Smoking–Thrombolysis Relationship Depends on Ischemic Stroke Subtype

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Background and Purpose—The relationship between smoking and the outcome in patients received thrombolysis is undetermined. The outcome could be influenced by different stroke subtypes. This study aimed to explore whether smoking had any impact on the outcome in patients with stroke of different subtypes who received intravenous thrombolysis.

Methods—All patients who received intravenous thrombolysis within 4.5 hours after symptom onset from the Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China (TIMS-China) database were eligible to be entered into this analysis. Smokers were considered if they smoked at least 1 cigarette/d for >6 months before stroke. Ischemic stroke subtype was classified by using the Trial of Org 10172 in Acute Stroke Treatment criteria. Outcome measurements included post–intravenous thrombolysis symptomatic intracranial hemorrhage within 7 days, mortality, and functional independence at 90 days. The relationship between smoking and thrombolysis was analyzed by using univariate and multivariate logistic regression models.

Results—Of 1118 patients enrolled, we identified 454 smokers and 664 nonsmokers. After stratifying for ischemic stroke subtypes, multivariate analysis revealed a significant relationship between smoking and functional independence in patients with noncardioembolism stroke subtypes (large artery atherosclerosis: odds ratio [OR], 1.452; 95% confidence interval [CI], 1.053–2.264; small artery occlusion: OR, 4.275; 95% CI, 1.098–16.649; other: OR, 3.120; 95% CI, 1.162–8.373). Furthermore, smoking was specially related to lower rates of symptomatic intracranial hemorrhage (OR, 0.316; 95% CI, 0.120–0.832) and mortality (OR, 0.272; 95% CI, 0.128–0.577) in patients with large artery atherosclerosis subtype.

Conclusions—In patients treated with intravenous thrombolysis, smoking could be related to a better chance of functional independence if their subtype of stroke was noncardioembolic, and a lower risk of symptomatic intracranial hemorrhage and mortality in those with large artery atherosclerosis. (Stroke. 2016;47:1811-1816. DOI: 10.1161/STROKEAHA.116.013124.)

Key Words: atherosclerosis ■ intracranial hemorrhages ■ smoking ■ stroke ■ thrombolytic therapy

Cigarette smoking is a well-known independent risk factor for the development of cerebrovascular diseases. Interestingly, previous studies have demonstrated that smoker with acute ischemic stroke (AIS) and treated with intravenous thrombolysis (IVT) had a higher rate of arterial recanalization, lower risk of developing an intracranial hemorrhage, and better clinical outcome than nonsmoker, even if after adjusting for potential confounders. However, other researchers insisted that smoking–thrombolysis paradox was from the difference in case mix, and therefore smoking did not independently affect the outcome in patients treated with IVT. To date, the association between smoking and post thrombolysis outcome continues to be debated. The underlying pathophysiologic mechanisms of smoking–thrombolysis paradox still need to be elucidated.

We hypothesize that smoking–thrombolysis paradox could be related to the different subtypes of stroke in patients...
presented with AIS. We therefore conducted this analysis of the data from the large multicenter prospective registry—the Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China (TIMS-China) to examine the relationship between smoking for >6 months and post-IVT outcome.

**Methods**

**Study Population**

TIMS-China was a national prospective stroke registry of thrombolytic therapy with intravenous alteplase for AIS patients in 67 major stroke centers in China. The study protocol was approved by the Ethics Committee of Beijing Tiantan Hospital. The registry was regularly monitored independently by the Quality Monitoring Committee of TIMS-China and the Contract Research Organization. All patients or legally authorized representatives gave written informed consents before thrombolysis, and AIS patients were followed up for 90 days.

From the TIMS-China database, all patients who received IVT within 4.5 hours from the onset were screened for the current analysis. As mentioned above, we aimed to investigate whether smoking for >6 months had any effect on the outcome in IVT-treated patients of different stroke subtypes. Thus, in this study, smokers were defined if they smoked at least 1 cigarette/d for >6 months, whether they were currently smoking, or had stopped smoking before the index stroke. Never smokers, occasional smokers, and passive smokers were classified as nonsmokers. The stroke subtypes of all eligible patients were classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria: large artery atherosclerosis (LAA), small artery occlusion (SAO), cardioembolism, stroke of other determined cause, and stroke of undetermined cause. Stroke subtype classification was based on the clinical features and the results of diagnostic tests, including brain imaging (computed tomography or magnetic resonance imaging), cerebral angiography (computed tomographic angiography or magnetic resonance angiography), electrocardiography, echocardiography, and laboratory examination of the prethrombotic state. The classification of stroke subtypes was performed by at least 2 experienced senior neurologists in each participating hospital. Because there were only a few patients in the stroke of other determined cause subtype (3.8%), they were combined with those with stroke of undetermined cause subtype and named together as the other group. Therefore, all patients in this study were classified into 4 stroke subtypes (LAA, SAO, cardioembolism, and other).

