Thrombolysis With Recombinant Tissue Plasminogen Activator and Tirofiban in Stroke
Preliminary Observations

Rüdiger J. Seitz, MD; Magnolia Hamzavi, MS; Ulrich Junghans, MD; Peter A. Ringleb, MD; Corinna Schranz, MD; Mario Siebler, MD

Background and Purpose—We sought to investigate the feasibility of the combined use of low-dose recombinant tissue plasminogen activator (rtPA) and tirofiban, a glycoprotein IIb/IIIa (GPIIb/IIIa) receptor antagonist, for systemic thrombolysis in acute stroke.

Methods—Consecutive patients who were treated with systemic application of low-dose rtPA and body weight–adjusted tirofiban (rtPA+T group; n=37) were evaluated retrospectively during 1999–2001. Patients in the rtPA+T group were compared with a group of patients treated with a dose of 0.9 mg/kg body weight in a different center (rtPA group; n=119). The 41 patients with infarctions of the middle cerebral artery territory who were not eligible for thrombolytic treatment because of medical contraindications or arrival in the hospital >3 hours after stroke onset served as controls. For matched comparisons, the National Institutes of Health Stroke Scale on admission and the Rankin Scale on discharge 5 days after stroke were used.

Results—The patients treated with rtPA+T or rtPA improved (P<0.05) compared with the controls at discharge; patients in the rtPA+T and rtPA groups reached a Rankin Scale score of 0 to 2 in 63% and 55%, respectively, while only 16% of the controls achieved this score. Death rates (8% in rtPA+T group and 5% in rtPA group) were similar among the 2 treatment groups. They included 1 fatal hemorrhage in the rtPA+T group and 4 fatal hemorrhages in the rtPA group. Five percent of the untreated patients developed symptomatic, nonfatal cerebral hemorrhage.

Conclusions—Systemic combined thrombolysis with rtPA+T seems to be a feasible treatment in acute stroke. (Stroke. 2003;34:1932-1935.)

Key Words: platelet glycoprotein GPIIb-IIIa complex • platelets • stroke • thrombolysis

Intravenous use of recombinant tissue plasminogen activator (rtPA) is the only thrombolytic treatment that has been approved in acute stroke.1 It is efficacious, but it needs to be administered within 3 hours after stroke, includes a notable risk of intracerebral bleeding, and probably has lower efficiency with a longer interval of treatment onset.2–6 Thus, alternative approaches, including substances that are more effective than rtPA and bear a lower risk of intracranial hemorrhage, are desirable.

The glycoprotein IIb/IIIa (GPIIb/IIIa) receptor antagonists have been advocated recently as potentially promising agents for acute stroke therapy.7–11 The platelet GPIIb/IIIa receptor mediates blood clotting by forming stable fibrin bonds between activated thrombocytes.12,13 The GPIIb/IIIa receptor antagonists selectively inhibit the platelet integrin α₅β₃ fibrinogen receptor and thereby inhibit ADP-induced platelet aggregation.14

In animal models of brain infarction, GPIIb/IIIa thrombocyte receptor antagonists have been shown to reduce the cerebral infarct volume considerably, probably by the prevention of microvascular thrombosis, resulting in improved postischemic cerebral blood flow.15–17 In humans the GPIIb/IIIa platelet receptor antagonist abciximab has been shown to dissolve intravascular thrombi18,19 and to improve neurological outcome after stroke and carotid artery stenting.20,21 Notably, the use of GPIIb/IIIa receptor antagonists in ischemic cerebrovascular disease and manifest brain infarction does not seem to be associated with a high rate of fatal or symptomatic intracranial hemorrhage.22,23 In particular, the combination of half the dosage of thrombolytic agents together with the GPIIb/IIIa receptor antagonists has been reported to be effective in terms of reperfusion and safe in terms of bleeding complications in acute myocardial ischemia.24–27

Tirofiban, a nonpeptide GPIIb/IIIa antagonist, appears particularly suited for thrombolytic action because its action can be controlled well: the half-life of tirofiban in plasma is
approximately 1.6 hours, ie, the prolonged bleeding time normalizes within 4 hours after discontinuation of drug administration. Since rtPA is known to induce hypercoagulation after thrombolysis, we hypothesized that tirofiban may antagonize this hypercoagulation and thereby help to maintain the cerebral blood vessels patent after induction of thrombolysis with a systemic low dose of rtPA. In a pilot trial we have applied tirofiban for this purpose since 1999. In a previous publication we were able to show that tirofiban does not increase the rate of asymptomatic or symptomatic hemorrhages in stroke. In this study we analyzed the patients treated with rtPA plus tirofiban (rtPA+T) in a case-control design compared with a different group of patients treated with rtPA to examine the following 2 questions: (1) Is rtPA+T associated with an increased complication rate, including intracranial hemorrhage? (2) Is systemic thrombolysis with the combined use of rtPA+T able to improve the neurological deficit to a degree similar to that obtained by treatment with rtPA alone?

