



REVIEW

Emerging therapies in acute ischemic stroke [version 1; peer review: 3 approved]

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Abstract




Thrombolysis and mechanical thrombectomy have revolutionized the care of patients with acute ischemic stroke. The number of patients who can benefit from these treatments continues to increase as new studies demonstrate that not just time since stroke onset but also collateral circulation influences outcome. Technologies such as telestroke, mobile stroke units, and artificial intelligence are playing an increasing role in identifying and treating stroke. Stroke-systems-of-care models continue to streamline the delivery of definitive revascularization in the age of mechanical thrombectomy.

Keywords

stroke, acute ischemic stroke, thrombolytics, tPA, thrombectomy, stent-retriever, neuroprotection, collaterals, perfusion, telestroke, artificial intelligence, mobile stroke unit

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Introduction

As recently as 25 years ago, all that was available to treat acute ischemic stroke was therapy to temporize the devastating sequelae of irreversibly injured brain tissue. The establishment of thrombolytic therapy and subsequent mechanical thrombectomy (MT) has revolutionized ischemic stroke therapy, allowing mitigation of ischemic stroke and at times outright complete recovery.

The goal of this article is to review advances in the diagnosis and treatment of ischemic stroke within the last 2 to 4 years. With the efficacy of thrombolytics and MT now well established, recent studies have pushed the boundaries of the type of patients who qualify for treatment and the window of opportunity for the efficacy of therapies after stroke onset. New imaging and selection technologies are being harnessed to help better identify patients who will benefit, and new systems are being set up to optimize the delivery of care to patients who need it. Finally, there have been advances and refinements in therapies aimed at prevention of strokes and rehabilitation of patients already afflicted with this disorder.

Basis of acute stroke treatment

Ischemic stroke results from a cerebral artery blockage that leads to a loss of oxygenation in downstream brain tissue, ultimately resulting in neuronal cell death and irreversible neurological deficit. If the blockage is removed before substantial tissue injury ensues, reperfusion of the ischemic tissue may reverse or offset such risk of injury. The timing of intervention is a critical factor: in general, as time progresses after a cerebral artery is blocked, more tissue undergoes irreversible cell death.

Stratification by collateral status

Despite a similar degree of vessel occlusion or the same degree of recanalization with MT or tissue plasminogen activator (tPA), patient outcomes can be significantly varied. The degree of collateral perfusion, mediated by arteries from adjacent vascular territories, determines the duration or time interval that ischemic tissue may survive before cell death ensues. Although it remains true in general that the sooner the intervention is given after stroke onset, the better the outcome¹, patients with better collaterals may benefit more from treatment when others with poor collaterals may not.

Collateral status can be determined via imaging, in which digital subtraction angiography (DSA) is the reference standard, delineating the time course or temporal features of the arterial, capillary, and venous phases of blood flow through the brain. Currently, computed tomographic perfusion (CTP) or magnetic resonance perfusion (MRP) is often used as a faster and less invasive alternative. Ischemic core (tissue that is irreversibly infarcted) and ischemic penumbra (tissue that is hypo-perfused and dependent on collaterals) can be inferred from the perfusion scans.

Using the RAPID automated software, the DEFUSE trials defined and validated cutoffs for penumbra as time to maximum

of residual function (T_{max}) of more than 6 seconds and core as the volume of brain where the magnetic resonance imaging (MRI) apparent diffusion coefficient was less than $600 \times 10^{-6} \text{ mm}^2/\text{s}$ ^{2,3}.

With CTP, mean transit time (MTT), cerebral blood flow (CBF), and cerebral blood volume (CBV) are calculated. Increased MTT with preserved or increased CBV suggests penumbra, whereas increased MTT with decreased CBV and decreased CBF is consistent with core⁴.

A volume mismatch of the core and penumbra suggests salvageable tissue and relatively robust collateral support. Studies demonstrate that favorable collaterals slow the progression of penumbra to core⁵ and that patients with better collaterals have better clinical outcome following intervention⁶.

Stroke imaging

The accurate selection of a treatable acute ischemic stroke is as important as the treatment itself. The current mainstays of evaluation include imaging technology, including computed tomography (CT)/CT angiography, MRI/magnetic resonance angiography (MRA), and DSA. CTP and MRP have become increasingly common. Commercial software such as RAPID (iSchemaView), Olea Sphere (Olea Medical), and Contact (Viz.ai) is now widely available and is able to process perfusion imaging for quick interpretation. RAPID in particular was used effectively to identify candidates for MT in the 2015 stent-retriever trials.

Recent years have seen an explosion of digital data. The emerging era of big data in stroke has led to the integration of artificial intelligence-based techniques such as deep learning and other forms of machine learning in which automated algorithms use large volumes of data to predict outcomes. Algorithms have been designed to identify and quantify the presence of acute stroke and vascular changes by using CT⁷ and MRI⁸ scans and have demonstrated non-inferiority compared with stroke experts. Clinical decision support software already available on the market uses artificial intelligence. Contact (Viz.ai), software that identifies large-vessel occlusions by using artificial intelligence, recently received US Food and Drug Administration approval⁹.