**Outcome Measurement**

For the purpose of this study, prespecified outcome measures included post-IVT symptomatic intracranial hemorrhage (SICH) within 7 days, and mortality and functional independence at 90 days. SICH was evaluated by using the National Institute of Neurological Disorders and Stroke definition, which was defined as hemorrhage that was not seen on a previous computed tomography scan, and there was subsequently a suspicion of hemorrhage with a neurological deterioration of ≥1 points on the National Institutes of Health Stroke Scale (NIHSS) score. Functional independence was defined as having a modified Rankin Scale score of 0–2.

**Statistical Analysis**

The baseline variables were compared between smokers and nonsmokers in each ischemic stroke subtype. The t test or Mann–Whitney U test was used to compare means or medians for continuous variables. The Pearson χ² test or continuity correction was used to compare the proportions for categorical variables. For comparing the outcomes between smokers and nonsmokers, odds ratios (OR) with their 95% confidence intervals and the adjusted ORs with their 95% confidence intervals were analyzed by univariate and multivariate logistic regression models. Age, sex, baseline NIHSS score, and the baseline variables with a difference at a level of P<0.2 between smokers and nonsmokers were retained in the multivariate model as covariates. Statistical significance was set at P<0.05. All analyses were performed with SAS statistical software (version 9.3; SAS Institute Inc., Cary, NC).

**Results**

Between May 2007 and April 2012, 1440 AIS patients treated with IVT were registered in the TIMS-China project. Because of missing data and delayed treatment (>4.5 hours), 322 patients was excluded. A total of 1118 patients were entered into the analysis. Among them, 454 (40.6%) were smokers and 664 (59.4%) were nonsmokers. Based on their stroke subtype, 606 (54.2%) patients were in the LAA subgroup, 117 (10.5%)...
in the SAO subgroup, 221 (19.8%) in the cardioembolism subgroup, and 174 (15.6%) in the other subgroup (Figure 1).

Baseline Characteristics of Patients Stratified by Stroke Subtype

Baseline characteristics of smokers and nonsmokers with different ischemic stroke subtypes are shown in Table 1. Among all stroke subtypes, the proportion of male sex was significantly higher in smoking group than in nonsmoking group (LAA, 94.2% versus 42.0%; \( P < 0.001 \); SAO, 96.2% versus 34.4%; \( P < 0.001 \); cardioembolism, 94.0% versus 31.6%; \( P < 0.001 \); other, 92.1% versus 38.8%; \( P < 0.001 \)). Furthermore, the age of stroke occurrence was younger in smoking group than in nonsmoking group (LAA, 56.4% versus 66.2%; \( P = 0.003 \)). Among LAA and SAO subtypes, the smokers less often had a history of hypertension than nonsmokers (LAA, 56.4% versus 71.9%; \( P = 0.003 \)). Among LAA and other subtypes, the smokers had more often a history of cardiovascular disease (LAA, 8.51 versus 7.64×10^9/L; \( P = 0.001 \); other, 8.62 versus 7.74×10^9/L; \( P = 0.047 \)). In LAA subtype alone, the smokers had less atrial fibrillation than nonsmokers (4.4% versus 8.5%; \( P = 0.047 \)). In cardioembolism subtype, the smokers had higher diastolic blood pressure than nonsmokers (90 versus 85 mm Hg; \( P = 0.024 \)). Other baseline variables (eg, baseline NIHSS score, onset-to-thrombolysis time, etc.) had no statistical difference between smoking and nonsmoking patients in 4 stroke subtypes (\( P > 0.05 \)).

