomy

Thrombus Aspiration and Stent Assisted Thrombectomy (SAT) used either in combination or alone are now the most accepted interventional methods in acute ischemic stroke treatment in large vessel occlusions. Different thrombectomy stent types and large bore aspiration catheters are introduced to increase the efficacy of endovascular stroke treatment and clot retrieval. The method used in endovascular stroke treatment for large vessel occlusions is mostly made according to the vessel involved, for example, the treatment of internal carotid artery (ICA) orifice, cervical or intracranial parts, or T occlusions is preferably started with thrombus aspiration, whereas SAT is usually applied in middle cerebral artery M2 section of anterior cerebral artery occlusions. However, if the individual methods are not successful alone, combining an aspiration catheter with the thrombectomy stent-method can be used to recanalize the occluded vessel in anterior circulation strokes.

Less RCT is performed in posterior circulation strokes as such cases are less frequent. Direct aspiration as the first pass technique (ADAPT) and stent retrievers are used to recanalize the occluded artery. One of the latest studies focusing on the influence of mechanical thrombectomy—ADAPT versus primary stent retriever—on basilar artery occlusion showed a successful reperfusion rate of 79%, favorable outcome rate of (mRS 0–2) 36.8%, and an all-cause 90-day mortality rate of 44.2%. ADAPT showed a higher complete reperfusion rate with a shorter duration of the procedure [49].

The latest studies that combined alteplase with stent-assisted thrombectomy to SAT alone have shown the noninferiority of mechanical thrombectomy on functional independence with less intracerebral hemorrhage in the hours following endovascular stroke treatment [50, 51].

The First pass effect is defined as the removal of the clot in stroke patients at the first thrombectomy attempt. The impact of the first pass effect was studied in the “Analysis of revascularization in ischemic stroke with EmboTrap” (ARISE 2) study, which focused on the speed of revascularization and the extent of tissue reperfusion [52]. The reperfusion obtained on the first pass with thrombolysis in cerebral infarction (TICI) score 2b-3 had a shorter procedure time compared to the group who obtained the same TICI result but with more thrombectomy passes. As a result, the 90-day mRS score 0–2 was better compared to the multiple pass group even though same the TICI scores were obtained [53] (**Figures 1 and 2**).

Figure 1.
DSA image of acute right MCA-M1 occlusion and partial recanalization of the occlusion after stent deployment.

Figure 2.
DSA image after stent assisted thrombectomy with TICI 3 recanalization.

2.5 Clot type

Clot type is also one of the major fields of study in terms of predicting the success of EVT treatment.

It is well known that Erythrocyte-rich thrombi are more responsive to thrombolysis, whereas when the length of the thrombus and its other constituents (i.e., fibrin, platelets, and calcium) result in a reduced success rate of thrombolysis. Although tenecteplase is more fibrin-specific and produces a higher reperfusion rate and better functional outcomes compared to alteplase, its overall success rate is 22% [5, 54, 55].

However, EVT is still less effective in strokes compared to other clot types due to the calcified emboli.

3. Conclusion

The aim of acute ischemic stroke treatment is to reverse the neurologic deficit and to regain function. Successful emergency reperfusion on time with intravenous (iv) thrombolysis with recombinant tissue plasminogen activator (rtPA) and/or endovascular thrombectomy with retrievable stent still remains the most important determinant of good clinical outcome, increasing functionality. Therefore, expanding the availability of reperfusion therapies to all patients including those in the extended period with recommended imaging modalities including collateral flow is crucial (Table 1).

I. Patients beyond 4.5-9 hours (receiving IV rtPA)
II. Patients upto 24 hours (receiving endovascular therapies)
III. Patients on warfarin /new oral anticoagulant therapies
IV. Patients with mild deficit and low NIHSS scores
V. Patients with unknown "last seen well"

Table 1.
Acute ischemic stroke patients beyond current guidelines discussed in this chapter.

Conflict of interest

The authors declare no conflict of interest.

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