Is the Benefit of Early Recanalization Sustained at 3 Months?
A Prospective Cohort Study

Lise A. Labiche, MD; Fahmi Al-Senani, MD; Anne W. Wojner, PhD; James C. Grotta, MD; Marc Malkoff, MD; Andrei V. Alexandrov, MD

Background and Purpose—Early arterial recanalization can lead to dramatic recovery (DR) during intravenous tissue plasminogen activator (tPA) therapy. However, it remains unclear whether this clinical recovery is sustained 3 months after stroke.

Methods—We studied consecutive patients treated with intravenous tPA (0.9 mg/kg within 3 hours) who had M1 or proximal M2 middle cerebral artery occlusion on pretreatment transcranial Doppler according to previously validated criteria. Patients were continuously monitored for 2 hours after tPA bolus to determine complete, partial, or no early recanalization with the Thrombolysis in Brain Ischemia (TIBI) flow grading system. A neurologist obtained the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) scores independently of transcranial Doppler results. DR was defined as a total NIHSS score of 0 to 3 points, and early recovery (ER) was defined improvement by ≥10 points at 2 hours after tPA bolus. Good long-term outcome was defined as an NIHSS score of 0 to 2 or an mRS score of 0 to 1 at 3 months.

Results—Fifty-four patients with proximal middle cerebral artery occlusion had a median prebolus NIHSS score of 16 (range, 6 to 28; 90% with ≥10 points). The tPA bolus was given at 130±32 minutes (median, 120 minutes; 57% treated within the first 2 hours). DR+ER was observed in 50% of patients with early complete recanalization (n=18), 17% with partial recanalization (n=18), and 0% with no early recanalization (n=18) (P=0.025). Overall, DR+ER was observed in 12 patients (22%), and 9 (75%) had good outcome at 3 months in terms of NIHSS (P=0.009) and mRS (P=0.006) scores compared with non-DR and non-ER patients. If early recanalization was complete, 50% of these patients had good outcome at 3 months, and 78% with DR+ER sustained early clinical benefit. If recanalization was partial, 44% had good long-term outcome, and 66% of patients with DR+ER sustained the benefit. If no early recanalization occurred, 22% had good long-term outcome despite the lack of DR within 2 hours of tPA bolus (P=0.046). Mortality was 11%, 11%, and 39% in patients with complete, partial, and no early recanalization, respectively (P=0.025). Reasons for not sustaining DR in patients with early recanalization were subsequent symptomatic intracranial hemorrhage and recurrent ischemic stroke.

Conclusions—DR or ER after recanalization within 2 hours after tPA bolus was sustained at 3 months in most patients (75%) in our study. Complete or partial early recanalization leads to better outcome at 3 months after stroke. Fewer patients achieve good long-term outcome without early recanalization. (Stroke. 2003;34:695-698.)

Key Words: recovery of function stroke thrombolysis ultrasonography, Doppler, transcranial

Intravenous tissue plasminogen activator (tPA) is currently the only Food and Drug Administration–approved therapy for acute ischemic stroke, and the National Institute of Neurologic Disorders and Stroke (NINDS) rt-PA Study showed improvement in clinical outcome 3 months after stroke. However, that trial did not show a statistically significant benefit at 24 hours, and no data have yet been disclosed on early response to tPA 2 hours after bolus. Also, the NINDS rt-PA Stroke Study included all ischemic stroke subtypes, and no continuous vascular monitoring was performed.

The benefit of tPA is due to lysis of thrombus and restoration of perfusion to ischemic but not yet infarcted brain tissue. This hypothesis is supported by both animal and human studies showing that the duration of impaired perfusion is associated with final infarct volume and that early recanalization correlates with smaller infarct size. Studies have also demonstrated relatively high rates of recanalization with continuous transcranial Doppler (TCD) monitoring and have linked this process to early recovery (ER) in real time.

The question of whether early clinical recovery after recanalization can be sustained long term remains. Some patients in the NINDS trial may have experienced ER, but this was not a predefined end point. In addition, the heterogeneity of this patient population would have made meaningful interpretation of such data difficult.
ity of ischemic stroke subtypes, we chose to focus our prospective study on patients with a proximal middle cerebral artery (MCA) occlusion who were eligible for standard treatment with tPA during the first 3 hours after stroke. We aimed to determine whether dramatic recovery (DR) or ER within 2 hours of bolus is sustained 3 months after stroke in these patients.

