Newer clot-busting medication may someday increase time for stroke treatment

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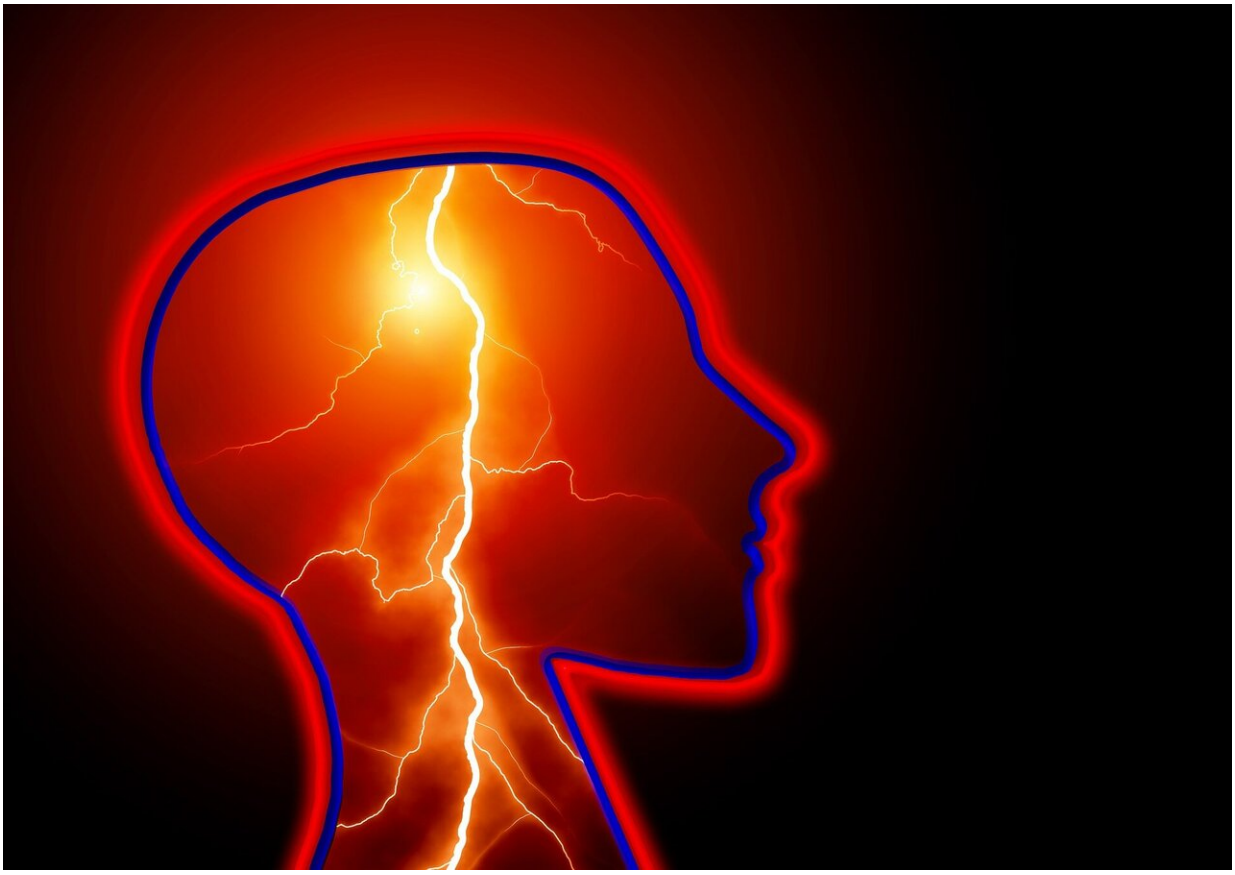

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If patients with clot-caused strokes obtain medical care more than 4½ hours after their symptoms are noticed, it is too late to receive the

standard clot-busting medication alteplase. However, in this study from China, tenecteplase appears to lengthen the window for additional stroke treatment to up to 24 hours, according to preliminary, late-breaking science presented today at the American Stroke Association's International Stroke Conference 2022.

A one-hour infusion of alteplase is the standard treatment for a clot-caused (ischemic) stroke, administered within 4.5 hours of first stroke symptoms. Alteplase dissolves blood clots that are blocking arteries supplying oxygen-rich blood to the lungs or brain and has been FDA-approved for the immediate treatment of ischemic stroke since 1996.

A newer medication, tenecteplase, is also a clot-busting medication and is a bioengineered variant of alteplase, and there are ongoing studies to determine its safety, efficacy and treatment parameters for ischemic stroke. Previous studies of Tenecteplase to treat acute ischemic stroke patients found it may be non-inferior to alteplase and may be superior for treating large-vessel strokes.

