Peer Review File

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Reviewers' Comments

Reviewer A

This is a well-written paper providing further evidence that tPA is safe in minor strokes. Would recommend the following minor change:

1. Considering that more than 50% of minor stroke patients were excluded due to lack of data or mrs>1, please add it to the limitations

Response: Thank you for your suggestion. Accordingly, we added it to limitations in Discussion Section (see Page 13, line 251-252).

2. please add at end of the conclusions that further studies are needed to confirm the findings.

Response: According to your suggestion, we added "further studies are needed to confirm the findings" to Conclusions (see Page 5, line 68 and Page 14, line 265).

Reviewer B

Summary of study: This is a retrospective study on short-term outcomes and predictors for the favorable functional outcome at discharge in 6,752 mild stroke patients who have received IV rtPA. Only 18.5% had an unfavorable functional outcome at discharge, 91.1% were discharged home, 89.9% could ambulate independently, 95.9% had a length of stay of 3 days or longer and 1.9% had sICH. The authors concluded that tPA is safe and more effective in mild stroke patients with age ≤80 within the 3 hour time window and in those without diabetes mellitus. There are several points to be concerned in this study.

1. Although 6752 patients were enrolled, 45% (5494/12246) patients fulfilled the criteria but with missing data were excluded from the same database. The large proportion of patients with missing data might cause bias during analysis.

Response: Thank you for your suggestion. Accordingly, we added it to limitations in Discussion Section (see Page 13, line 251-252).

2. The criteria for IV rtPA, such as range of NIHSS, need to be clarified. Did all patients who presented as acute stroke symptoms receive IV rtPA treatment in the CSCA stroke registry? The reasons of IV rtPA for patients with NIHSS 0 or 1 need to be addressed as well. If not all patients received IV rtPA, a control group of patients with same NIHSS, particular in patients with NIHSS = 0 and 1, but without IV rtPA

treatment, is necessary for comparison of the safety and effectiveness.

Response: Patients with initial NIHSS = 0 and 1 receive IV rtPA treatment could be due to symptoms getting worsen rapidly before treatment or fluctuating or because the NIHSS score's inability to capture certain cerebellar and brainstem symptoms. Not all patients who presented as acute stroke symptoms receive IV rtPA treatment in the CSCA stroke registry. Due to lack of variables including stroke etiology, stenosis information, the variability of antiplatelet therapy, we don't think the CSCA database can provide an even comparisons between tPA group and antiplatelet group. Therefore, we described the effectiveness and safety of tPA, and to offer some data for future trial design. According to your question, we added the reason for tPA use in NIHSS 0-1 (Page 11, Line 204-206).

3. For patients with initial NIHSS = 0 and 1, the rates of discharge mRS > 2 were 11.9% and 9.2%, respectively. The rate of sICH was 1.4%. There were no further analyses of predictors among these two groups of patients. It is difficult to make the conclusion that IV rtPA is safe and more effective in patients with NIHSS = 0 and 1.

Response: Thank you for your question, we added subgroup analysis in NIHSS 0-1 group, the logistic regression analysis identified that ole age and DM were independent predictors for mRS > 2 in NIHSS 0-1 group. This is consistent with our current understanding as well. (see Page 10-11, Line 186-189)

4. Old age, longer time window, and diabetes mellitus are well known risk factors of

unfavorable outcomes in IV thrombolytic therapy. This study provides little novelty for the readers.

Response: Thank you for your comment. We agree that old age, longer time window, and diabetes mellitus are known risk factors for unfavorable outcomes in IV thrombolytic therapy, and our study focus on mild stroke Asian patients . We confirmed that risk factors of unfavorable outcomes in IV thrombolytic therapy in patients with mild stroke were similar to general population. We added this to the Discussion Section (see Page 11, line 195).

Reviewer C

This is an article focusing on the efficacy and safety of thrombolysis in mild acute ischemic stroke, a current important topic in stroke research.

