Safety of Antiplatelet Therapy Prior to Intravenous Thrombolysis in Acute Ischemic Stroke

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Background: There is some uncertainty whether prior use of antiplatelet (AP) drugs increases the risk of symptomatic intracerebral hemorrhage (SICH) and influences functional outcome in patients with ischemic stroke treated with intravenous thrombolysis.

Objective: To assess whether prior use of AP drugs is related to outcome following intravenous tissue plasminogen activator therapy in patients with ischemic stroke.


Main Outcome Measures: The occurrence of SICH and favorable outcome reflecting independence defined as a modified Rankin Scale score of 2 or lower at 3 months.

Results: Of the 301 patients who received intravenous tissue plasminogen activator, 89 used AP drugs prior to thrombolysis. Symptomatic intracerebral hemorrhage occurred in 12 patients (13.5%; 95% confidence interval, 7.8%-22.3%) who had received AP drugs and in 6 patients (2.8%; 95% confidence interval, 1.2%-6.2%) without prior AP therapy (P = .001). Multivariate analysis revealed that prior AP therapy was an independent predictor of SICH (odds ratio, 6.0; 95% confidence interval, 2.0-17.1). Nonetheless, prior AP therapy was independently associated with a favorable outcome (odds ratio, 2.0; 95% confidence interval, 1.0-4.3).

Conclusion: Despite a higher incidence of SICH, the net benefit of intravenous tissue plasminogen activator therapy for acute ischemic stroke was greater in patients using AP drugs.

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INTRAVENOUS THROMBOLYSIS WITH tissue plasminogen activator (tPA) improves outcome in a selected group of patients with acute ischemic stroke but is associated with a 10-fold increased risk of symptomatic intracerebral hemorrhage (SICH). It is critical to select those patients who are likely to benefit from tPA treatment without having an increased risk of SICH. Antiplatelet (AP) therapy impairs thrombocyte function and might increase the risk of a bleeding complication after intravenous thrombolysis. In the guidelines of the American Heart Association, prior AP drug use is no contraindication for tPA treatment, although starting AP therapy within 24 hours after tPA treatment is discouraged.

The question of whether tPA treatment is safe in patients receiving AP therapy merits further investigation because a number of patients with acute ischemic stroke have a history of previous vascular events and receive AP therapy at the time of the ischemic stroke. In this study, we compared the incidence of SICH and the 3-month functional outcome following intravenous thrombolysis between patients with and without prior AP therapy.

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METHODS

PATIENTS

All of the consecutive patients with ischemic stroke receiving tPA treatment at the University Medical Center Groningen stroke care unit
were included in a prospective registry starting April 1, 2002. For this study, we analyzed data acquired until November 30, 2006. Inclusion and exclusion criteria for tPA treatment within 3.0 hours were adopted from the National Institute of Neurological Disorders and Stroke trial protocol. On the basis of the pooled analysis from the 3 large tPA randomized placebo-controlled trials, we offered tPA treatment to patients up to 4.5 hours following stroke onset after explaining the off-label use and obtaining informed consent. For patients treated between 3.0 and 4.5 hours after stroke onset, we used the European Cooperative Acute Stroke Study II protocol. Inclusion was extended to patients older than 80 years. We performed a subgroup analysis on patients treated within 3.0 hours following stroke onset.

Neurological deficit was measured with the National Institutes of Health Stroke Scale (NIHSS). All of the patients underwent a brain computed tomographic (CT) scan, blood investigations, and electrocardiography before tPA treatment. We did not routinely perform posttreatment brain CT scans. Stroke subtype was classified as total anterior circulation infarction, partial anterior circulation infarction, lacunar infarction, or posterior circulation infarction according to the Oxfordshire Community Stroke Project. Demographics, vascular risk factors, glucose concentration, and prior AP drug use were recorded in the registry. Use and dosage of AP drugs were documented at admission in the clinical record file. Early ischemic changes on brain CT scan were defined as hypoattenuation of brain parenchyma, loss of the insular ribbon, obscuration of the lentiform nucleus, or focal or diffuse swelling of the cerebral cortex. All of the brain CT scans were reassessed with the investigator blinded for patient outcome.

