Different Doses of Intravenous Tissue-Type Plasminogen Activator for Acute Ischemic Stroke: A Network Meta-Analysis

Bing-Hu Li, Jian-Hong Wang, Han Wang, Duo-Zi Wang, Shu Yang, Fu-Qiang Guo and Neng-Wei Yu

Department of Neurology, Sichuan Provincial People’s Hospital, University of Electronic Science and Technology of China, Chengdu, China. Department of Outpatient, People’s Liberation Army the General Hospital of Western Theater Command, Chengdu, China

Background: This study aims to assess the efficacy and safety of different doses of intravenous tissue-type plasminogen activator (tPA) for acute ischemic stroke (AIS) by adopting a network meta-analysis (NMA).

Methods: Studies comparing different doses of tPA in AIS were identified by retrieving electronic databases. NMAs of outcome measures included favorable functional outcome with a modified Rankin scale score (mRS) of 0 or 1 at 3 months after treatment (3M-FF), the functional independence with a mRS of 0, 1, or 2 at 3 months (3M-FI), symptomatic intracranial hemorrhage (sICH) and 3-month all-cause mortality (3M-M). Symptomatic intracranial hemorrhage (sICH) and 3-month all-cause mortality (3M-M) were assessed. Probability-based ranking and surface under cumulative ranking (SUCRA) were performed to identify the best dose of tPA. Inconsistency was evaluated by node-splitting analysis and a loop-specific approach. Publication bias was analyzed by funnel plots.

Results: A total of 14 studies were included in the quantitative synthesis. The NMA results revealed no difference among low (<0.7 mg/kg), moderate (0.8 mg/kg), and standard (0.9 mg/kg) doses of tPA with regard to efficacy and safety. The SUCRAs of 3M-FF and 3M-FI showed that the standard dose ranked first, the moderate dose ranked second, and the low dose ranked third. The SUCRA of sICH showed that the standard dose ranked first (78.1%), the low dose ranked second (61.0%), and the moderate dose ranked third (11.0%). The SUCRAs of 3-month mortality showed that the standard dose ranked first (73.2%), the moderate dose ranked second (40.8%), and the low dose ranked third (36.1%). No significant inconsistency was shown by node-splitting analysis and no publication bias was shown in funnel plots.

Conclusion: Lower dose tPA was comparable to the standard dose with regard to efficacy and safety. Based on the SUCRA results and American Heart Association/American Stroke Association (AHA/ASA) guidelines, the standard dose was still the optimal selection for AIS.

Keywords: tissue-type plasminogen activator, ischemic stroke, network meta-analysis, intravenous thrombolysis, symptomatic intracranial hemorrhage
INTRODUCTION

Globally, stroke remains the second-leading cause of death. Prevalent cases of stroke were estimated to be 101 million in 2019, 62.4% of which were ischemic stroke (1). Until now, tissue plasminogen activator (tPA) is the only treatment approved by the US Food and Drug Administration (FDA) serving as the first line of treatment for acute ischemic stroke (AIS) (2). However, due to the high cost, narrow therapeutic time window, and risk of intracranial hemorrhage, tPA is clinically limited. Therefore, it is urgent to find ways to reduce the medical burden and risk of intracranial hemorrhage. Under this context, several studies (3–5) were performed to explore the efficacy and safety of a lower dose of tPA for AIS in Japan, which demonstrated that the efficacy and safety of low dose (0.6 mg/kg) tPA was comparable to a dose of 0.9 mg/kg from published data.

Thereafter, numerous studies compared the efficacy and safety of different doses of tPA for AIS, which remain inconclusive. A previous meta-analysis aimed at analyzing whether low dose tPA can effectively reduce symptomatic intracranial hemorrhage (sICH) and has the same efficacy as standard dose tPA showed that low dose tPA was comparable to standard-dose tPA in terms of efficacy and safety in Asian patients with AIS (6). However, in this meta-analysis, the low dose was defined as <0.75 mg/kg, and the standard dose was defined as >0.75 mg/kg. In addition, five new studies (7–11) were reported after this meta-analysis. Moreover, traditional meta-analysis is difficult to use to assess the effects of two or more interventions. By contrast, network meta-analysis (NMA) can make comparisons of all the interventions and can also provide information on which is the best treatment by ranking analysis. Thus, in this study, we will perform an NMA by combining all studies concerning different doses of tPA for AIS to compare their efficacy and safety.

