Low-Dose Tissue Plasminogen Activator in Acute Ischemic Stroke: A Systematic Review and Meta-Analysis

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Background: Intravenous thrombolysis using tissue plasminogen activator (tPA) improves significantly the neurologic function in patients with acute ischemic stroke (AIS). However, it brings financial burden to patients and is associated with symptomatic intracranial hemorrhage (SICH). Whether low-dose tPA can effectively reduce SICH and has the same efficacy as standard-dose tPA is still controversial. *Methods:* We searched for English clinical trials published before March, 2017on the comparison of the efficacy and safety between low and standard dose of tPA in the treatment of AIS using MEDLINE, Embase, and Cochrane Library. The modified Rankin scale (mRS) score was used as the primary efficacy outcome. The mRS1 corresponded to 0-1, whereas mRS2 corresponded to 0-2. The SICH and mortality were adopted as primary safety outcomes. *Results:* Twelve high-quality studies were selected, including 7686 patients (low-dose: 2888, standard-dose: 4798). With no statistical heterogeneity, the fixed effects model was adopted in the analysis. Similarly to standard doses, low-dose tPA improved the mRS scores (mRS1: odds ratio [OR] = .92, 95% confidence interval [CI] .84-1.02; P = .12; mRS2: OR = .97, 95% CI .88-1.08; P = .57). Compared with standard-dose tPA, low-dose tPA reduced the incidence of SICH (by National Institute of Neurological Disorders and Stroke [NINDS] definition: OR = .71, 95% CI .57-0.89; P = .003; by Safe Implementation of Thrombolysis in Stroke Monitoring Study [SITS-MOST] definition: OR = .64, 95% CI .42-0.99; P = .04), while both reduced mortality (OR = .87, 95% CI .74-1.02; P = .08). *Conclusions:* Low-dose tPA is comparable to standard-dose tPA in improving the neurologic function and reducing mortality in AIS patients. Moreover, low-dose tPA can reduce the incidence of SICH compared with standard-dose tPA. Therefore, low-dose tPA is highly recommended in AIS patients. **Key Words:** Acute ischemic stroke—alteplase—intravenous thrombolysis—low dose—meta-analysis.

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Introduction

Stroke is currently a major cause of death and disability. Acute ischemic stroke (AIS) accounts for 87% of the stroke cases. Arterial occlusion induces blood deprivation followed by progressive cell death and subsequent neural dysfunctions. Intravenous thrombolysis is the most effective therapy in cases with AIS.[1] Early reversal of vascular occlusion with endovascular therapy could limit the volume of the damaged tissue and improve functional recovery. Studies have shown that early intravenous thrombolysis intervention scan improve the neurologic function significantly in patients with stroke. However, this therapy is clinically limited due to its high costs, narrow therapeutic time window, and symptomatic intracranial hemorrhage (SICH). Therefore, identifying ways to reduce the medical burden and SICH has become an important concern for clinicians. A report from Japanese researchers demonstrated that compared with standard doses (.9 mg/kg), a low dose of tissue plasminogen activator (tPA) (.6 mg/kg) had similar effects on improving the neurologic functions and significantly reducing the incidence of intracranial hemorrhage and cost of treatment.[2] However, although low-dose tPA can reduce the incidence of SICH, its efficacy was reported to be lower than that of standard doses.[3] The results of published trials on intravenous thrombolysis using low-dose tPA are inconsistent, and the clinical benefits of the procedure remain to be further determined.

A previous meta-analysis study on the benefits of different tPA regimens demonstrated that low and standard doses of tPA have comparable effectiveness and safety,[4] thus resolving the selection dispute between the 2 tPA doses. However, new important findings were reported in 2016.[5,6] In particular, a high-quality, multicenter randomized controlled trial (RCT) study demonstrated that compared with standard doses, low-dose tPA failed to show noninferiority with respect to death and disability at 90 days, although it resulted in a lower incidence of SICH.[5] Therefore, we conducted a new systematic review and meta-analysis to re-explore the efficacy and safety of different doses of tPA in the treatment of AIS.

Methods

Search Strategy

We searched the MEDLINE, Embase, and Cochrane Library databases for studies on the efficacy and safety of low-dose and standard-dose tPA in the treatment of AIS. The search deadline was set for March 2017, and the language of the selected reports was limited to English. The search keywords were ("cerebral infarction" OR "cerebral thrombosis" OR "ischemic stroke" OR "cerebrovascular accident" OR "thrombosis") AND ("alteplase" OR "tPA" OR "tissue plasminogen activator" OR "thrombolysis") AND ("dose"). The study protocol was registered at PROSPERO (CRD42017062406).

Selection Criteria

The studies that were included in the meta-analysis met the following inclusion criteria: (1) RCTs or cohort studies with sample size exceeding 5 patients; (2) literature concerned with the clinical efficacy and safety of low-dose and standard-dose tPA intravenous therapy; (3) availability of data including the modified Rankin Scale (mRS) score, rates of SICH, and mortality 3 months after treatment; and (4) evaluation of indicators using internationally recognized assessment criteria.

Data Extraction and Quality Evaluation

Two investigators (L.Z., X.Z.) independently extracted the data from the full text of the selected literature. The data included the trial name, year of publication, authors, recruitment period, number of patients in each treatment group, age, sex, baseline National Institute of Health Stroke Scale (NIHSS) score, efficacy outcomes (mRS score), and safety outcomes (SICH and mortality).

The quality of the included studies was assessed independently by 2 reviewers (L.C., G.L.). We used the Newcastle-Ottawa Scale and the improved Jadad 7 score to assess the risk of selection and reporting biases among the included studies. Disagreements between the 2 reviewers were resolved by consensus, and, if necessary, consultation with a third reviewer.

Outcomes

The efficacy outcomes analyzed at 3 months were (1) degree of disability assessed across 6 levels of mRS,[7] with ranks 5 and 6 combined into a single worst outcome rank; (2) excellent outcome defined as mRS scores of 0 through 1 (mRS1); and (3) functional independence defined as mRS scores of 0 through 2 (mRS2). The safety outcomes evaluated were 90-day mortality and SICH within 3 months.

The following are 3 different definitions of SICH: (1) The European Cooperative Acute Stroke Study (ECASS) definition[8]: A hemorrhage at any site in the brain on the computed tomography (CT) scan (as assessed by the CT reading panel independently of the assessment by the investigator), documentation by the investigator of clinical deterioration, or adverse events indicating clinical worsening (e.g., drowsiness, increase of hemiparesis) or causing a decrease in the NIHSS score of 4 or more points. (2) The Safe Implementation of Treatments in Stroke-Monitoring Study (SITS-MOST) definition[9]: Local or remote parenchymal hemorrhage type 2 on the 22- to 36-hour post-treatment imaging scan, combined with neurologic deterioration of 4 points or more from baseline on the NIHSS, or from the lowest NIHSS value between baseline and 24 hours, or leading to death. (3) The National Institute of Neurological Disorders and Stroke (NINDS) definition[10]: A hemorrhage is considered symptomatic if it has not been seen on a previous CT scan and there