"The stroke burden continues to grow across the world, and particularly in China where stroke is the leading cause of death," said Xin Cheng, M.D., Ph.D., lead author of the study and associate professor of neurology at the Huashan Hospital of Fudan University and the National Center for Neurological Disorders in Shanghai, China. "There are two major limitations in thrombolysis [treatment to dissolve dangerous clots and restore blood flow] with alteplase: the restricted time window of 4.5 hours, and a low rate of success in re-opening arteries and restoring blood flow when a large brain vessel is blocked."

To evaluate the potential of using tenecteplase to treat patients with large-vessel strokes, Cheng and colleagues studied 86 patients with ischemic strokes, treated at 13 different hospitals in China. The patients had brain imaging between 4.5 and 24 hours after they were last known to be free

of stroke symptoms. On imaging, all study participants were found to have large, affected brain areas that could potentially be salvaged if blood flow was re-established and a few small areas that were unlikely to benefit from treatment (called a penumbral mismatch).

Study participants were randomly assigned to two groups:

- 43 patients (average age of 68 years; 58.1% male) received a lower (0.25 mg/kg) dose of tenecteplase; and
- 43 patients (average age of 67 years; 72.1% male) received a higher (0.32 mg/kg) dose of tenecteplase.

The researchers had determined a pre-established, combined, positive outcome of effectiveness and safety if there was major restoration of blood flow without symptomatic brain bleeding 24-48 hours after treatment. If more than 7 of 43 patients met the positive outcome criteria, that intervention dose of tenecteplase would be deemed of sufficient promise to warrant further study. In addition to tenecteplase, some patients underwent endovascular therapy (thrombectomy) to mechanically remove a clot, at the discretion of the treating physician.

The researchers found:

- At the lower dose of tenecteplase, 14 of 43 patients (32.6%) achieved the designated positive outcome criteria.
- At the higher dose of tenecteplase, 10 of 43 patients (23.3%) achieved the designated positive outcome criteria.
- Among all study participants evaluated 3 months after treatment, more than half (53.5%) of the patients were no more than slightly disabled, not able to carry out all previous activities but did not require daily assistance, and 38.4% of the participants either had no significant symptoms of residual neurological deficits or had mild symptoms but were able to return to pre-stroke activities of

daily living.

"Tenecteplase appears to be safe and potent in reestablishing blood flow through blocked, large brain vessels, thereby preventing damage to brain tissue at risk of dying. Using perfusion imaging [to measure blood flow throughout the blood vessels] to assess patients with larger areas of potentially salvageable brain tissue and smaller areas that have already been lost to the stroke, it seems feasible that with tenecteplase we may be able to extend the time window for treatment to 24 hours after the time the patient was last known to be well. However, we still need more data from randomized controlled trials before practice changes to routinely include tenecteplase," Cheng said.

In the subset of patients who received tenecteplase and underwent endovascular therapy (also known as thrombectomy or mechanical clot removal), fewer patients (3 of 34, or 8.8%) reached the primary outcome measure of restoring blood flow without symptomatic brain bleeding, compared to those who received only tenecteplase (21 of 52, or 40.4%).

"In our study, tenecteplase seems to be quite effective and safe in patients who do not need endovascular therapy. More research is needed to understand why tenecteplase was less effective in restoring blood flow and more likely to result in symptomatic brain bleeding among those who had endovascular therapy," Cheng said.

As a Phase 2a trial, the focus of this research was to evaluate whether a treatment is safe and effective enough to proceed to a larger clinical trial with more study participants and to determine the potential medication doses appropriate for further research. Based on the results of this trial, the lower dose of tenecteplase is being evaluated in a larger, nationwide, Phase 2b study in China to compare the effectiveness and safety of tenecteplase versus standard treatment.

The study's limitations include being a phase 2a clinical trial without a control group and these results from China may not be generalizable to other non-Chinese populations.

"Strokes involving large arteries in the brain due to plaque build-up are much more common among people of Chinese or Asian ethnicity compared with people of Caucasian descent. These types of strokes usually have more sustained blood flow through collateral vessels than embolic strokes, which are caused by a blood clot that forms elsewhere in the body and travels to the brain. The optimal strategy to restore blood flow in patients with large-artery plaque build-up is unknown, and there is a question of whether endovascular treatment [thrombectomy] is appropriate and effective in this type of stroke. With a huge stroke burden and limited access to centers capable of endovascular treatment in China, a potent intravenous thrombolytic like tenecteplase may be more meaningful," Cheng said.

The latest ischemic stroke treatment guidelines from the American Heart Association recommend it may be reasonable to consider tenecteplase to treat ischemic stroke among select patients. Several recent clinical trials focused on ischemic stroke have directly compared alteplase and tenecteplase, however, large, Phase 3 trials are still ongoing.

More information: professional.heart.org/en/meet … al-stroke-conference

Provided by American Heart Association