Methods

We prospectively studied consecutive patients treated with intravenous tPA within 3 hours of symptom onset according to standard protocol (0.9 mg/kg dose, 10% bolus, 90% continuously infused over 60 minutes, 90-mg/kg maximum). These patients did not receive intra-arterial rescue and were not enrolled in any experimental therapeutic protocols. All study patients had an M1 or proximal M2 MCA occlusion on pretreatment TCD according to previously validated criteria. Patients were continuously monitored for 2 hours after tPA bolus according to an institutional review board–approved sonation study protocol (Committee for Protection of Human Subjects, University of Texas). We performed 2-MHz single-channel monitoring using portable TCD equipment (TCD 100M, Spencer Technologies; Ez-Dop, DWL/Neuroscan; Multigon 500M, Multigon Industries). The residual flow signals were identified along the proximal MCA depths (range, 65 to 40 mm) and the transducer position was fixed by use of Marc series head frame (Spencer Technologies). TCD was performed and interpreted online by an experienced sonographer who identified complete, partial, or no early recanalization using the Thrombolysis in Brain Ischemia (TIBI) flow grading system. Complete recanalization was diagnosed as improvement to stenotic or normal (TIBI 4 to 5 flow grades) waveforms; partial recanalization was diagnosed as an improvement in residual flow signals by at least 1 TIBI flow grade up to TIBI flow grades 2 to 3; and no recanalization was defined as the absence of improvement of the residual flow signal from baseline TCD examination. Our criteria have been previously validated against angiography with 91% sensitivity and 93% specificity for identification of M1 and M2 MCA occlusions.

A neurologist who was not involved in TCD monitoring obtained the National Institutes of Health Stroke Scale (NIHSS) score before treatment, 2 hours after bolus, and 24 hours after symptom onset. This neurologist was informed of TCD findings before and during tPA therapy. Modified Rankin Scale (mRS) scores were obtained via outpatient stroke visit or structured telephone interview (17% of all patients) 3 months after stroke. In patients available for outpatient follow-up, a 3-month NIHSS score was also obtained. All 3-month outcome scores were obtained by a neurologist independently of TCD results and previous NIHSS scores (pretreatment, 2 hours after bolus, and 24 hours after onset).

DR was defined as improvement to a total NIHSS score of 0 to 3 points, and ER was defined as improvement by ≥10 points 2 hours after tPA bolus. Good long-term outcome was defined as an NIHSS score of 0 to 2 or an mRS score of 0 to 1 three months after stroke.

Independent-sample Student’s t test was used to test the hypothesis that patients experiencing DR demonstrate improved neurological outcome at 3 months compared with those not experiencing DR. Levene’s test was first undertaken to determine the equality of variances between the 2 groups (DR+ER and no DR+ER), followed by 2-tailed Student’s t test for the differences in good outcomes between those groups. A χ² analysis was used to test for differences in DR+ER and mortality rates in patient subgroups. SPSS 8.0 statistical package was used.

Results

A total of 54 patients were studied (28 men, 26 women; mean age, 68 ± 15 years; median age, 68 years). All patients had a proximal MCA occlusion before tPA bolus, and the median prebolus NIHSS score was 16 points (range, 6 to 28; 90% of patients with total scores ≥10 points). The tPA bolus was given at 130 ± 32 minutes (median, 120 minutes; 57% treated within the first 2 hours). Overall, DR+ER was observed in 12 patients (22%) at 2 hours and in 19 patients (35%) at 24 hours. A total of 21 patients (39%) achieved good outcome at 3 months (Figure 1). Of those with good 3-month outcome, 19 patients reached mRS scores of 0 to 1, 18 patients had NIHSS scores of 0 to 1, and 3 patients had NIHSS scores of 2 points (mild extremity weakness and mild word-finding difficulties). DR+ER accounted for 11 of 15 patients (73%) with recovery at 24 hours and 9 of 21 patients (43%) with good long-term functional outcome at 3 months. A total of 25 patients (46%) achieved mRS scores of 0 to 2 at 3 months.