METHODS

Literature Search

The presentation of this study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline (12). A systematic search of PubMed, Embase, and Web of Science (last search was updated on 4 January 2022) was performed with a combination of the following keywords: (stroke/cerebral infarction/cerebral ischemia) with (alteplase OR tissue plasminogen activator OR intravenous...
TABLE 1 | Characteristics of the included studies.

| References | Country     | Study design           | Intervention | N  | 3M-FF | 3M-FI | sICH | 3M-M |
|------------|-------------|------------------------|--------------|----|-------|-------|------|------|
| Sharma et al. (31) | Singapore | Retrospective cohort | 0.67 mg/kg | 48 | 17/48 | 7/48  | 5/48 |
|             |             |                        | 0.9 mg/kg   | 82 | 48/82 | 1/82  | 11/82|
| Zhou et al. (32) | China      | Retrospective cohort   | 0.6–0.7 mg/kg | 23 | 8/23  | 12/23 | 1/23 | 4/23 |
|             |             |                        | 0.8 mg/kg   | 31 | 12/31 | 16/31 | 1/31 | 5/31 |
|             |             |                        | 0.9 mg/kg   | 51 | 26/51 | 33/51 | 2/51 | 6/51 |
| Chen et al. (33) | China       | Retrospective cohort   | 0.7 mg/kg   | 105| 39/95 | 50/95 | 5/105*| 8/105|
|             |             |                        | 0.9 mg/kg   | 156| 56/146| 79/146| 4/156*| 9/156|
| Aulicky et al. (35) | Czech      | Retrospective cohort   | 0.78 ± 0.06 mg/kg | 62 | 31/62 | 1/62  | 13/62|
|             |             |                        | 0.9 ± 0.03 mg/kg | 171| 87/171| 8/171 | 11/171|
| Chao et al. (19) | China       | Prospective cohort     | 0.6–0.7 mg/kg | 380| 100/302| 147/302| 16/380| 33/380|
|             |             |                        | 0.8 mg/kg   | 202| 46/171| 76/171| 11/202| 18/202|
|             |             |                        | 0.9 mg/kg   | 422| 124/367| 173/367| 21/422| 35/422|
| Liao et al. (36) | China       | Prospective cohort     | 0.64 mg/kg  | 75 | 31/74 | 42/74 | 0/75 | 14/74|
|             |             |                        | 0.79 mg/kg  | 131| 61/127| 69/127| 11/131| 11/127|
|             |             |                        | 0.9 mg/kg   | 678| 358/665| 429/665| 21/678| 49/666|
| Kim et al. (37) | Korea       | Prospective cohort     | 0.6 mg/kg   | 450| 146/450| 205/450| 38/450| 57/450|
|             |             |                        | 0.9 mg/kg   | 1,076| 380/1,076| 526/1,076| 69/1,076| 151/1,076|
| Anderson et al. (20) | Worldwide | Randomized controlled trial | 0.6 mg/kg | 1,854| 752/1,807| 1,002/1,807 | 98/1,807*| 140/1,807*|
|             |             |                        | 0.9 mg/kg   | 1,843| 782/1,599| 1,007/1,599 | 131/1,599*| 170/1,599*|
| Yang et al. (38) | China       | Retrospective cohort   | 0.6 mg/kg   | 46 | 34/46 | 2/46  |      |      |
|             |             |                        | 0.9 mg/kg   | 62 | 44/62 | 3/62  |      |      |
| Ong et al. (8) | China       | Retrospective cohort   | 0.6–0.7 mg/kg | 130| 40/130| 48/130 | 6/130| 7/130|
|             |             |                        | 0.8 mg/kg   | 88 | 34/88 | 43/88 | 1/88 | 1/88 |
|             |             |                        | 0.9 mg/kg   | 56 | 13/56 | 17/56 | 3/56 | 1/56 |
| Chao et al. (9) | China       | Prospective cohort     | 0.6 mg/kg   | 108| 15/108| 24/108 | 7/108*| 10/108|
|             |             |                        | 0.9 mg/kg   | 141| 32/141| 49/141 | 6/141*| 19/141|
| Liu et al. (7) | China       | Prospective cohort     | 0.5–0.7 mg/kg | 60 | 17/60 | 22/60 | 2/60 | 11/60|
|             |             |                        | 0.85–0.95 mg/kg | 494| 209/494| 259/494 | 20/494| 66/494|
| Škrbić et al. (10) | Srpska | Retrospective cohort   | 0.6 mg/kg   | 45 | 24/45 | 0/45  |      |      |
|             |             |                        | 0.9 mg/kg   | 165| 106/165| 10/165 | 10/165|
| Salem et al. (11) | Egypt     | Prospective cohort     | 0.6 mg/kg   | 40 | 27/40 | 0/40  | 3/40 |      |
|             |             |                        | 0.9 mg/kg   | 40 | 25/40 | 3/40  | 2/40 |      |

