Low-dose versus standard-dose alteplase for intravenous thrombolysis in patients with acute ischemic stroke in Iran: Results from the safe implementation of treatments in stroke registry

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Abstract
Background: Rates of intracranial hemorrhage (ICH) after intravenous thrombolysis (IVT) differ depending

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developing countries.1 may be an especially important factor in the price of tissue plasminogen activator (tPA), which hemorrhages.1 Another important factor is the who fear its complications, such as secondary for not receiving IVT has been reluctance of doctors of patients with acute stroke, one important reason from in-hospital delays in the initial management in the standard group and 29 (19.4%) patients in the 3-month outcome was achieved in 481 (53%) patients (n = 149) received a low dose of alteplase. Favorable outcome at 3 months was assessed using the modified Rankin Scale (mRS). Multivariate logistic regression including adjusted analysis was used for comparison between groups. Results: Of 6615 patients, 1055 were enrolled. A total of 86% (n = 906) received a standard dose and 14% (n = 149) received a low dose of alteplase. Favorable 3-month outcome was achieved in 481 (53%) patients in the standard group and 71 (48%) patients in the low-dose group [adjusted odds ratio (AOR) = 1.24, 95% confidence interval (CI): 0.87-1.75, P = 0.218]. SICH occurred in 14 (1.5%) patients in the standard group and 3 (2%) patients in the low-dose group [odds ratio (OR) = 2.77, 95% CI: 0.36-21.04, P = 0.120]. At 3 months, mortality occurred in 145 (16.0%) patients in the standard group and 71 (48%) patients in the low-dose group [adjusted odds ratio (AOR) = 1.22, 95% CI: 0.78-1.91, P = 0.346]. Conclusion: Low-dose compared to standard-dose alteplase for patients with acute ischemic stroke (AIS) was not associated with fewer hemorrhagic events and there was no significant difference in the favorable 3-month outcome (mRS: 0-2) or mortality rate.

Introduction

Stroke is a major burden on health systems worldwide, but with the advent of new therapy options and better patient care, the clinical outlook has become more favorable.1,2 One of the most significant contributions to this decline in mortality and morbidity has been growing accessibility to intravenous thrombolysis (IVT) with alteplase.2 Studies have shown that, apart from in-hospital delays in the initial management of patients with acute stroke, one important reason for not receiving IVT has been reluctance of doctors who fear its complications, such as secondary hemorrhages.1 Another important factor is the price of tissue plasminogen activator (tPA), which may be an especially important factor in developing countries.1 A combination of all of the above reasons as well as safety concerns led Japanese authorities to suggest a lower dose of alteplase.2 The conclusions of their trial were promptly incorporated in local clinical guidelines, and were the basis for widely-adopted low-dose treatment in Japan.3 Although some similar trials showed similar results, these results of the study were met with some speculation due to numerous limitations of the study. Recent studies have not shown a significant difference in adverse effects of therapy. In 2016, a large-scale trial was published [Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED)] which did not show non-inferiority, but found that a modest reduction was seen in intracranial hemorrhages (ICH).4 The results of the ENCHANTED trial are being debated, as some point out that a reduction in the risk of ICH was met with a non-significant decline in 90-day/3-month mortality, debunking the idea of ICH risk reduction as a justification to administer low-dose alteplase.5 Systemic reviews in this regard were of little help, as different non-inferiority margins, different populations, and haphazard reporting of clinical end points made overall conclusions less reliable.6 It has been reported that the incidence of ICH and prevalence of cerebral microbleeds (CMBs) are higher in Asians and the risk of hemorrhage after IVT may vary according to ethnicity. Similar data are scarce in the Middle Eastern region.7,8 The present article evaluated the safety and efficacy of low-dose alteplase compared to standard dose in Iran (Middle Eastern region) for patients with acute ischemic stroke (AIS) based on the Safe Implementation of Treatments in Stroke (SITS) registry.

Materials and Methods

Patients: This retrospective study was performed on data extracted from Iranian centers participated in the SITS registry. At the time of data extraction, eleven centers from Iran were registered in SITS. Exclusion criteria for participating centers included: missing values in more than 25% of variables, with each patient lacking demographic data or those related to the results of patient weight, alteplase dose, 3-month outcome, or hemorrhagic complications. Centers with fewer than 20 patients were not enrolled. Following application of these exclusion criteria, data from six centers were included. Missing data of patients included were not entered into the analysis. SITS contains information regarding demographic aspects of patients, pre-existing medical conditions, timetable of workflow, treatment procedures and results, and imaging and follow-up outcomes. Data extraction was done on July 31, 2019.