Thrombolysis

In 1995, the National Institute of Neurological Disorders and Stroke published a landmark study establishing the efficacy of the use of tPA¹⁰. Since that time, additional studies have expanded inclusion criteria for tPA use up to 4.5 hours after symptom onset¹¹. There is demonstrated benefit across varying age, ischemic stroke type, and stroke severity.

However, tPA does carry a risk of hemorrhage and therefore its use in patients with a mild National Institutes of Health Stroke Scale (NIHSS) score remains ill defined. A recent study did not show benefit in providing treatment to stroke patients with an NIHSS score of less than 5, compared with aspirin therapy alone, but this study was terminated prematurely because

of low trial recruitment¹². Other studies have explored further expanding the tPA time window on the basis of evidence of good collateral markers with moderate success. The WAKE-UP study selected “wake-up” strokes (where exact time of stroke onset is unknown, as the patient was asleep when the stroke occurred) with MRI acute diffusion restriction without more chronic changes on fluid-attenuated inversion recovery (FLAIR) sequences. tPA treatment in this population improved 90-day functional outcome but had increased symptomatic hemorrhagic transformation (HT)¹³. In another study, collateral perfusion was assessed with either MRP or CTP, and patients with perfusion mismatch received tPA in an extended window up to 9 hours after symptom onset¹⁴. A higher percentage of patients in the treatment arm had mild to no deficits but also had increased symptomatic HT¹⁴.

The risk of HT after tPA has also been an impetus to find alternative pharmacologic thrombolytic agents. The most promising of these is tenecteplase, which is designed to have higher specificity than fibrin and has a longer half-life than tPA. NOR-TEST, a phase III clinical trial published 2017, demonstrated non-inferiority to tPA¹⁵, and a meta-analysis of the tenecteplase clinical trials shows a lower risk of HT in the serious stroke subgroup at baseline¹⁶. An ongoing phase III trial (TIMELESS) is investigating the efficacy of tenecteplase in an extended time window from 4.5 to 24 hours¹⁷.

Mechanical thrombectomy

Although tPA has been shown to be effective, its effectiveness may diminish with more proximal or larger occlusions¹⁸. MT potentially solves this by physically removing the clot through endovascular approaches. Widespread acceptance of the efficacy of MT in treating acute stroke occurred in 2015 with the publication of a series of five clinical trials demonstrating benefit in MT up to 6 hours following stroke symptom onset using primarily second-generation stent-retriever devices¹⁹⁻²⁴. More recently, the DAWN²⁵ and DEFUSE-3² studies further expanded the therapeutic window for MT to up to 24 hours after symptom onset for patients with small core and large penumbra. These studies inform and shape the basis of the current standard of practice for MT.

There is a trend of studies that explore the expansion of treatment candidates for MT, just as there is for tPA. The landmark trials in 2018 limited inclusion to patients with small ischemic core and large penumbra (core of less than 70 mL in DEFUSE3² and less than 51 mL in DAWN²⁵) but also with significant neurological deficit (NIHSS score of at least 6 in DEFUSE-3). In the recent SELECT study, a cohort prospective analysis of 105 patients showed that large core patients can also benefit from MT, with favorable outcome in patient with core sizes up to 100 mL²⁶. SELECT 2, a follow-up randomized clinical trial, is ongoing. Regarding MT in patients with mild stroke symptoms, a retrospective analysis and meta-analysis showed efficacy and safety similar to those of medical therapy alone²⁷.

Although the landmark MT trials focus on the efficacy of stent-retriever devices alone or in combination with an aspiration catheter, there is ongoing debate regarding the use of aspiration alone, which can make the procedure faster and less expensive²⁸. The COMPASS trial recently demonstrated that direct aspiration as first-pass thrombectomy (“ADAPT” technique) was non-inferior to using a stent-retriever device with respect to 90-day functional outcome²⁹.

New MT devices continue to be developed and undergo clinical trials. Notably, new stent-retriever devices are able to reach more distal vasculature (for example, M3 branches of the middle cerebral artery). Examples include the Tigertriever device (Rapid Medical), a stent-retriever that includes a slider to control the degree of stent expansion³⁰, and smaller versions of commercially available stent-retrievers, such as the Trevo XP ProVue 3x20 mm stent-retriever (“baby Trevo”) (Stryker)³¹.

Neuroprotective therapy

Current effective therapy for acute stroke focuses on removal of the arterial occlusion. Investigation into directly treating the ischemic brain tissue with pharmacologic and non-pharmacologic neuroprotective therapies has been ongoing since the 1990s but unfortunately has not yet yielded clear breakthroughs. Candidate agent mechanisms include excitotoxicity inhibitors, apoptosis inhibitors, free radical scavengers, and anti-inflammatory agents^{32,33}.