N, number of patients; 3M-FF, 3-month favorable functional outcome (mRS of 0, 1); 3M-FI, 3-month functional independence (mRS of 0, 1, or 2); 3M-M, 3-month mortality; sICH, symptomatic intracranial hemorrhage; *sICH was defined by NINDS.

thrombolysis OR rtPA) and low dose (Supplementary Table 1). The language was restricted to English. We manually searched the references of articles retrieved. When the same patient population was used in several publications, only the complete or largest study was included. Two investigators screened each of the titles, abstracts, and full texts to determine inclusion independently. The results were compared and disagreements were resolved by consensus.

**Selection Criteria**

The inclusion criteria were as follows: (1) studies with retrospective and prospective cohort design; (2) studies should report functional outcome (with modified Rankin scale score [mRS] assessment) at 3 months after symptom onset, incidence of mortality, and sICH; (3) studies with full-text articles; and (4) studies comparing the effect of different doses of tPA in AIS.

The exclusion criteria were as follows: (1) non-control study or placebo-control studies; (2) studies sharing the same patient population; (3) studies with data that could not be extracted or converted into valid data.

**Data Extraction**

Information was carefully extracted from all included publications independently by the two authors according to the inclusion criteria listed above. Disagreement was resolved by consensus or discussion with a third reviewer. The following data were collected from each study: first author's name, publication date, country, number of patients, the dose of
tPA, the incidence rate of favorable functional outcome at 3 months after treatment (3M-FF), functional independence at 3 months (3M-FI), sICH, and 3-month all cause-mortality (3M-M), respectively.

**Data Synthesis**
The doses of tPA were classified as low (<0.7 mg/kg), moderate (0.8 mg/kg), and standard (0.9 mg/kg).
FIGURE 3 | Results of functional independence at 3 months (3M-FI). (A) Network plots of eligible comparisons. The width of the lines represents the number of studies being compared, and the node size reflects the sample size. (B) The forest plot of network results. The black diamonds represent the combined ORs; OR > 1 indicates that the proportion of 3M-FI in the former group is greater than that in the latter group. (C) The cumulative ranking curve of 3M-FI. (D) The ranking of different doses of tPA is based on the cumulative probability plots. Ranking first means having the highest proportion of 3M-FI.

Outcome Measures
The efficacy outcomes included the proportion of patients achieving an mRS of 0 or 1 at 3M-FF and an mRS of 0, 1, or 2 at 3M-FI. The safety outcome included the incidence rate of sICH and 3M-M. The sICH is defined by the European Cooperative Acute Stroke Study (ECASS) criteria (13). If the sICH data defined by ECASS criteria were not available, the incidence rate of sICH defined by National Institute of Neurological Disorders and Stroke (NINDS) (14) was applied.

Assessment of Risk of Bias
Risk of bias was assessed using the Cochrane Collaboration Tool. Judgment as “low,” “unclear,” or “high” risk
of bias was provided in each of the domains for each study.

**Statistical Analyses**
A network meta-analysis was carried out using STATA version 15.0 based on the Bayesian framework model. The corresponding odds ratios (ORs) with 95% CIs were calculated. Rank plots based on probabilities and the surface under cumulative ranking (SUCRA) for different outcomes were performed to identify the best treatment. Inconsistency was evaluated by node-splitting analysis and a loop-specific approach. Publication bias was analyzed by funnel plots.

**RESULTS**

**Characteristics of the Study**
The study selection process is detailed in Figure 1. There were 1,568 potentially relevant articles identified after the search. After screening titles and abstracts, a total of 34 studies were included for full-text article assessment. Five studies were non-control
FIGURE 5 | Results of 3-month all-cause-mortality (3M-M). (A) Network plots of eligible comparisons. The width of the lines represents the number of studies being compared, and the node size reflects the sample size. (B) The forest plot of network results. The black diamonds represent the combined ORs; OR > 1 indicates that the incidence rate of 3M-M in the former group is higher than in the latter group. (C) The cumulative ranking curve of 3M-M. (D) The ranking of different doses of tPA is based on the cumulative probability plots. Ranking first means having the lowest incidence of 3M-M.

