

Access this article online
Quick Response Code:

Website: http://www.braincirculation.org
DOI: 10.4103/bc.bc_36_18

Treatment for ischemic stroke: From thrombolysis to thrombectomy and remaining challenges

Tiandong Leng, Zhi-Gang Xiong

Abstract:

Stroke is a leading cause of death and long-term disabilities. Despite decades of extensive efforts in search of brain injury mechanisms and therapeutic interventions, pharmacological treatment is limited to the use of thrombolytic agent tissue plasminogen activator, which has limited therapeutic time window and potential side effect of intracranial hemorrhage. Over the past few years, endovascular thrombectomy with stent-retriever devices combined with advanced imaging modalities has transformed the standard of stroke care, offering an opportunity to improve the outcome in selected patients as late as 24 h after the onset of stroke. This mini-review summarizes the advancement in the treatment of ischemic stroke, from thrombolysis to thrombectomy and remaining challenges in the field.

Keywords:

Stroke, thrombectomy, thrombolysis, tissue plasminogen activator

Introduction

Stroke remains as a leading cause of death.^[1] In the United States alone, nearly 800,000 people suffer from a new stroke every year, and stroke kills ~ 140,000 Americans, about 1 out of every 20 deaths.^[2] For those people who survive the acute stroke, many of them will have severe long-term disabilities. Therefore, stroke is one of the most devastating neurological diseases, which imposes an enormous burden on the society.

There are two major types of stroke. The most common one is the ischemic stroke, which accounts for ~ 85% of the total stroke cases in the United States.^[2] It occurs as a result of an obstruction (a clot) within a blood vessel leading to or within the brain. Ischemic stroke may be further divided into two subtypes: cerebral thrombosis,

which refers to a blood clot that develops at the clogged part of the vessels, or cerebral embolism, which refers to a blood clot that forms at another location in the circulatory system (e.g., in the heart). In this case, a portion of the blood clot breaks loose and travels through the blood vessels in the brain until it reaches vessels too small to let it pass.

Another major type of stroke is the hemorrhagic stroke, which accounts for 10%–15% of the total stroke cases.^[3] It results from a weakened blood vessel that ruptures and bleeds in the brain. The blood then accumulates and compresses the surrounding brain tissue, resulting in brain damage. For decades, enormous effort has been made in search of brain injury mechanisms and therapeutic interventions for stroke patients. As of now, no effective targeted therapy for hemorrhagic stroke exists other than basic life support, as well as control of seizures, blood pressure, and intracranial pressure, etc.^[4] In contrast,

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Leng T, Xiong ZG. Treatment for ischemic stroke: From thrombolysis to thrombectomy and remaining challenges. *Brain Circ* 2019;5:8-11.

*Department of
Neurobiology,
Neuroscience Institute,
Morehouse School of
Medicine, Atlanta, GA,
USA*

Address for correspondence:

Dr. Tiandong Leng,
Department of
Neurobiology, Morehouse
School of Medicine, 720
Westview Drive SW,
Atlanta, GA 30310, USA.
E-mail: tleng@msm.edu
Dr. Zhi-Gang Xiong,
Department of
Neurobiology, Morehouse
School of Medicine,
720 Westview Drive SW,
Atlanta, GA 30310, USA.
E-mail: zxiong@msm.edu

Submission: 13-12-2018
Revised: 27-02-2019
Accepted: 10-03-2019

targeted therapies including thrombolysis and thrombectomy have shown promising results for ischemic stroke.

