Commentary

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Opening the time window

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Abstract

The recently completed EXTEND trial tested the idea that tissue plasminogen activator thrombolysis can be safely extended up to 9 h after stroke onset if automated perfusion imaging indicates the presence of a salvageable penumbra. This important trial contributes to an ongoing paradigm shift for stroke therapy. Combined with the introduction of endovascular therapy, image-guided patient selection is expanding the toolbox of the stroke practitioner. At the same time, pushing the limits of reperfusion has raised important questions about mechanisms to pursue for combination therapy as well as potential approaches to mitigate side effects and optimize treatments for patients with various co-morbidities.

Keywords

Thrombolysis, acute stroke, clinical trials, brain imaging, neuroprotection

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These are exciting times in stroke research. After many years of mostly futile efforts to improve stroke therapy pharmacologically, decisive progress in stroke treatment has recently come from two different directions: first the successful trials of endovascular therapies for large vessel occlusions that have brought a flurry of new initiatives to better define the optimal context for the use of stent retrievers; and more recently, a number of trials that incorporate imaging to identify the best patient pool for both thrombolytic and endovascular treatment. EXTEND,[1] the most recent of these, and the recently published meta-analysis[2] of individual patients from the EXTEND, ECASS4-EXTEND and EPITHET trials excitingly suggest that extending the treatment window for tissue plasminogen activator (tPA) thrombolysis out to 9 h may be acceptable when imaging has indicated the presence of hypoperfused but salvageable tissue. Together with the DAWN, DEFUSE 3, and WAKE-UP trials, these findings clearly support loosening the strict time constraints previously placed on the stroke practitioner, thus widening the patient pool that is eligible for reperfusion therapy. Importantly, these impressive advances in clinical trials are also opening up a plethora of new questions and challenges.

As we push the limits of reperfusion, where could further improvements be achieved?[3] First and foremost, there is a need to continue to develop novel tools in penumbral imaging. Multimodal imaging that includes parameters like pH and oxygen extraction fraction may improve diagnostic accuracy and precision, if it can be completed with sufficient speed.[4] Second, added basic research is warranted to dissect the mechanisms that convert penumbral tissue into irreversibly infarcted tissue. It is increasingly recognized that for certain cellular subsets, this process need not be unstoppable. Hypothermia and similar measures may help to stabilize the penumbra and prolong the window of opportunity for amplifying the efficacy of reperfusion.[5] Third, a one-size-fits-all approach may not work for all stroke patients. For example, comorbidities like hypertension alter not just the risk of stroke, but also its underlying mechanisms of pathologic progression. Typically, this may involve poor collateral capacity and a diminished penumbra. Beyond blood pressure control, improving collateral circulation with treatments like carboxyhemoglobin may help to increase the amount of salvageable tissue.[6] Similar mechanistic advances have been

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obtained for diabetic strokes.[7] Ultimately, the goal might be to optimize combination therapies depending on the stroke comorbidity involved. Fourth, despite successful reperfusion, many patients go on to suffer debilitating deficits. This has become especially clear in the endovascular therapy trials. Neuroprotective approaches can ameliorate these deficits, if we have a clear understanding of the mechanisms involved before, during and after reperfusion. For example, there may be physiological differences between brain tissue rescued by reperfusion versus tissue salvaged by neuroprotection per se. Remarkably, these differences may even extend to the cellular level; a recent study found that the transcriptome of neurons subjected to early reoxygenation following oxygen-glucose deprivation differed from that of neurons protected pharmacologically, despite similarly improved survival rates.[8] What the overall effect of these differences in pathway activation is will require further study. Fifth, beyond pure neuroprotection, several treatment approaches have shown an added effect of neurovascular protection. One important factor that still limits the use of thrombolytic treatment is the propensity of tPA to promote hemorrhagic transformation of the infarct, especially when given at later time points. This was confirmed in the EXTEND trial and the aforementioned meta-analysis,[2] reinforcing the need to limit tPA-associated symptomatic intracerebral hemorrhage. Numerous approaches at reducing the risk of hemorrhagic transformation have been attempted, although none have yet made it into the clinic. The recently completed Phase II RHAPSODY trial tested Activated Protein C derivative 3K3A-APC combined with thrombectomy or endovascular treatment and showed a trend towards reduced hemorrhage for 3K3A-APC.[9] A more recent mechanism-based approach utilizes a lipoxygenase inhibitor, which both reduces neuronal cell death and prevents hemorrhagic conversion.[10] This type of dual efficacy approach may provide neuroprotection, and in addition increase the safety profile of tPA. Again, translational challenges must be overcome, but finding multi-modal treatments may be what is needed to further shift the needle towards higher rates of reperfusion usage and efficacy.[11]

The initially approved time window for tPA reperfusion of 3 h after stroke onset contributed to restricted usage. With more time, a better picture of the infarct and its environment, and additional new treatment options, there is now much hope for further improvements that will benefit a greater number of patients.

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