OUTCOME MEASURES

The incidence of SICH was compared between patients with and without AP therapy before tPA treatment. We defined SICH as a neurological deterioration (NIHSS score ≥ 4 points) within 36.0 hours and a parenchymal hematoma on brain CT in a location compatible with the clinical symptoms according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study definition.

The modified Rankin Scale was used to determine functional outcome after 3 months. Favorable outcome was defined as a modified Rankin Scale score of 2 or lower, corresponding to independence with regard to activities of daily living.

AP THERAPY AND RISK OF SICH

Patients with prior AP therapy are likely to be older, to have a higher prevalence of vascular risk factors, and to have more previous vascular events. These imbalances in patient characteristics may confound the relation between AP therapy and SICH. To investigate whether prior AP therapy was independently associated with SICH, we assessed differences in baseline characteristics between patients with and without AP therapy; variables with \( P < .20 \) were selected as covariates for the multivariate analysis. Serum glucose level, age, early ischemic changes on initial brain CT scan, and higher NIHSS scores were also entered in the multivariate model regardless of the univariate analysis because these variables have previously been associated with an increased risk of SICH. In the final logistic regression model with SICH as a dependent variable, adjusted variables with \( P > .20 \) were removed.

AP THERAPY AND FUNCTIONAL OUTCOME

The same approach was used to investigate whether prior AP therapy was independently associated with a favorable outcome. Variables that were different between patients with and without prior AP therapy (with \( P < .20 \)) were selected as covariates for the multivariate analysis. The following covariates were also considered to be possible confounders and were entered in the multivariate analysis regardless of the univariate analysis: age, NIHSS score, serum glucose level, sex, stroke subtype (lacunar vs nonlacunar), time between onset and treatment, occurrence of SICH, and early ischemic changes on brain CT scan. In the final logistic regression model with favorable outcome as a dependent variable, adjusted variables with \( P > .20 \) were removed.

STATISTICAL ANALYSIS

Fisher exact tests, Pearson \( \chi^2 \) tests, and Mann-Whitney \( U \) tests were used for comparisons of the baseline characteristics and univariate analyses where appropriate. Multivariate analyses were done using logistic regression models. Goodness of fit of all regression models was assessed with the Hosmer-Lemeshow statistic. Multicollinearity of the regression models was evaluated using collinearity statistics. The variance inflation factor measures the degree of collinearity among covariates. A variance inflation factor greater than 2.5 points toward relevant collinearity. Statistical significance was taken to be at the 2-tailed .05 level. All of the statistical analyses were performed with SPSS statistical software version 14.0 for Windows (SPSS, Inc, Chicago, Illinois).

RESULTS

The 301 patients with ischemic stroke receiving tPA treatment, 89 (29.6%) were receiving AP therapy. One hundred eighty-eight patients (62.5%) were treated within 3 hours of stroke onset. Baseline characteristics of patients with and without AP therapy are presented in Table 1. As expected, patients pretreated with AP drugs were older, smoked less frequently, and more frequently had a history of previous arterial hypertension, diabetes mellitus, hyperlipidemia, and previous stroke.

Treatment with AP drugs consisted of aspirin in 65 patients (73.0%), the combination of aspirin and dipyridamole in 22 (24.7%), dipyridamole monotherapy in 1 (1.1%), and clopidogrel bisulfate monotherapy in 1 (1.1%).

OUTCOME

In the overall group (treated between 0.0 and 4.5 hours), SICH occurred in 18 patients (6.0%; 95% confidence interval [CI], 3.8%-9.3%), of whom 12 (13.5%; 95% CI, 7.8%-22.3%) were receiving prior AP therapy and 6 (2.8%; 95% CI, 1.2%-6.2%) were not (\( P = .003 \)). The absolute risk difference of approximately 10% translates into 1 additional SICH in every tenth patient receiving thrombolysis and prior AP therapy.

Ten of the 12 patients with SICH used aspirin alone, in a dose of 30 to 50 mg in 2 patients, a dose of 80 to 100 mg in 7 patients, and an unknown dose in 1 patient. Two patients used the combination of aspirin and dipyridamole in a dose of 25 mg and 200 mg, respectively. There were 10 SICHs in 65 patients pretreated with aspirin (15.4%; 93%
CI, 8.6%-26.1%) vs 8 SICHs in 212 patients in the nonaspirin group (3.8%; 95% CI, 1.9%-7.3%) (P = .002).