Tissue Plasminogen Activator for Ischemic Stroke

For many years, scientists have considered using thrombolytic agents to help dissolve the clots for ischemic stroke through animal studies and clinical trials. In fact, small controlled trials of thrombolysis were initiated several decades ago, but the early therapy was discarded because of negative results or increased risk of death.^[5-7] The trials with streptokinase, for example, failed to show a positive outcome.^[5,6] However, in 1995, clinical studies led by the National Institute of Neurological Disorders and Stroke provided convincing evidence that patients treated with recombinant tissue plasminogen activator (tPA) within 3 h of symptom onset achieved better neurologic recovery and experienced less disability than those who received placebo.^[8] Subsequently, in 1996, the US Food and Drug Administration approved the use of tPA for ischemic stroke patients. Since then, the use of tPA has saved hundreds of thousands of patients, and it has been considered a significant milestone in the field of stroke. Unfortunately, because of various limitations and potentially severe side effects, the use of tPA had very strict inclusion criteria.^[9] For example, it needed to be administered early after symptom onset (within 3 h), often failed to break up large clots, and could cause uncontrolled bleeding in the brain.^[10] As such, the American Heart Association and the American Academy of Neurology jointly developed strict guidelines which excluded the majority of stroke patients from tPA treatment.^[9,11] It was estimated that only about 1% of patients reaching hospital in time were treated with tPA, although a slightly high rate of treatment has also been reported.^[12-14]

Can a delayed administration of tPA still be feasible for some patients? For years, scientists tried to determine whether a time window longer than 3 h was beneficial for stroke patients that otherwise did not qualify for tPA treatment. In 2008, an influential clinical study, the Third European Cooperative Acute Stroke Study III, showed that, as compared with placebo, intravenous (IV) tPA administered between 3 and 4.5 h after the onset of symptoms also improved clinical outcomes in patients with ischemic stroke, even though tPA administration was more frequently associated with symptomatic intracranial hemorrhage.^[15] Thus, in 2009, the American Heart Association/American Stroke Association issued a new guideline recommending the use of tPA for patients up to 4.5 h from the onset of symptoms.^[16] With this change in clinical practice, more stroke patients are now eligible for and can benefit from the use of tPA.

However, despite this expansion in time window, the majority of stroke patients arrived at hospitals either too late,^[17] or were ineligible for tPA treatment for some other reasons.^[9] It has been reported that, even for patients that did receive tPA treatment, up to 2/3rd of the patients with large-vessel occlusions did not achieve recanalization.^[8] As such, <50% of the patients treated with tPA achieved a complete reperfusion by 24 h and up to 40% of the stroke patients remained severely disabled or died.^[8] Thus, new interventions and more broad time windows are needed for most of the stroke patients.

In 2012, a pragmatic, multicenter, phase 3 randomized clinical trial, the Norwegian Tenecteplase Stroke Trial (NOR-TEST), was started to compare the efficacy and safety of tenecteplase versus tPA. Tenecteplase is a modified tPA that is more fibrin specific, more resistant to plasminogen activator inhibitor, and has a longer half-life than alteplase. It was anticipated that it would work better than tPA. However, the finding of NOR-TEST trial was that tenecteplase is not superior to tPA and shows a similar safety profile, at least for mild stroke patients.^[18]

How about patients who arrive at hospitals beyond the recommended 4.5 h time window since they were last known to be well? At about a similar time, another important trial, the MR WITNESS trial, was conducted to determine whether stroke patients of unwitnessed onset at 4.5–24 h since they were last known to be well were treatable within 4.5 h of symptom discovery with IV tPA.^[19] In this study, a quantitative mismatch between diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) was used to identify stroke patients that were within 4.5 h of biological symptom. With tPA treatment at a median of 11.2 h from when patients were last known to be well, tPA treatment appeared to be safe and was warranted in patients without large-vessel occlusions.^[19] Similar to MR WITNESS trial, the recently concluded WAKE UP trial^[20,21] also showed that, using a mismatch between DWI and FLAIR as a criterion for treatment in patients with an unknown time of onset, IV tPA treatment resulted in a better functional outcome at 90 days than that of placebo.

Endovascular Thrombectomy for Ischemic Stroke

Besides thrombolysis, for years, scientists have considered mechanical removal of the clot, a procedure termed endovascular thrombectomy, for patients not eligible for tPA treatment, particularly those who came to hospitals beyond the time window for tPA. The findings have been inconclusive.^[22] In 2017, however, a multicentered clinical trial, the Diffusion-Weighted Imaging or Computerized Tomography Perfusion

Assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo, or DAWN trial, brought an exciting news to the field: in selected stroke patients presented to the trial centers between 6 and 24 h from symptom onset, removal of a clot by endovascular thrombectomy significantly reduced disability.^[23]