Association Between Smoking and Post-IVT Outcomes in Patients With 4 Stroke Subtypes

Twenty-one patients (1.9%) were lost to follow-up at 90 days. The distribution of modified Rankin Scale scores at 90 days in smoking and nonsmoking patients with 4 stroke subtypes is shown in Figure 2. For LAA subtype, after adjustment for the potential confounders, smoking patients had not only less risk of SICH (2.6% versus 8.8%; OR, 0.316; \( P = 0.020 \)) and lower mortality (6.0% versus 13.9%; OR, 0.272; \( P = 0.001 \)) but also more opportunity for functional independence (61.9% versus 50.9%; OR, 1.452; \( P = 0.027 \)) than nonsmoking patients in multivariate logistic regression model. For SAO subtype, no patients developed SICH, and only 1 (0.9%) died. However, multivariate regression analysis revealed that smokers also presented with a better chance of functional independence as compared with nonsmokers (88.2% versus 70.3%; OR, 4.275; \( P = 0.036 \)). For the other subtype, as in those with LAA and SAO subtypes, smokers

Table 1. Baseline Characteristics of Smoking and Nonsmoking Patients With Different Ischemic Stroke Subtypes

<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>LAA (n=606)</th>
<th>SAO (n=117)</th>
<th>CE (n=221)</th>
<th>Other (n=174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>60 (11)</td>
<td>66 (10)</td>
<td>63 (9)</td>
<td>57 (12)</td>
</tr>
<tr>
<td>Male sex</td>
<td>259 (94.2)</td>
<td>91 (82.9)</td>
<td>77 (57.6)</td>
<td>64 (71.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>155 (56.4)</td>
<td>219 (66.2)</td>
<td>119 (55.1)</td>
<td>104 (63.5)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>53 (19.3)</td>
<td>78 (23.6)</td>
<td>74 (33.5)</td>
<td>72 (41.1)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>23 (8.4)</td>
<td>25 (7.6)</td>
<td>23 (10.4)</td>
<td>24 (14.1)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12 (4.4)</td>
<td>28 (8.5)</td>
<td>14 (6.3)</td>
<td>23 (7.6)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>76 (27.6)</td>
<td>96 (29.0)</td>
<td>69 (31.3)</td>
<td>57 (32.9)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>149 (56.9)</td>
<td>151 (50.9)</td>
<td>148 (68.0)</td>
<td>144 (84.1)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mm Hg</td>
<td>86 (27.9)</td>
<td>86 (27.9)</td>
<td>85 (47.1)</td>
<td>83 (47.1)</td>
</tr>
<tr>
<td>Blood glucose, mean (SD), mmol/L</td>
<td>7.82 (3.18)</td>
<td>8.15 (3.61)</td>
<td>7.30 (2.72)</td>
<td>7.20 (2.40)</td>
</tr>
<tr>
<td>White blood cell, mean (SD), x 10^9/L</td>
<td>8.51 (3.02)</td>
<td>7.64 (2.69)</td>
<td>7.30 (2.72)</td>
<td>7.20 (2.40)</td>
</tr>
<tr>
<td>Fibrinogen, mean (SD), g/L</td>
<td>3.26 (1.14)</td>
<td>3.34 (1.19)</td>
<td>3.53 (1.82)</td>
<td>3.40 (0.99)</td>
</tr>
<tr>
<td>Baseline NIHSS score, median (IQR)</td>
<td>11 (7–16)</td>
<td>12 (8–17)</td>
<td>7 (5–10)</td>
<td>10 (7–13)</td>
</tr>
<tr>
<td>Signs of current infarction at baseline CT scan</td>
<td>33 (12.0)</td>
<td>48 (14.5)</td>
<td>1 (1.9)</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>Full dose of alteplase</td>
<td>182 (66.2)</td>
<td>231 (69.8)</td>
<td>32 (60.4)</td>
<td>34 (68.0)</td>
</tr>
<tr>
<td>Onset-to-thrombolysis time, median (IQR), min</td>
<td>170 (140–189)</td>
<td>170 (140–189)</td>
<td>164 (138–180)</td>
<td>168 (144–210)</td>
</tr>
</tbody>
</table>

Values are numbers with percentages in parentheses, unless indicated otherwise. CE indicates cardioembolism; CT, computed tomography; IQR, interquartile range; LAA, large artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; and SAO, small artery occlusion.
had a higher rate of functional independence than nonsmokers (84.0% versus 64.2%; OR, 3.120; \( P = 0.024 \)) in multivariate model although there was no statistical difference in the occurrences of SICH (2.6% versus 3.1%; \( P = 0.930 \)) and mortality (1.3% versus 6.3%; \( P = 0.648 \)) between smokers and nonsmokers. But for cardioembolism subtype, multivariate analysis demonstrated that the incidence of SICH (12.0% versus 12.9%; \( P = 0.438 \)), mortality (20.0% versus 18.2%; \( P = 0.687 \)), and functional independence (42.0% versus 44.1%; \( P = 0.455 \)) were comparable between smokers and nonsmokers (Table 2).