Clinical management and follow-up: All patients included in the study were hospitalized in...
wards with stroke expertise and were treated by board-certified neurologists. Information was entered into the system by each center separately, and was consolidated in a single archive. Follow-up of patients was done by each center, and the relevant data were included in SITS. Computed tomography (CT) image analysis was based on the SITS-Monitoring Study (SITS-MOST) definition for symptomatic ICH (SICH): local or remote parenchymal hemorrhage type 2 on the 22-36 hours post-treatment imaging scan combined with a neurologic deterioration of 4 points or more compared to baseline National Institutes of Health Stroke Scale (NIHSS). Type 2 indicates a hematoma exceeding 30% of the infarct with substantial space-occupying effect.

Functional outcome at 3 months was assessed using the modified Rankin Scale (mRS) by board-certified neurologists or neurology residents. An mRS of 0-2 was considered a favorable outcome, and an mRS of 3-6 was considered an unfavorable outcome. On the SITS registry, an mRS of 7 indicated that the patient was alive at the time of assessment, but the exact score was unknown. Data from patients with an mRS of 7 were not included in determining prognosis but were included in the mortality analysis. This manuscript was reviewed and approved by the SITS Scientific Committee.

Statistical analysis was done using SPSS software (version 23, IBM Corporation, Armonk, NY, USA). Multivariate logistic regression was used to compare the groups in terms of mRS at 3-month follow-up. Comparisons were also done adjusting age, sex, and other pre-existing conditions that were significantly different between the groups. Categorical values were evaluated using chi-square test or Fisher’s exact test and continuous variables were compared using Student’s t-test. Odds ratio (OR) was used to report the data as needed. Missing data were not entered into analysis.

**Ethical considerations:** The present study was approved by the local Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran (Ethics Code: IR.TBZMED.REC.1397.1067). Data were extracted from the SITS registry. All of the patients included were selected from medical educational centers, where patients were asked to sign written informed consent. The study was carried out in accordance to the latest version of the Declaration of Helsinki.

**Results**

At the time of data extraction, 6615 patients were registered at Iranian SITS centers. After selecting patients who were treated with IVT and excluding cases with no reported 3-month mRS and alteplase dosage, centers with fewer than 20 cases, and cases that had interventional procedures for recanalization after IVT, the data from 1055 patients were included in the analysis (Figure 1). In all, 596 were men (56.4%) and the median age was 69 years [interquartile range (IQR): 58-79]. A total of 906 (86%) patients received a standard dose and 149 (14%) patients received a low dose of alteplase.

Table 1 shows the comparison of demographic data between the two groups. As evident, history of ischemic heart disease (IHD), aspirin use, and current smoking was more common in the standard group. Patients in the low-dose group were significantly older (77 vs. 68 years), and had more severe stroke at presentation (11 vs. 10).
Table 1. Baseline characteristics of patients in low and standard groups

| Baseline characteristics          | Low-dose group (n = 149) | Standard-dose group (n = 906) | P  |
|----------------------------------|--------------------------|-------------------------------|----|
| Age (year) [median (IQR)]        | 77 (63.0-82.5)           | 68 (57.0-78.0)                | < 0.001 |
| Gender (men) [n (%)]             | 72 (48.4)                | 524 (57.8)                    | 0.680  |
| Hypertension [n (%)]             | 117 (78.5)               | 642 (70.8)                    | 0.058  |
| Diabetes mellitus [n (%)]        | 29 (19.4)                | 204 (22.5)                    | 0.456  |
| Atrial fibrillation [n (%)]      | 32 (21.4)                | 118 (13.0)                    | 0.060  |
| Current smoking [n (%)]          | 8 (5.3)                  | 103 (11.3)                    | 0.030  |
| Hyperlipidemia [n (%)]           | 32 (21.4)                | 136 (15.0)                    | 0.067  |
| IHD [n (%)]                      | 0 (0)                    | 29 (3.2)                      | 0.027  |
| Prior use of aspirin [n (%)]     | 50 (33.5)                | 363 (40.0)                    | 0.001  |
| Prior use of anticoagulants [n (%)] | 7 (4.0)                | 43 (4.7)                      | 0.900  |
| Prior ischemic stroke [n (%)]    | 0 (0)                    | 21 (2.3)                      | 0.900  |
| Prior TIA [n (%)]                | 3 (2.0)                  | 15 (1.6)                      | 0.700  |
| Congestive heart failure [n (%)] | 2 (1.3)                  | 26 (2.8)                      | 0.282  |
| SBP (mmHg) [median (IQR)]        | 150 (130.0-170.0)        | 150 (130.0-170.0)             | 0.216  |
| DBP (mmHg) [median (IQR)]        | 90 (80.0-90.0)           | 90 (80.0-90.0)                | 0.635  |
| Stroke severity (NIHSS) [median (IQR)] | 11 (6.2-18.0)           | 10 (6.0-16.0)                 | 0.009  |
| Onset to hospital arrival (minute) (mean ± SD) | 154 ± 12                 | 139 ± 16                      | 0.091  |
| Door to needle time (minute) (mean ± SD) | 53 ± 6                   | 56 ± 13                       | 0.121  |