In the DAWN trial, patients with a large-vessel occlusion arrived between 6 and 24 h after symptom onset went through computed tomography perfusion or diffusion-weighted magnetic resonance imaging analysis. Patients were selected for the trial if they had targeted mismatch, i.e., a small core infarct volume and a large area of brain at risk but still potentially salvageable. The exact requirements varied with ages. For example, patients aged >80 years with National Institutes of Health Stroke Scale (NIHSS) score >10 and a core volume <21 ml were selected. While for patients <80 years, an NIHSS score >10 and a core volume <31 ml or an NIHSS score >20 and a core volume <51 ml were considered as the selection criteria.

Results showed a two-point difference in weighted modified Rankin Scale (mRS) score at 90 days in favor of the thrombectomy group. This difference was translated into a 73% relative reduction of dependency in daily living activities. In addition, there was ~ 35% increase in the number of patients that achieved functional independence (i.e., with a mRS score of 0–2). The success of the DAWN trial significantly expanded the population eligible for therapeutic intervention, a finding which has been hailed as a ground-breaking achievement in the treatment of ischemic stroke. The 24 h time window now gives doctors an opportunity to screen almost every stroke patient with a large-vessel occlusion for endovascular thrombectomy. It also suggests that time should not be the most important factor that determines whether a patient is considered for the endovascular therapy.

Following the success of DAWN trial, another multicenter, randomized clinical study, the Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke, or DEFUSE 3 trial, which had less strict selection criteria (e.g., an initial infarct size of smaller than 70 ml and a ratio of tissue at risk versus ischemic core of 1.8 or above), reported the efficacy of endovascular thrombectomy that occurred 6–16 h after symptom onset.^[24] At 90 days, for example, there was a 28% difference in the rate of functional independence in favor of the endovascular therapy group. Although approximately 40% of the patients in the DEFUSE 3 trial did not meet the DAWN selection criteria, endovascular thrombectomy still achieved a positive outcome.

Challenges and Opportunities

With no doubt, the results of DAWN and DEFUSE 3 trials are very exciting. However, one cannot be overly excited. Despite the extended time window to 24 h, most stroke patients still do not qualify for the therapy. A recent retrospective review^[25] of stroke patients admitted to a single DAWN trial-participating center to identify patients meeting the criteria of DAWN or DEFUSE-3 reported that, of a total of 2667 patients admitted with acute ischemic stroke, 30% arrived within the 6–24 h time window. Among those, 47% had a NIHSS ≥ 6 . After applying additional trial-specific selection criteria (i.e., the presence of large-vessel occlusion, core infarct volume, and perfusion imaging), only 1.7% of patients met the DAWN trial criteria with an additional 0.6%–1% meeting the DEFUSE-3 trial criteria. Therefore, although the outcome of both trials was clearly positive, only small percentages (~3%) of patients were qualified for the treatment. For the patients who were qualified for the treatment, many of them still experienced some degree of neurological deficits following the therapy.^[23] It is worth mentioning that only the hospitals with advanced imaging facilities and well-experienced doctors can perform the thrombectomy procedure. Surgical thrombectomy also has the risks of vascular injury (1%–5%), emboli (5%–9%), vasospasms (20%–26%), symptomatic hemorrhage (up to 8%), etc.^[26]

Nevertheless, the advancement in endovascular thrombectomy with the extended time window for intervention may offer a new opportunity to reconsider other adjunctive therapies such as neuroprotective agents to improve long-term functional outcome. In this regard, further evaluation of the benefit of neuroprotection in the context of mechanical revascularization may yield potential fruitful outcomes. Other ongoing studies in the field, for example, neuroregeneration and stem cell therapy, may provide additional benefit to stroke patients.

Financial support and sponsorship

The work in our laboratories were supported by NIH grants R01NS104349 (z.x.) and SC3GM122593 (t.l.).

Conflicts of interest

There are no conflicts of interest.

References

1. Kochanek KD, Murphy S, Xu J, Arias E. Mortality in the United States, 2016. NCHS Data Brief 2017;293:1-8.
2. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, *et al.* Heart disease and stroke statistics-2017 update: A report from the American Heart Association. *Circulation* 2017;135:e146-603.
3. Romero JM, Rosand J. Hemorrhagic cerebrovascular disease. *Handb Clin Neurol* 2016;135:351-64.