When excluding patients who received tPA beyond 3.0 hours of stroke onset, there were 9 SICHs in 60 patients with prior AP therapy (15.0%; 95% CI, 7.9%-26.4%) vs 3 SICHs in 128 patients without prior AP therapy (2.3%; 95% CI, 0.5%-7.0%) (P = .002).

In the group treated between 3.0 and 4.5 hours, there were 3 SICHs in 29 patients with prior AP therapy (5.3%; 95% CI, 2.9%-27.4%) vs 3 SICHs in 84 patients without prior AP (3.6%; 95% CI, 0.8%-10.5%) (P = .18).

In the final regression model (Table 2), prior AP therapy together with higher serum glucose levels and higher NIHSS scores were independent predictors of SICH in the total cohort (odds ratio, 5.96; 95% CI, 2.01-17.11). In the subgroup analysis of patients treated within 3.0 hours, prior AP therapy together with higher serum glucose levels remained independent predictors (odds ratio, 10.89; 95% CI, 2.40-49.34).

This study demonstrates that patients receiving AP therapy have a substantially higher risk of SICH after tPA treatment than patients without prior AP therapy. Despite this increased risk, prior AP therapy increased the odds of a favorable outcome. Therefore, our study suggests that tPA treatment should not be withheld from patients receiving AP therapy.

Acute ischemia may lead to endothelial injury and disruption of the blood-brain barrier. Therapy with AP drugs may further predispose to SICH after tPA treatment by impairing platelet aggregation. Previous studies reported conflicting results about the safety of AP drug use prior to intravenous thrombolysis. One study that investigated the relation between aspirin pretreatment and SICH following intravenous tPA treatment found no association with intracerebral hemorrhage.11 In the Multicenter rt-PA Stroke Study,11 patients receiving aspirin were at higher risk for SICH in the univariate analysis, whereas AP drugs other than aspirin were predictive of

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**Table 1. Characteristics of Patients With and Without Prior Antiplatelet Therapy in the University Medical Center Groningen Tissue Plasminogen Activator Registry**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Prior AP Therapy (n=301)</th>
<th>No Prior AP Therapy (n=212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>73 (11)</td>
<td>66 (15)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>46 (51.6)</td>
<td>112 (52.8)</td>
<td>.88</td>
</tr>
<tr>
<td>NIHSS score, median (range)</td>
<td>12 (2-25)</td>
<td>13 (2-25)</td>
<td>.26 b</td>
</tr>
<tr>
<td>Time until treatment, median (range), min</td>
<td>165 (30-270)</td>
<td>175 (70-285)</td>
<td>.43 b</td>
</tr>
<tr>
<td>Stroke subtype, No. (%)</td>
<td></td>
<td></td>
<td>.72</td>
</tr>
<tr>
<td>TACI</td>
<td>26 (29.2)</td>
<td>76 (35.8)</td>
<td></td>
</tr>
<tr>
<td>PACI</td>
<td>44 (49.4)</td>
<td>95 (44.8)</td>
<td></td>
</tr>
<tr>
<td>LACI</td>
<td>16 (18.0)</td>
<td>33 (15.6)</td>
<td></td>
</tr>
<tr>
<td>SICH</td>
<td>3 (3.4)</td>
<td>7 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>158 (26)</td>
<td>152 (28)</td>
<td>.06 b</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mm Hg</td>
<td>83 (14)</td>
<td>83 (17)</td>
<td>.84 b</td>
</tr>
<tr>
<td>Glucose level, mean (SD), mg/dL</td>
<td>115 (36)</td>
<td>115 (34)</td>
<td>.66 b</td>
</tr>
<tr>
<td>Early ischemic changes on brain CT, No. (%)</td>
<td>34 (38.2)</td>
<td>92 (43.6)</td>
<td>.39</td>
</tr>
<tr>
<td>Vascular risk factors, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>52 (58.4)</td>
<td>82 (38.6)</td>
<td>.002</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17 (19.1)</td>
<td>19 (9.0)</td>
<td>.01</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>43 (48.3)</td>
<td>48 (23.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>22 (24.7)</td>
<td>24 (25.5)</td>
<td>.89</td>
</tr>
<tr>
<td>Smoking</td>
<td>20 (23.5)</td>
<td>30 (14.3)</td>
<td>.03</td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>41 (46.1)</td>
<td>11 (5.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SICH, No. (%)</td>
<td>12 (13.5)</td>
<td>6 (2.8)</td>
<td>.003</td>
</tr>
</tbody>
</table>