Our preliminary results suggest that rtPA+T is a promising option for acute stroke treatment.

**Subjects and Methods**

**Patients**

Patients with acute ischemic stroke (aged 65±14 years) who arrived at the hospital early and in whom systemic thrombolysis could be started within 180 minutes after stroke onset were eligible for this study. As detailed below, the study was performed in the stroke units of 2 university hospitals. Cerebral hemorrhage was excluded by MRI or CT. Cerebral arterial occlusion was determined by transcranial sonography and time-of-flight MR angiography or intra-arterial contrast angiography. The neurological deficit was scored with the use of the National Institutes of Health Stroke Scale (NIHSS) in each patient. At follow-up on discharge from the stroke unit, ie, at an average of 5 days after stroke onset, scoring on the Rankin Scale was determined. Scoring was done prospectively by the residents, who were not aware that their data would be used for a retrospective analysis.

**Treatment**

Three subgroups of patients were formed on the basis of different treatment regimens. First, in this retrospective analysis, 37 consecutive patients treated with rtPA+T were identified in the prospective database of 1006 patients who were admitted to the stroke unit in Düsseldorf University Hospital during 3 years since 1999. Of these patients with all types of stroke, 23 with an infarction in the middle cerebral artery territory were selected for a matched group comparison (see below). All patients first received an intravenous bolus of rtPA (24±9 mg; range, 20 to 50 mg), followed by intravenous tirofiban. Tirofiban was given in a body weight–adjusted dosage starting with a bolus of 0.4 µg/kg body weight per minute for 30 minutes followed by continuous infusion of 0.1 µg/kg body weight per minute. The tirofiban treatment scheme was adopted from the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study. The reduced dose of rtPA was in accordance with a recent report about the combination of rtPA with the GPIIb/IIIa receptor antagonist abciximab. Tirofiban treatment was continued for at least 24 hours. In addition, the patients received a continuous infusion of 10 000 IU of unfractionated heparin and 3 g magnesium in saline per day, which was started with tirofiban. Twenty-four hours after treatment onset, the patients received a cerebral CT scan for control. The study was approved by the Ethics Committee of the Heinrich-Heine University Düsseldorf. All patients or their relatives gave informed consent before treatment.

**Statistical Analysis**

Descriptive statistics were used for the demographic data and treatment regimens. Group comparisons based on neurological scores were performed with distribution-free tests such as the Wilcoxon rank test. The comparison of matched subgroups minimized epidemiological confounds, which compensated for the relatively small number of patients.

**Results**

Second, as a control group, 119 consecutive patients with acute stroke in the middle cerebral artery territory treated at the collaborating stroke unit of the University of Heidelberg during 1999–2001 were studied. These patients received a dose of rtPA that was adjusted to 0.9 mg/kg body weight over 1 hour with a 10% bolus. Within the first 24 hours, these patients did not receive any further anticoagulant medication but were started on low-dose heparin and aspirin thereafter or on high-dose heparin in the case of absolute arrhythmia or arterial dissection. Twenty-four hours after treatment onset, the patients received a cerebral CT scan for control. Of these patients, 20 were selected a posteriori to match the rtPA+T patients with respect to middle cerebral artery infarction, sex, age ≥75 years, and scores of ≤4 U on the NIHSS.

Third, a pooled group of 41 patients served as controls; these patients with acute stroke in the middle cerebral artery territory arrived in the hospital ≥3 hours but ≤6 hours after stroke onset and were not eligible for systemic thrombolytic treatment for that reason or because of medical contraindications to thrombolysis. For subgroup comparisons, treated patients and controls were matched with respect to sex, age categories of 5 years, and scores of ≤4 U on the NIHSS.

The patients treated with rtPA+T showed a wide range of acute neurological impairment on admission as assessed by the NIHSS (median, 15; range, 6 to 37). As evident from the matched comparison according to sex, age, and initial neurological impairment, the patients in the rtPA+T, rtPA, and control groups were affected similarly (Table). On discharge, both treatment groups had improved (P<0.05), showing a better Rankin Scale score than the controls (Figure). The Figure shows that almost two thirds of the rtPA+T–treated patients were not impaired or only slightly impaired (Rankin Scale score of 0, 1, or 2) at follow-up compared with more than half of the patients treated with rtPA with a similar outcome. In contrast, less than one fifth of the controls reached a Rankin Scale score of 0 to 2, while more than half of them remained severely disabled. Specifically, 12 patients (63%) treated with rtPA+T reached a Rankin Scale score of 0 to 2, as did 9 patients (55%) treated with rtPA alone. In contrast, only 4 controls (16%) had recovered to a Rankin Scale score of 0 to 2 on day 5.

