Systemic Thrombolysis With Recombinant Tissue Plasminogen Activator and Tirofiban in Acute Middle Cerebral Artery Occlusion

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Background and Purpose—In acute ischemic stroke, thrombolytic treatment with recombinant tissue plasminogen activator (rtPA) is limited by a concomitant activation of the coagulatory system, leading to incomplete or delayed reperfusion, microcirculatory disturbances, or even repeated vessel occlusions. Our pilot study sought to assess the therapeutic potential of a new treatment strategy combining rtPA at reduced dosages with a platelet glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitory agent in acute middle cerebral artery occlusion.

Methods—Nineteen patients suffering from acute middle cerebral artery occlusion (Thrombolysis in Myocardial Infarction [TIMI] flow grade 0 to 1) underwent combined intravenous thrombolytic treatment using rtPA at reduced dosages and the GPIIb/IIIa antagonist tirofiban. Stroke MRI (diffusion- and perfusion-weighted imaging) and MR angiography were performed at baseline and between days 1 and 2 after treatment. Clinical scores (National Institutes of Health Stroke Scale and modified Rankin Scale) were assessed at baseline and after 1 week.

Results—Middle cerebral artery recanalization (TIMI flow grade 2 and 3) occurred in 13 of 19 patients (68%). The ischemic lesion on follow-up MRI was significantly smaller in patients with recanalization compared with those without recanalization (P<0.001). Only patients with recanalization improved neurologically (P<0.001). Because no symptomatic hemorrhage was observed, the power of our study to detect a symptomatic bleeding rate of ≥8% was at least 80%.

Conclusions—Combined thrombolysis with a GPIIb/IIIa antagonist and rtPA at reduced dosages is promising but cannot be recommended for general use before prospective randomized clinical trials are completed. (Stroke. 2004;35:705-709.)

Key Words: intracranial embolism and thrombosis ■ magnetic resonance imaging ■ platelet glycoprotein GPIIb-IIIa complex ■ tissue plasminogen activator

Intravenous recombinant tissue plasminogen activator (rtPA) is an approved treatment for acute ischemic stroke within 3 hours of symptom onset. Clinical efficiency of thrombolysis is limited not only by an inherent risk for cerebral hemorrhage but sometimes also by delayed reperfusion, resulting in the evolution of ischemic brain lesions. Moreover, circumstantial evidence suggests potentially harmful effects of the serine protease rtPA on brain tissue itself. As in myocardial infarction, treatment of acute ischemic stroke with thrombolytic agents such as rtPA inevitably leads to concomitant activation of the coagulatory system. Thus, even in successful initial recanalization, neurological deterioration related to repeated vessel occlusions is observed in every third case after rtPA treatment. Combined thrombolytic treatment with fibrinolytic and platelet glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitory agents led to improved patency rates in myocardial reperfusion therapy compared with rtPA alone. These clinical data demonstrate that the combination of thrombolytic and GPIIb/IIIa inhibitory agents has synergistic effects in achieving fast and complete arterial reperfusion. Recent experimental results obtained in a thromboembolic rat stroke model revealed that, even within an enlarged time frame, anti-GPIIb/IIIa agents can be combined safely with low doses of thrombolytic agents to produce significant attenuation of neuronal damage with no increase in the incidence of cerebral hemorrhage.

Present clinical studies suggest that GPIIb/IIIa antagonists may carry a relatively low risk for intracerebral bleeding in acute ischemic stroke patients. The high reperfusion potential of combined systemic thrombolysis with rtPA at reduced dosages and the nonpeptide platelet GPIIb/IIIa antagonist tirofiban in basilar artery thrombosis prompted us to investigate the feasibility of this new treatment strategy in the setting of acute middle cerebral artery (MCA) occlusion.
Consecutive patients admitted to our stroke unit with sudden onset of neurological symptoms attributed to the anterior circulation who were willing to participate in the study were enrolled (Figure 1). The study was approved by the local ethics committee, and informed consent was given by all patients or their relatives. All patients met the following inclusion criteria: (1) sudden onset of MCA stroke, (2) complete acute stroke MRI protocol (MR angiography, diffusion-weighted imaging [DWI] and perfusion-weighted imaging [PWI]) performed at baseline as a routine workup of our acute stroke patients,15–16 (3) combined thrombolytic treatment with rtPA and the GP IIb/IIIa antagonist tirofiban given within 3 hours after symptom onset, (4) MCA occlusion (Thrombolysis in Myocardial Infarction [TIMI] flow grades 0 and 1) on baseline MR angiography, (5) follow-up MR angiography and DWI performed between days 1 and 2 after treatment, and (f) clinical scoring after 1 week.