Although the authors present results from a prospective registry with a large patient sample, there are some concerns about this article that, in my view, could be improved:

1. Introduction is well written, exposing the current knowledge on this research topic and stressing the importance of this new information in Asian population.

Response: Thank you very much for your comment.

2. On Methods section it is lacking information regarding stroke diagnosis like which radiological means were used (CT, angio-CT, MRI?).

Response: Thank you for your suggestions. Accordingly, we have added the stroke diagnostic information to the Methods section (see Page 7, line 122).

3. Definition of sICH is not clear (how was clinical worsening measure? Was it a worsening of 4 points in NIHSS as is usually the definition of sICH?). was there a control CT after 24h in every patient? Could you account for not symptomatic intracranial bleeding?

Response: Thank you for your questions. This is a national quality improvement database, clinical worsening was adjudicated by local investigators based on the NINDS sICH criteria, so we did not require a worsening of 4 points in NIHSS (ECASS III criteria). We stated the definition of sICH in Method Section and explained it in Discussion Section (see Page 8, line 141-143 and Page 12, line 211-214). Most of the repeated CT was performed 24h after tPA, it's a pity that we did not record asymptomatic intracranial hemorrhage in this study.

4. You should include death in safety outcome (there is no data on death rate throughout the text or tables).

Response: Death is included in the mRS >2. mRS 6 was death. No one died in this study. We added the death result on Page 10, line 169.

5. Do you have information regarding stroke localization and etiology? That data would be important to see differences in outcomes in different stroke etiologies.

Response 5: Thank you for your comment. We agree that stroke localization and etiology are very important factors for 90 days mRS. However, we do not have the information of stroke localization and etiology in this nationwide study, and we added this in the limitations (see Page 14, line 253-254).

6. It is also important to state on acute angiographic data to look for intracranial vessel oclusions. Did any of these patients undergo additional mechanical thrombectomy?

Response 6: Thank you for your question. It is a pity that we lacked the information about additional mechanical thrombectomy. We stated the limitation of lacking confirmation of large vessel occlusion data in our study. But considering 2.7% stroke patients with mild stroke have large vessel occlusion(1)**, the findings in the current study may not affected by the lack of information on large vessel occlusion. (see Page 14, line 254-259).**

1. Manno C, Disanto G, Bianco G, et al. Outcome of endovascular therapy in stroke with large vessel occlusion and mild symptoms. Neurology 2019;93(17):e1618-e26.

7. Could you define rtpa dose? Was it standard dose 0.9mg/kg 10% bolus and 90% perfusion in 1h?

Response: The rt-PA dose was determined by the physicians. We did not record the dosage information of tPA for this study. However, a Chinese study have shown that low does rt-PA (0.6 mg/kg) shared similar effectiveness and safety profile compared with that of standard dose (0.9 mg/kg) in treating mild stroke (2).

2. Yang J, Yu F, Liu H, et al. A Retrospective Study of thrombolysis with 0.6 mg/kg Recombinant Tissue Plasminogen Activator (rt-PA) in Mild Stroke. Scientific reports 2016;6:31344.

8. Could you refer stroke symptoms to needle time and door to needle time?

Response: Thank you for your question. We added stroke symptoms to needle time and door to needle time in table 1.

9. The major limitation of this study is that there is not a comparative arm including

patients with mild acute ischemic stroke that were not treated with thrombolysis. It is important to do this comparative analysis to discuss on the thrombolysis' efficacy. You cannot do that with only a descriptive cohort.

Response: Thank you very much for your comment. We agree that a comparative arm including patients with mild acute ischemic stroke that were not treated with thrombolysis will be better to elucidate the efficacy of tPA in mild stroke. However, in this study, due to lack of variables including stroke etiology, stenosis information, the variability of antiplatelet therapy, we don't think the CSCA database can provide an even comparisons between tPA group and antiplatelet group. Therefore, we described the effectiveness and safety of tPA, and to offer some data for future trial design.