**Table 2. Final Logistic Regression Model for Prediction of Symptomatic Intracerebral Hemorrhage in the University Medical Center Groningen Tissue Plasminogen Activator Registry**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP therapy</td>
<td>5.96 (2.01-17.11)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>1.12 (1.02-1.22)</td>
<td>.01</td>
</tr>
<tr>
<td>Glucose level</td>
<td>1.25 (1.02-1.54)</td>
<td>.04</td>
</tr>
</tbody>
</table>

Abbreviations: AP, antiplatelet; CT, computed tomography; NIHSS, National Institutes of Health Stroke Scale; PACI, partial anterior circulation infarction; POCI, posterior circulation infarction; SICH, symptomatic intracerebral hemorrhage; TACI, total anterior circulation infarction; TIA, transient ischemic attack.

| SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555. |

For each 1-point increase in the NIHSS score.

For each 18-mg/dL increase in the glucose level (to convert glucose to millimoles per liter, multiply by 0.0555).

Forty-five of the 89 patients (50.6%) with prior AP therapy and 95 of the 212 patients (44.8%) without prior AP therapy had a favorable outcome (modified Rankin Scale score of 0-2) (P = .38). In the final logistic regression analysis (Table 3) with adjustment for age, NIHSS score, systolic blood pressure, diabetes, history of hypertension, occurrence of SICH, and presence of early ischemic changes, AP therapy was associated with a favorable outcome (odds ratio, 2.01; 95% CI, 1.03-4.26). In the subgroup treated within 3.0 hours, a nonsignificant trend toward an association of AP therapy with a favorable outcome was observed (Table 3).

There was no significant collinearity among the covariates in any regression model.
and higher glucose levels also predicted SICH in our cohort. Previous study\(^1\) showed that patients using aspirin before tPA treatment might prevent early reocclusion after tPA treatment. A possible mechanism behind this beneficial effect is that aspirin remains biologically active for 4 to 6 days and might prevent early reocclusion after tPA treatment. A previous study\(^2\) showed that patients using aspirin before tPA treatment developed early clinical deterioration less frequently than patients without aspirin.

In our study, no association was found between prior AP therapy and outcome of tPA treatment in the univariate analysis. This confirms the subgroup analysis of the National Institute of Neurological Disorders and Stroke trial, which did not find any effect of aspirin on the clinical outcome in univariate models.\(^3\) However, both outcome and prior AP therapy are known to be related to age, hypertension, and prior vascular events.\(^4\) Consequently, the multivariate analysis needs to be adjusted for confounders. In our cohort, the multivariate analysis showed an association of prior AP therapy with a favorable outcome.

Our study has limitations. First, we did not perform routine brain CT scans after tPA treatment; therefore, we have no information on the effect of prior AP therapy on the development of asymptomatic hemorrhagic transformation. Second, the incidence of SICH in our study was low. On the other hand, even in a relatively small sample, the relation between SICH and AP therapy was highly significant in both univariate and multivariate analyses. Although we treated patients up to 4.5 hours after stroke onset, the subgroup analysis of the patients treated within 3.0 hours revealed no important differences compared with the analyses of the entire cohort regarding the risk of SICH and the chance of a favorable outcome. Among the patients treated between 3.0 and 4.5 hours, the incidence of SICH was not significantly higher in patients with prior AP treatment, but this may be explained by the low patient numbers in this group.

In summary, despite an increased risk of SICH, prior AP therapy before intravenous thrombolysis was independently associated with a favorable outcome. Larger prospective studies are warranted to further investigate the influence of AP therapy on outcome after thrombolytic therapy for acute ischemic stroke.

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