As a side effect of the rtPA+T treatment, we observed esophageal bleeding after excessive vomiting in 1 of the 37

<table>
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<tr>
<th>Patient Subgroups Used for Matched Comparisons</th>
<th>rtPA+T</th>
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<th>Controls</th>
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<tr>
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<td>65±16</td>
<td>66±12</td>
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<td>14; 7–25</td>
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<tr>
<td>Sex (F/M)</td>
<td>12/11</td>
<td>12/8</td>
<td>12/13</td>
</tr>
</tbody>
</table>

*Median, range.

None of the demographic data differed among the subgroups (P>0.1). rtPA+T indicates rtPA and tirofiban, rtPA (0.9 mg/kg body weight); NIHSS, NIH Stroke Scale; L.o.S., length of stay on Stroke Unit.
patients in whom this treatment had to be terminated after 24 hours. One patient showed an asymptomatic hemorrhagic transformation of the infarct on follow-up CT scanning. Despite the general improvement in the treatment groups, a few patients expired in the intervention groups. In the rtPA+T group, 3 patients (8%) died: 2 patients died because of lack of recanalization and malignant middle cerebral artery infarction, and 1 patient developed a fatal intracranial bleeding in relation to an incidentally exaggerated heparin infusion. Of the 119 patients of the rtPA group, 6 patients (5%) died: 4 developed a fatal intracranial hemorrhage, 1 had a malignant brain infarction, and 1 died of cardiac arrest. Five additional patients suffered from an asymptomatic intracerebral hemorrhage that was detected by CT scanning 24 hours after rtPA treatment. Given the relatively small number of patients, the death rates were similar in the treatment groups. Two of the 41 untreated controls (5%) developed cranectomy for malignant brain infarction.

Discussion

The major finding of this retrospective pilot study is that a combination of low-dose rtPA and tirofiban appears to have an acceptable safety margin and a potential to reduce the neurological deficit in a manner similar to that of the standard dose of rtPA given within the first 3 hours after stroke onset. This preliminary observation was obtained by comparison of a small number of patients who were treated in 2 different centers and control patients with an acute stroke onset >3 hours before admission and a survival of at least 5 days. These methodological limitations are only partially compensated for by the matched group comparison and therefore provide only indicative results. Nevertheless, our results are promising and should be subjected to a prospective randomized clinical trial, which has been estimated to require at least 800 patients.

Our clinical data correspond to our recent reports in which we showed that tirofiban treatment resulted in early restitution of cerebral blood flow and in salvage of tissue at risk as defined by critically impaired perfusion. As was recently described for rtPA use, thrombolytic artery recanalization induces a dramatic neurological recovery. Before tirofiban was applied to neurological patients, it was successfully used in the peri-intervention period after coronary angioplasty for acute coronary syndrome and has been shown to prevent recurrence of myocardial infarction. Pharmacologically, tirofiban acts as a reversible receptor antagonist of the GPIIb/IIIa receptor on platelets. It is therefore possible that the enhanced thrombotic activity induced after cessation of the action of rtPA can be blocked by tirofiban, thereby augmenting and protracting the thrombolytic effect of rtPA. In our clinic a study is under way specifically addressing the rate of recanalization after rtPA+T treatment.

Treatment with rtPA+T seems to have an acceptable benefit-to-hazard profile. In a previous report we did not observe an increased rate of intracranial hemorrhage related to this treatment of tirofiban in acute stroke. Actually, hemorrhagic transformation of ischemic tissue in contrast to intracerebral hemorrhage may suggest a beneficial course after thrombolysis, as recently shown for rtPA treatment. The only intracranial hemorrhage we observed in this study in relation to the combined used of rtPA+T was probably due to an exaggerated dose of intravenous heparin and therefore may not be attributed to tirofiban. Since then we have limited the dose of the accompanying heparin to 10 000 IUs to avoid the risk of early mortality, as reported for GPIIb/IIIa monotherapy. In contrast, rtPA treatment is known to be complicated by a notable rate of therapy-related intracranial bleedings. Indeed, in the rtPA group, 4 fatal bleedings occurred, while a half dosage of rtPA precluded the occurrence of intracranial hemorrhages. Thus, we suggest that a low dose of rtPA in combination with tirofiban involves a low bleeding risk, which is in accordance with dose escalation in the National Institute of Neurological Disorders and Stroke study, although thrombolytic efficacy may be less. Given the relatively small number of patients studied thus far, it was estimated that approximately 10 000 patients are needed to establish this difference at a 5% probability level. This will require a multicenter study.

A major problem for thrombolysis in stroke is the time delay between symptom onset and the patient’s arrival in a centers dedicated to acute stroke treatment. In general, this results in low numbers of patients who can be subjected to thrombolysis in both our centers and other centers. Our data suggest the need to launch phase I and phase II studies in the window of 3 to 6 hours after stroke onset to establish the efficacy and acceptable safety of rtPA+T treatment. As suggested by our data, rtPA+T treatment may be a promising option for smaller hospitals as well and with a less strict time limit of 3 hours, as was established for rtPA treatment.

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References


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