Low- versus Standard-Dose Intravenous Tissue-Type Plasminogen Activator for Acute Ischemic Stroke: An Updated Meta-Analysis

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Background: We performed a meta-analysis to compare the efficacy and safety between low- and standard-dose intravenous (IV) tissue-type plasminogen activator (tPA) for acute ischemic stroke (AIS) patients within 4.5 hours of symptom onset. *Methods:* We searched PubMed and EMBASE for relevant studies from inception to June1, 2017. Cohort or randomized controlled studies for AIS within 4.5 hours of symptom onset with comparison between low-dose and standard-dose tPA were included. The primary efficacy end point was favorable functional outcome (modified Rankin scale scores [mRS] of 0-1) at 90 days. The primary safety end point was the incidence rate of symptomatic intracerebral hemorrhage (sICH). The secondary end points were independent functional outcome (mRS scores of 0-2) and mortality. *Results:* A total of 11 studies were pooled in this meta-analysis. The low-dose strategy appeared to be as effective as standard-dose tPA (43.4% versus 45.4%; odds ratio [OR] = 0.93, 95% confidence interval [CI]: 0.78-1.10; $P = .38$) in primary efficacy outcome. The secondary efficacy outcome produced similar results (57.3% versus 57.0%; OR = 0.95, 95% CI: 0.86-1.05; $P = .33$). There was no evidence of statistical difference for sICH (4.2% versus 4.9%; OR = 1.02 [0.66-1.55]; $P = .94$) and mortality (9.0% versus 10.6%; OR = 0.99 [0.74-1.31]; $P = .92$) at 90 days between low- and standard-dose therapy. In a subgroup analysis by ethnicity, there was no significant difference between patients of Asian and non-Asian descent for any of the end points. *Conclusions:* This study showed that AIS patients receiving low-

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dose IV-tPA had comparably efficacy and safety to those receiving standard-dose IV-tPA. However, the effect is especially pronounced within the Asian population, which limits the generalizability of these results. **Key Words:** Tissue plasminogen activator—dose—stroke—efficacy—safety.

To date, intravenously (IV) administered tissue plasminogen activator (t-PA) is still the most effective evidence-based therapy for patients with acute ischemic stroke (AIS). In Western countries, despite certain incidence of intracerebral hemorrhagic conversion, .9 mg/kg tPA has been the accepted therapeutic dose since the publication of the National Institute of Neurological Diseases and Stroke (NINDS) trial.[1] In Asian countries, because of the concerns over racial difference, cost, and safety, lower doses of tPA became a common preferred treatment. In Japan, the Japan Alteplase Clinical Trial (J-ACT) study demonstrated that the safety and efficacy of .6 mg/kg tPA was equivalent to those of the standard dose used in the NINDS trial[2]; this dose was then approved in Japan. Subsequently, a series of clinical studies on lower doses of tPA or the comparison between low-dose and full-dose tPA were carried out in Asian countries.[3-7] However, the results from these trials were inconsistent in terms of safety and efficacy. The 2015 meta-analysis that included these studies showed that the lower doses were comparable to the standard dose of tPA both in efficacy and in safety.[8] However, all of these studies were observational, not randomized until the recently published multicenter prospective randomized controlled trial (RCT), the ENCHANTED (the Enhanced Control of Hypertension and Thrombolysis Stroke Study).[9] This trial was conducted on the premise that .6 mg/kg tPA is an effective strategy with possible lower risk of symptomatic intracranial hemorrhage (sICH). At the conclusion, the trial failed to show the noninferiority of low-dose to standard-dose tPA in the primary outcome of death or disability. It is therefore necessary to conduct an updated meta-analysis to help understand the impact of lower doses of tPA by comparing the efficacy and safety of lower doses to those of the full dose to treat patients with AIS.

Methods

Protocol and Guidance

This study updated the meta-analysis of study on low-dose versus standard-dose tPA treatment for AIS patients published in 2015.[8] The methods and reporting of the meta-analysis followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10]

Eligibility Criteria

We selected cohort and RCT studies published since 1995 in English, focusing on the efficacy and safety of low-dose versus standard-dose IV-tPA. We included both retrospective and prospective studies as well as observational and controlled studies. Furthermore, these studies also included functional outcome (with modified Rankin scale scores [mRS] assessment) at 3 months after symptom onset as an efficacy end point, as well as incidence of mortality and sICH as safety end points. We excluded studies with other combined treatments, such as endovascular intervention and other IV-anticoagulation, IV-antiplatelet, or thrombolytic therapies.

Information Sources and Search Strategy

An electronic literature search was conducted using EMBASE and PubMed within the time period between January 1, 1995, and June 1, 2017. We combined search terms (stroke OR cerebral ischemia OR cerebral infarction) with (alteplase OR tissue plasminogen activator OR intravenous thrombolysis OR rtPA) and "dose." As mentioned previously, language was limited to only English. From the initial results of the EMBASE search, we further limited the drug to "alteplase," "tissue plasminogen activator," or "fibrinolytic agent." Finally, a total of 3373 results were included. We also obtained additional information from study supplements.

Study Selection and Data Collection

Two reviewers (L.H.H. and Z.H.G., both neurologists) independently screened the titles of all papers identified in the search to eliminate duplicates and reviewed abstracts for potential eligibility. Disagreements were resolved with the help of a third reviewer (C.Y.J.).

The following information was extracted from the included studies: (1) general information: author names, country, publication year, study design; (2) baseline information: inclusion and exclusion criteria, the number of patients, the baseline characteristics of patients (age, gender, National Institutes of Health Stroke Scale [NIHSS] score, dosages of IV-tPA [<.85 mg/kg defined as low dose, .85 to .95 mg/kg defined as full dose], common vascular risk factors); (3) outcomes: the number of patients with favorable functional outcome (mRS score of 0-1) or proportion of patients with favorable functional outcome (which can be used to calculate the total number of patients with mRS of 0-1), the incidence of sICH, and all-cause mortality at 3 months. Data from the Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China study was provided by the principal investigator of the study.