The National Institutes of Health Stroke Scale (NIHSS) score and modified Rankin Scale (mRS) score were assessed immediately before baseline MRI and after 1 week after symptom onset. All patients received a combined thrombolytic treatment with rtPA at reduced dosages (ie, a single 20-mg bolus in 15 cases and a 10-mg bolus followed by a 40-mg infusion over 1 hour in 4 cases) and body weight–adjusted tirofiban. Tirofiban was started with an infusion rate of 0.4 μg·kg⁻¹·min⁻¹ over half an hour followed by 0.1 μg·kg⁻¹·min⁻¹ for at least 48 hours according to the PRISM PLUS protocol (see also the report by Junghans et al13). In each case, combined thrombolytic treatment was initiated at least within 3 hours of symptom onset. Concomitant unfractionated heparin was given only at low dose and did not exceed 15 000 IU/d. The activated partial thromboplastin time was targeted to normal values and did not exceed 10% of the upper threshold limit.

Imaging, Postprocessing, and Image Analysis

Imaging was performed on 1.5-T clinical whole-body MR scanner (Siemens Magnetom Vision) equipped with a gradient override using the standard head coil. The MRI protocol was part of our routine clinical protocol and comprised axial T2-weighted and DWI sequences, an MR angiographic investigation, and serial T2*-weighted measurements, with serial images obtained for measurement of tissue perfusion. Typical sequence parameters and locally established computer software programs were described previously.15,17 To evaluate volumetric results, we used a segmentation technique consisting of thresholds that are relative to the unaffected contralateral hemisphere. The segmentation was performed on manually defined regions by 2 investigators blinded to the clinical data and the time point of investigation.

Two independent investigators blinded to clinical data (including the respective PWI and DWI sequences) and time point of the respective examination rated the MCA patency grade according to the TIMI criteria18 on MR angiographies obtained before and within 1 to 2 days after treatment with TIMI flow grades defined as follows:14 TIMI flow grade 0 = complete occlusion (no perfusion), 1 = nearly complete occlusion (minimal perfusion with a very faint reconstitution of distal flow on MR angiography), 2 = partial occlusion (an obstruction that results in decreased intensity of distal slow-flow signals at MR angiography), and 3 = complete recanalization (unimpeded perfusion of the distal vasculature with no residual stenosis). On follow-up MR angiography, TIMI flow grades 0 and 1 represented persistent occlusion, whereas TIMI flow grades 2 and 3 indicated that a recanalization occurred.

Statistical Analysis

Demographic data, time intervals, and descriptive statistics of scores are given as median values with range. Nonparametric tests (Wilcoxon signed-rank test and Mann-Whitney U test) were conducted with the use of a standard software package (SPSS 11.0).

Results

A total of 19 patients (median age, 66; range, 44 to 80 years; 9 men; for recruitment see Figure 1) presenting with acute MCA stroke (10 times left hemisphere) met the inclusion criteria and were recruited for the study (results are given in the Table and Figure 2). Before treatment, MR angiography, PWI, and DWI were obtained within a median of 90 minutes (range, 45 to 135 minutes) after symptom onset in all cases. MR angiography revealed complete (TIMI flow grade 0; n = 17) or nearly complete (TIMI flow grade 1; n = 2) occlusion of the respective MCA trunk (M1; n = 14) or MCA branch (M2; n = 5). The corresponding perfusion deficit volume (median, 111 mL; range, 10.5 to 188.2 mL) was significantly larger in M1 occlusions (P = 0.027), but there was no systematic difference in initial DWI lesions (P = 0.1, the Table). A median NIHSS score of 17 (range, 3 to 25) at baseline illustrates the severe neurological impairment observed before initiation of treatment. In accordance with the larger perfusion deficit, patients with M1 occlusions were neurologically more severely affected than those with M2 occlusions (P = 0.02). Interestingly, the size of potentially salvageable ischemic brain tissue as defined by the PWI/DWI mismatch region was of comparable magnitude in both the M1 and M2 occlusion groups (P = 0.4). All patients received a combined thrombolytic treatment (median, 135 minutes; range, 90 to 180 minutes after symptom onset) with rtPA at reduced dosages and tirofiban as described in Patients and Methods. Overall, combined thrombolysis resulted in a significant neurological improvement (median NIHSS after treatment, 2; P = 0.002). As judged by follow-up MR angiography, recanalization (TIMI flow grade 2 and 3) occurred in 13 patients (68%). The NIHSS score before treatment was not
different between patients with and without recanalization ($P=0.6$). Only patients with recanalization had neurologically improved ($P=0.001$); those with persistent MCA occlusion had not ($P=0.2$). The ischemic lesion on follow-up DWI was significantly smaller in patients with recanalization (median, 17 mL; range, 0.3 to 115 mL) compared with those without recanalization (median, 168 mL; range, 43 to 229 mL; $P=0.001$). Correspondingly, DWI lesion growth was significantly smaller in patients with recanalization (median, 7.2 versus 55.4 mL; $P=0.005$). In none of the patients was symptomatic cerebral or extracerebral bleeding observed. T2* images revealed asymptomatic hemorrhagic transformation of infarction in a single patient (patient 14; the Table).