4. Sembill JA, Huttner HB, Kuramatsu JB. Impact of recent studies for the treatment of intracerebral hemorrhage. *Curr Neurol Neurosci Rep* 2018;18:71.
5. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. Multicentre Acute Stroke Trial – Italy (MAST-I) Group. *Lancet* 1995;346:1509-14.
6. Donnan GA, Davis SM, Chambers BR, Gates PC, Hankey GJ, McNeil JJ, *et al*. Streptokinase for acute ischemic stroke with relationship to time of administration: Australian Streptokinase (ASK) Trial Study Group. *JAMA* 1996;276:961-6.
7. Fisher M, Bogousslavsky J. Further evolution toward effective therapy for acute ischemic stroke. *JAMA* 1998;279:1298-303.
8. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581-7.
9. Practice advisory: Thrombolytic therapy for acute ischemic stroke – Summary statement. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 1996;47:835-9.
10. Wang X, Tsuji K, Lee SR, Ning M, Furie KL, Buchan AM, *et al*. Mechanisms of hemorrhagic transformation after tissue plasminogen activator reperfusion therapy for ischemic stroke. *Stroke* 2004;35:2726-30.
11. Toni D, Gallo V, Falcou A, Argentino C, Fieschi C. Treatment of cerebrovascular diseases: State of the art and perspectives. *J Cardiovasc Pharmacol* 2001;38 Suppl 2:S83-6.
12. Bunch ME, Nunziato EC, Labovitz DL. Barriers to the use of intravenous tissue plasminogen activator for in-hospital strokes. *J Stroke Cerebrovasc Dis* 2012;21:808-11.
13. Alvaro LC, Timiraos J, Sádaba F. In-hospital stroke: Clinical profile and expectations for treatment. *Neurologia* 2008;23:4-9.
14. Dulli D, Samaniego EA. Inpatient and community ischemic strokes in a university hospital. *Neuroepidemiology* 2007;28:86-92.
15. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, *et al*. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317-29.
16. Del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr.; American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: A science advisory from the American Heart Association/American Stroke Association. *Stroke* 2009;40:2945-8.
17. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, *et al*. Heart disease and stroke statistics–2014 update: A report from the American Heart Association. *Circulation* 2014;129:e28-92.
18. Logallo N, Novotny V, Assmus J, Kvistad CE, Alteheld L, Rønning OM, *et al*. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): A phase 3, randomised, open-label, blinded endpoint trial. *Lancet Neurol* 2017;16:781-8.
19. Schwamm LH, Wu O, Song SS, Latour LL, Ford AL, Hsia AW, *et al*. Intravenous thrombolysis in unwitnessed stroke onset: MR WITNESS trial results. *Ann Neurol* 2018;83:980-93.
20. Thomalla G, Fiebich JB, Østergaard L, Pedraza S, Thijs V, Nighoghossian N, *et al*. A multicenter, randomized, double-blind, placebo-controlled trial to test efficacy and safety of magnetic resonance imaging-based thrombolysis in wake-up stroke (WAKE-UP). *Int J Stroke* 2014;9:829-36.
21. Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, *et al*. MRI-guided thrombolysis for stroke with unknown time of onset. *N Engl J Med* 2018;379:611-22.
22. Smith WS, Furlan AJ. Brief history of endovascular acute ischemic stroke treatment. *Stroke* 2016;47:e23-6.
23. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, *et al*. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2018;378:11-21.
24. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, *et al*. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med* 2018;378:708-18.
25. Jadhav AP, Desai SM, Kenmuir CL, Rocha M, Starr MT, Molyneaux BJ, *et al*. Eligibility for endovascular trial enrollment in the 6- to 24-hour time window: Analysis of a single comprehensive stroke center. *Stroke* 2018;49:1015-7.
26. Kurre W, Bätzner H, Henkes H. Mechanical thrombectomy: Acute complications and delayed sequelae. *Radiologe* 2016;56:32-41.