Li et al. rtPA in Ischemic Stroke

studies (3–5, 15, 16). One study was a placebo-control study (17). Two studies reported the same cohort (18, 19), and the larger study (19) was included. Four studies reported the same cohort (20–23), and the largest study (20) was included. One study was an individual patient data pooling study from six Asian countries (China, Japan, Philippines, Singapore, South Korea, and Taiwan) (24). One study was a letter to the editor (25). Four studies provided no data on indexed outcomes (26–29).

Finally, 18 studies were included in the qualitative synthesis (7–11, 19, 20, 30–40). The doses of three studies (30, 34, 39) did not meet the design of the present study and one study (40) without specific data was excluded from the final quantitative analysis. Fourteen studies were included in the quantitative synthesis (7–11, 19, 20, 31–33, 35–38). Table 1 summarizes the characteristics of the 14 included studies. In brief, these studies were reported between 2010 and 2021. The majority (10/14) were two-arm studies; four studies had three arms. Seven studies were retrospective cohort studies, one study was a randomized controlled trial, and six studies were prospective cohort studies. Eight studies were from China, one study was from Singapore,
one study was from Korea, one study was from the Czech Republic, one study was from Srpska, one study was from Egypt, and one study was worldwide. The risk of bias of included studies in this NMA was generally low to unclear. Details about the risk of bias assessment are graphically summarized in Supplementary Figure 1.

### Results of Network Meta-Analysis

Twelve studies with 8,332 patients reported 3M-FF (Figure 2A). The pooled meta-analysis results (Figure 2B) showed no significant difference between different doses of tPA. The probability-based ranking result is shown in Figures 2C,D. Results of SUCRA showed that the standard dose ranked first (90.2%), the moderate dose ranked second (36.9%), and the low dose ranked third (22.9%). In this result, the first rank had the highest proportion of 3M-FF.

Eleven studies involving 8,151 patients reported 3M-FI (Figure 3A). The pooled results showed no significant difference between different doses of tPA (Figure 3B). The probability-based ranking result is shown in Figures 3C,D. Results of SUCRA showed that the standard dose ranked first (90.2%), the moderate dose ranked second (36.9%), and the low dose ranked third (22.9%). In this result, the first rank had the highest proportion of 3M-FI.

Fourteen studies involving 8,614 patients reported incidences of sICH (Figure 4A). The pooled results showed no significant difference between different doses of tPA (Figure 4B). The probability-based ranking result is shown in Figures 4C,D. Results of SUCRA showed that the standard dose ranked first (78.1%), the low dose ranked second (61.0%), and the moderate dose ranked third (11.0%). In this result, the first rank had the lowest incidence of sICH.

Thirteen studies involving 8,699 patients reported incidences of 3M-M (Figure 5A). The pooled results showed no significant difference between different doses of tPA (Figure 5B). The probability-based ranking result is shown in Figures 5C,D. Results of SUCRA showed that the standard dose ranked first (73.2%), the moderate dose ranked second (40.8%), and the low dose ranked third (36.1%). In this result, the first rank had the lowest incidence of 3M-M.
REFERENCES

1. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the global burden of disease study 2019. Lancet Neurol. (2021) 20:795–820. doi: 10.1016/S1474-4422(21)00252-0

2. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American heart association/American stroke
37. Kim BJ, Han MK, Park TH, Park SS, Lee KB, Lee BC, et al. Low-versus standard-dose alteplase for ischemic strokes within 45 hours: a comparative effectiveness and safety study. *Stroke.* (2015) 46:2541–8. doi: 10.1161/STROKEAHA.115.010180

38. Yang J, Yu F, Liu H, An H, Xiong R, Huang D. A retrospective study of thrombolysis with 0.6 mg/kg recombinant tissue plasminogen activator (rt-PA) in mild stroke. *Sci Rep.* (2016) 6:31344. doi: 10.1038/srep31344

39. Zhao G, Huang T, Zheng M, Cui Y, Liu Y, Cheng Z, et al. Comparative analysis on low- and standard-dose regimes of alteplase thrombolytic therapy for acute ischemic stroke: efficacy and safety. *Eur Neurol.* (2018) 79:68–73. doi: 10.1159/000485460

40. Herath H, Rodrigo C, Alahakoon A, Ambawatte SB, Senanayake S, Senanayake B, et al. Outcomes of stroke patients undergoing thrombolysis in Sri Lanka: an observational prospective study from a low-middle income country. *BMC Neurol.* (2021) 21:434. doi: 10.1186/s12883-021-02475-3

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Li, Wang, Wang, Wang, Yang, Guo and Yu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.