**Discussion**

As a main result of our small, nonrandomized, open-label trial, we observed a high rate of MCA recanalization. Patients with recanalization developed significantly smaller infarcts as determined by DWI that were associated with improved clinical scores. No symptomatic cerebral or extracerebral bleeding occurred. For full-dosage intravenous rtPA, a bleeding rate of $\approx 8\%$ was reported.$^2$ Assuming an individual bleeding rate of $P=0.08$ yields a probability of $(1−0.08)^{19} = 0.2$. Thus, the power of our study to detect a symptomatic bleeding rate of $\approx 8\%$ was $\approx 80\%$.

Recanalization and Lesion Size After Combined Thrombolysis

In acute ischemic stroke, concomitant activation of the coagulatory system by treatment with thrombolytic agents contributes to incomplete or delayed reperfusion, microcirculatory disturbances, or even repeated vessel occlusion.$^5,19$ From experimental data obtained in a rat thromboembolic stroke model, simultaneous treatment with thrombolytic and GPIIb/IIIa inhibitory agents significantly attenuates neuronal damage with no increase in the incidence of cerebral hemorrhage.$^9,10$ Compared with full-dosage rtPA, an enhancement in large- and small-vessel patency contributed to smaller infarct sizes and a better neurological outcome. Correspondingly, in acute basilar artery thrombosis, combined rtPA plus tirofiban thrombolytic treatment was shown to resolve a platelet-rich thrombus that resisted intra-arterial thrombolysis.$^{14}$

In acute MCA occlusion, several case-control studies suggest a recanalization rate of $\approx 50\%$ to 60$\%$ after full-dosage rtPA treatment,$^3,16,20,21$ but early MCA reocclusion occurs in $\approx 34\%$ of rtPA-treated patients despite initial recanalization.$^6$ These recurrences account for two thirds of deteriorations after improvement. Recanalization rates after systemic rtPA plus tirofiban are of comparable magnitude compared with the results reported for intra-arterial recombinant prourokinase treatment in the PROlyse in Acute Cerebral Thromboembolism (PROACT II) study, but the intra-arterial
approach was associated with a 10% risk for symptomatic bleeding complications within the first day after treatment.\textsuperscript{22} This may be attributed in part to the longer time needed to initiate treatment in PROACT II (median time >5 hours) with the consequence of a more severely impaired microvasculature. In acute stroke, GPIb/IIa inhibitors were shown to inhibit a sustained accumulation of fibrinogen and platelets, thereby preventing the occurrence of new thrombotic occlusions of the small downstream arteries.\textsuperscript{23–26} Moreover, tirofiban is capable of completely blocking cerebral microembolism,\textsuperscript{27} often observed during vessel recanalization.\textsuperscript{28}

At baseline, the patients recruited for our study were neurologically as severely affected as those included in recent investigations monitoring full-dosage rtPA thrombolysis with transcranial Doppler ultrasound.\textsuperscript{1,2} The clinical scores corresponded very well to the extent of critically ischemic brain tissue as demonstrated by the severe perfusion deficit. Recently, Molina and coworkers\textsuperscript{3} showed that infarct volume and duration of MCA occlusion are strongly associated. This assumption is supported by the better neurological recovery observed in patients with recanalization because a good clinical outcome has been shown to be strongly associated with early recanalization.\textsuperscript{3,29} Here, we are not aware of the exact time point of recanalization, but the observation that, after combined rtPA plus tirofiban thrombolysis, patients with TIMI flow grades 2 and 3 developed significantly smaller infarcts (Figure 2) may indicate a fast MCA recanalization.

Our study was designed as a small, nonrandomized, open-label trial. Thus, although combined thrombolysis with low-dose rtPA plus tirofiban looks promising in patients with acute MCA occlusion, there is no evidence of superiority above full-dosage rtPA treatment. Prospective, randomized, placebo-controlled multicenter trials are needed and justified to confirm and extend our observations. Combined thrombolysis can be recommended for use only if favored by results of these randomized trials.

\begin{figure}[h]
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\caption{Effect of recanalization on ischemic lesion growth (A) and clinical course (B). Gray boxes indicate perfusion deficit volume (A) and NIHSS score (B) at baseline (n=19). On follow-up, ischemic lesion size (A) as determined on DWI (see Methods) and NIHSS score (B) were significantly different between patients with (n=13, white boxes) and without (n=6, dark gray boxes) recanalization. Solid lines indicate median values; boxes, 25th to 75th percentiles; and vertical lines, 5th to 95th percentiles. **P<0.001; ***P<0.0001.}
\end{figure}

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\section*{References}


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