TIA: Transient ischemic attack; DBP: Diastolic blood pressure; IQR: Interquartile range; NIHSS: National Institutes of Health Stroke Scale; SBP: Systolic blood pressure; IHD: Ischemic heart disease; SD: Standard deviation

Table 2 summarizes the clinical findings. A favorable 3-month outcome was achieved in 481 (53%) patients in the standard group and 71 (48%) patients in the low-dose group [OR = 1.24, 95% confidence interval (CI) 0.87-1.75, P = 0.218]. SICH occurred in 14 (1.5%) patients in the standard group and in 3 (2%) patients in the low-dose group (OR = 2.77, 95% CI: 0.36-21.04, P = 0.12). Three-month mortality was seen in 145 (16%) patients in the standard group and 29 (19.4%) patients in the low-dose group (OR = 1.22, 95% CI: 0.78-1.91, P = 0.346). Figure 2 summarizes the functional outcomes at 3 months, according to scores on the mRS.

Discussion

In this retrospective study, low-dose compared to standard-dose tPA for patients with AIS was not associated with fewer hemorrhagic events and there was no significant difference in the rate of favorable 3-month outcome.

Table 2. Adjusted and unadjusted frequencies comparing outcomes between two groups

| Total (n = 1055) | Low-dose group (n = 149) | Standard-dose group (n = 906) | OR (95% CI) | P         | P (adjusted) |
|------------------|--------------------------|-------------------------------|-------------|-----------|-------------|
| 3-month favorable outcome* [n (%)] | 552 (52.3) | 71 (47.6) | 481 (53.0) | 1.24 (0.87-1.75) | 0.218 | 0.642 |
| SICH [n (%)] | 17 (1.6) | 3 (2.0) | 14 (1.5) | 2.77 (0.36-21.10) | 0.120 | N/A |
| Mortality [n (%)] | 183 (17.3) | 29 (19.4) | 145 (16.0) | 1.22 (0.78-1.91) | 0.346 | N/A |
| Discharge NIHSS (mean ± SD) | 2.64 ± 5.44 | 1.79 ± 3.85 | N/A | N/A | 0.242 | N/A |

*Modified Rankin Scale (mRS): 0 or 2

OR: Odds ratio; CI: Confidence interval; NIHSS: National Institutes of Health Stroke Scale; SICH: Symptomatic intracranial hemorrhage; SD: Standard deviation
As mentioned, scholars from Asian countries, especially Japan, proposed a lower dose of alteplase in Asian patients, justifying this by a higher rate of ICH and smaller body dimensions in Asian patients. They suggested that low-dose alteplase (0.6 mg/kg) could be as effective as standard-dose alteplase, reducing hemorrhage. One of the first observations was made by Yamaguchi et al. They designed a prospective study that included 103 patients treated with low-dose alteplase. They defined an mRS of 0-1 as a favorable outcome, and examined all patients in regard to hemorrhage. They found that 36.9% of patients had a favorable outcome at the 3-month follow-up. Six patients (5.8%) experienced hemorrhage. The authors concluded that for Japanese patients, outcomes for 0.6 mg/kg intravenous (IV) alteplase were likely comparable to data reported for patients in North America and Europe at a 0.9 mg/kg dose. More comprehensive evidence was presented by Nakagawara et al. that encompassed 4944 patients over a 2-year time period who were treated with low-dose alteplase. These patients were pooled from various trials, and might have been treated or selected without a single method, but all had received the same dose of alteplase. Results of mRS of 0-1 ranged from 26% to 33% across the studies. Overall, 259 (5.2%) patients had hemorrhage in the first 36 hours and 70 (0.9%) had a fatal hemorrhage. The numbers for hemorrhages suggested by Nakagawara et al. were significantly lower compared to similar studies using standard-dose alteplase. The authors found a clinical benefit to low-dose tPA, which was comparable to the standard dose, and reported to be higher than the minimal expected threshold. Another clinical trial performed in Japan during the time period of the previous study was in agreement with previous studies.