Notably, however, the majority of neuroprotective clinical trials were performed prior to the thrombectomy era. Adjunct delivery of neuroprotective agents post- or peri-reperfusion is an unexplored and attractive possible therapy. Post hoc analyses have shown some neuroprotective agents to be more beneficial in the sub-population of patients who underwent MT, as seen in the uric acid trial³⁴. Nerinetide, an excitotoxic cell death pathway inhibitor, was recently tested in patients with MT in a large trial (ESCAPE NA1)³⁵. Although it failed to show a difference in 90-day functional outcome, the outcome was improved in nerinetide patients who did not receive tPA.

Some studies have explored tighter control of glucose³⁶ and blood pressure³⁷ immediately after acute stroke and in general have not shown these interventions to be beneficial. Regenerative medicine through stem cell therapy is an attractive concept that is pervasive throughout all of medicine. Trials investigating delivery of stem cells both acutely hours following ischemic stroke and chronically months to years after ischemic stroke are ongoing. Initial results show that therapy is safe but have yet to show functional efficacy^{38,39}.

Stroke care delivery

Delivery and access of acute stroke care are major issues regarding maximizing stroke treatment. Despite the benefit of acute intervention, only a small percentage of patients with stroke

actually receive that intervention: with an estimated 691,000 acute ischemic strokes yearly in the US⁴⁰, only 13,000 MT were performed nationally as of 2016⁴¹ (less than 2%). This is due in part to system delays in arrival to and workflow at an intervention-capable center and to the lack of nearby intervention-capable centers (as in rural areas).

Different peri-hospital systems have been developed to quickly identify patients with acute stroke and decrease “door to needle” (DTN) (time from arrival to hospital to delivery of tPA) and “door to puncture” (time from arrival to hospital to groin access for MT) times. Policies such as pre-hospital notification, single call activation of the stroke team, moving patients to the scanner using the ambulance stretcher, and administering tPA in the scanner have helped to decrease DTN times. Individual centers have developed their own optimization schemes. The Helsinki University Central Hospital developed the seminal Helsinki protocol at their institution, leading to average DTN times of 20 minutes⁴². There have been more systemic multi-hospital policy efforts as well. The American Heart Association/American Stroke Association developed the “Target: Stroke” initiative, leading to an improvement to DTN times of 59 minutes in participating hospitals⁴³.

Regarding geographical inaccessibility, solutions that have been developed include telestroke and mobile stroke units (MSUs). Current telestroke systems include a two-way video communication to allow a neurological exam to be conducted by the vascular neurologist and some method of remotely evaluating acute imaging. In this way, decision and treatment for tPA can be given prior to or without need for transfer from a remote hospital. Studies show improved DTN times in small hospitals with telestroke⁴⁴. In the event that MT or an otherwise higher level of care is indicated, the patient is transferred out (“drip and ship”). Frequently, multiple hospitals are funneled to a single transfer hospital, the so-called “hub and spoke” model. Alternatives include the “mothership” model, where hospitals without neurocritical care capability are bypassed in favor of a central hospital if acute stroke is suspected by emergency medical services (EMS). There is ongoing debate on which

model leads to the best outcomes, DTN times, and general cost efficiency⁴⁵.

MSUs are ambulances that have been fitted with CT imaging technology and staffed with nurses, technicians, and physicians so that tPA can be delivered to the patient in the field after initial evaluation and imaging. In this way, the time spent during transfer by EMS to the hospital is eliminated, and decision making can be carried out directly by the stroke team. MSUs were first implemented in Germany in 2011⁴⁶. Since that time, almost 20 locations have been using this technology worldwide. Reports from individual sites show improved time to tPA without decreasing safety⁴⁶, but the cost of creating and maintaining these units is high⁴⁷. The generalizability of MSUs remains to be fully determined.

Conclusions

Our understanding of the mechanism and time course of acute ischemic stroke continues to advance. Now more than ever, ubiquitous digital connectivity and artificial intelligence technology are being leveraged to help treat this disorder. Recent years have seen a substantial increase in the fraction of patients whose acute ischemic stroke can be treated with tPA and MT and this population continues to expand. Although there have been advances in optimizing peri-hospital workflow and improving access to acute stroke therapy, more should be done to optimize care delivery, especially in rural areas and areas far from academic hospitals.

Abbreviations

CBF, cerebral blood flow; CBV, cerebral blood volume; CT, computed tomography; CTP, computed tomographic perfusion; DSA, digital subtraction angiography; DTN, door to needle; EMS, emergency medical services; HT, hemorrhagic transformation; MRI, magnetic resonance imaging; MRP, magnetic resonance perfusion; MSU, mobile stroke unit; MT, mechanical thrombectomy; MTT, mean transit time; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator

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