**Discussion**

Our study has demonstrated that smoking–thrombolysis paradox may be dependent on the subtypes of ischemic stroke. Specifically, cigarette smoking for >6 months was associated with an increased chance of functional independence in IVT-treated patients with noncardioembolism subtype, and a decreased risk of SICH and mortality in those with LAA subtype after adjustment for the potential confounders. By the end of last decade, limited studies on this subject have showed conflicting results. As early as in 1997, post hoc analysis of the National Institute of Neurological Disorders and Stroke trial noted that IVT-treated patients who smoked had a lower risk of intracranial hemorrhages (symptomatic or asymptomatic) than nonsmokers,\(^2\) which had prompted many to speculate that increased plasminogen activator inhibitor-1 production caused by nicotine reduced the risk of intracranial hemorrhage in smokers who received IVT.\(^3\) In 2005, secondary analysis of the National Institute of Neurological Disorders and Stroke database indicated that recent smokers treated with IVT had a significantly greater improvement of their median NIHSS scores at 24 hours from the baseline and a lower rate of mortality >1 year than those in nonsmokers, even after the adjustment of covariates.\(^1\) Subsequently, 3 studies, respectively, reported that smoking was independently related to a lower incidence of SICH,\(^4\) a higher rate of recanalization and reperfusion,\(^5\) and a better short-term outcome after IVT.\(^6\) However, Aries et al\(^7\) found that current smoking did not affect the odds of SICH or 3-month favorable outcome in AIS patients treated with IVT by using both univariate and multivariate models. Moulin et al\(^8\) also considered that the better outcome observed in smoking patients who received IVT was mainly because of the effect of case mix, and smoking had no effect on any thrombolytic outcome after adjusting for the confounders, especially age and stroke severity. Therefore, reasons for smoking–thrombolysis paradox phenomenon remained unclear. However, our analysis has found that this paradoxical effect would only occur in patients with certain stroke subtypes. For example, if the proportion of cardioembolism patients in the study population was relatively high, the effect of smoking on the IVT-related outcome would be negligible. In contrary, if there were less cardioembolism patients in the thrombolysis cohort, the benefit of smoking could be more prevalent.
In this analysis, the odds of all outcomes were equally distributed between smokers and nonsmokers in the cardioembolism subgroup. This could be explained by the poor prognosis after IVT in patients with cardioembolism stroke caused by its larger and tightly organized thrombus, large infarct, high NIHSS score at presentation, often hemorrhagic transformation, and lack of time to establish effective collateral circulation.\(^ {14-19}\) When these factors were taken into account, the interaction between smoking and thrombolysis was not present. However, in SAO and other subgroups, we also did not find a statistical difference in SICH and mortality between smokers and nonsmokers, because of small patient numbers and low event rate, these results should therefore be interpreted with caution.

This study has several limitations. First, the design of this study is prospective observational cohort by nature. The confounding factors may not be completely removed by using the multivariate model. In addition, there may be some hidden confounders we did not collect in this study. We should be careful to interpret the results. Second, we did not distinguish current smokers from ex-smokers and had no record of the quantity of smoking (eg, pack-year). Thus, the effects of smoking status and quantity on the thrombolytic outcome could not be evaluated. Third, classifying ischemic stroke subtype was arbitrary and may subject to human error. And finally, we studied the smoking–thrombolysis relationship only in Chinese AIS patients. However, ethnic differences may have an impact on the relationship observed in this analysis. Our findings should be interpreted with caution and could not easily be extrapolated to other populations.

To our best knowledge, this is the first report to explore the influence of smoking on clinical outcome after IVT in AIS patients by analyzing their stroke subtypes. Our study suggested that smoking for >6 months was associated with a better chance of functional independence in IVT-treated patients who had noncardioembolism subtype of stroke and a lower risk of SICH and mortality in those with LAA subtype of stroke. Our findings need to be confirmed by plockspecific prospective cohort studies in different populations.

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Disclosures
None.

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