Although the results of these studies showed some benefits to low-dose alteplase, many institutions did not alter their treatment guidelines, especially in western countries. In 2016, the ENCHANTED trial randomly allocated 3310 patients to two groups, one receiving standard-dose alteplase and the second receiving low-dose alteplase. The groups were matched for age, sex, and pre-existing medical conditions. In the standard-dose group, 170 (10.3%) patients died and in the low-dose group, 140 (8.5%) died within 90 days; the difference was not statistically significant. At 90 days, 46.9% in the standard-dose group and 46.8% in the low-dose group had mRS of 0-1, respectively, with no significant difference. Subgroup analyses based on various determinants such as age, sex, and NIHSS score also did not yield significant results. Regarding hemorrhages, patients receiving low-dose alteplase had a significantly lower level of fatal ICH (P = 0.020). Of interest, this lower rate of fatal ICH did not result in significant decrease in the 3-month mortality rate. The authors noted that they could not show non-inferiority for low-dose alteplase therapy. The authors of this study questioned the results of the studies performed in Japan, as none were clinical trials, and importantly all of them included fewer patients compared to theirs. Secondary analysis of the results found that decisions about using a lower dose of alteplase should not be based on age, ethnicity (Asian or non-Asian), or neurological severity at baseline.

A systematic review on this topic was carried out in 2016 following the ENCHANTED trial to further assess the available evidence. The authors suggested that the use of low-dose alteplase might be indicated in clinical practice, but notably most studies included in this review (11 of 12) were retrospective studies or short-term cohort studies, limiting the generalizability of the data. A novel aspect of the current study was an assessment of safety and efficacy of low-dose alteplase in a Middle Eastern country in a multicenter study. Similar studies have been conducted in both Western and Eastern countries, but to our knowledge, this is the first report in this region.

As mentioned earlier, patients in the low-dose group were significantly younger, had more severe stroke at presentation, and were presented later. There are two points worthy of mention: first, treating physicians tended to use low-dose alteplase in older patients, presenting with more severe symptoms at onset and with longer onset to hospital arrival time and second, dissimilar to Japanese studies and similar to the ENCHANTED trial, the rate of SICH was not lower in low-dose group. Age and stroke severity are important determinants of SICH after IVT and it is possible that if patients in the low-dose group were younger and had milder stroke, the rate of SICH could be significantly lower. Thus, we cannot draw a generalized conclusion based on the results of this study.

This study has some limitations. First, although there was no difference in outcome, there was a 5% non-statistically significant difference in 3-month mRS of 0-2 outcome, which is clinically important; therefore, maybe this study was not powered
enough to reach statistical significance. Second, quality and validity of data entry is a challenge with any registry-based study, and selection bias (i.e., not registering all patients with all outcomes) may occur; thus, registry data must be analyzed with caution. The modest data collection rate of 3-month functional outcome and alteplase dose (low or standard) is an inevitable limitation of this study. Third, this study was not a non-inferiority study; therefore, these results do not warrant the substitution of the standard dose with a low-dose regimen. Matched double-blind randomized trials should be performed to better assess the application of low-dose alteplase in wide-scale clinical contexts.

In Iran, only 50-mg vials of alteplase is available and that is an important reason for some physicians to use just one vial for their patients (low-dose alteplase). Price of alteplase makes its affordability a challenge in developing countries and it is another compelling factor for reinvestigation. Positive results from such trials may prove to be of public health importance.14

**Conclusion**

Low-dose compared to standard-dose alteplase for patients with AIS was not associated with fewer hemorrhagic events and there was not significant difference in favorable 3-month outcomes (mRS of 0-2) or mortality rate in Iranian patients. More studies, including non-inferiority and equivalence trials, are indicated to make relevant clinical decision-making.

**Conflict of Interests**

The authors declare no conflict of interest in this study.

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