DR+ER was observed in 9 of 18 patients (50%) with early complete recanalization, in 3 of 18 patients (17%) with partial recanalization, and in 0 of 18 with no early recanalization (P = 0.025; Figure 2). Of 12 patients with DR+ER, 9 (75%) had good outcome at 3 months. In the non–DR+ER group (n = 42), only 12 patients achieved good outcome (28%). Student’s t test demonstrated a significant difference in outcome variables, NIHSS score (P = 0.009), and mRS score (P = 0.006) between DR+ER patients and non–DR+ER patients (the Table).

If early recanalization was complete, 50% of these patients had good outcome at 3 months, and 78% of patients with DR+ER sustained the early clinical benefit. If recanalization was partial, 44% had good long-term outcome, and 66% of patients with DR+ER sustained the benefit. If no early recanalization occurred, 22% had good long-term outcome despite the lack of DR or ER within 2 hours of tPA bolus (P = 0.046, χ²).

Figure 1. Pretreatment stroke severity, early clinical improvement, and stroke outcome at 3 months. NIHSS indicates the National Institutes of Health Stroke Scale.

Figure 2. Dramatic recovery (DR, at 2 hours), arterial recanalization, and sustained (at 3 months) early clinical benefit. Complete, partial, or none indicates recanalization within 2 hours after tPA bolus (P = 0.046).
Intracerebral symptomatic hemorrhage occurred in 4 patients (7.4%): 2 had complete recanalization, and 2 had no early recanalization. All 4 hemorrhages were fatal. Our \( \chi^2 \) analysis shows that mortality rates were significantly higher in patients with no early recanalization (39%) compared with those with complete (11%) or partial (11%) early recanalization (\( P=0.025 \)). The reasons that DR or ER was not sustained in patients with early recanalization included subsequent symptomatic intracranial hemorrhage (\( n=1 \)) and recurrent ischemic stroke (\( n=2 \)).

Despite early occurrence of recanalization, 8 patients with complete and 8 with partial recanalization had poor outcomes at 3 months (mRS, 3 to 5 points and death). The poor functional outcomes in these patients were attributed to the following: fatal intracerebral hemorrhage (\( n=2 \)), reocclusion within 2 hours of tPA bolus (\( n=5 \)), recurrent stroke (\( n=2 \)), and no change in stroke severity (NIHSS) or stroke progression (by \( \geq 2 \) NIHSS points) without hemorrhage (\( n=4 \)). In addition, 1 patient experienced complete motor and speech recovery but had poor outcome because of blindness as a complication of diabetes.

**Discussion**

Our study showed that most patients who experience early clinical improvement within 2 hours of tPA bolus sustain this clinical benefit 3 months after stroke. DR and ER occur in the setting of early complete or partial recanalization, in accordance with previous observations.\(^2,5–7\) In this series, DR and ER occurred in 43% of all patients who had good outcome 3 months after receiving intravenous tPA therapy. This finding indicates that partial early recanalization and mechanisms other than early reperfusion may also have a substantial role in long-term recovery from ischemic stroke.

Our study population is different from that of the NINDS rt-PA Stroke Study\(^14\) because we selected patients with a proximal MCA occlusion on TCD and excluded those with suspected lacunar syndromes or vertebrobasilar ischemia based on urgent vascular ultrasound assessment. The proximal MCA occlusions identified in our patient population parallel those treated in the Intra-Arterial Prourokinase for Acute Ischemic Stroke (PROACT) study.\(^15\) However, the timing of thrombolytic therapy, and hence recanalization, differs between these 2 studies because PROACT allowed treatment within 6 hours of stroke onset. The outcomes found in our study are comparable to those in the PROACT study. For example, mRS scores of 0 to 2 at 3 months were found in 40% in PROACT and 46% in our patients. Mortality rates were also comparable.

Early recanalization and reperfusion of ischemic penumbra are the hypothesized mechanisms for DR and subsequent good long-term outcome.\(^2,5–6\) However, DR in the emergency room was observed in fewer than half of the patients with an ultimate good functional outcome. Alternative mechanisms that may be responsible for this long-term benefit include collateralization of flow despite persistence of arterial occlusion; resolution of edema; slow, partial, and late but still nutritious recanalization; neuronal reorganization; and brain tissue metabolic recovery independent of thrombolysis.\(^16,17\)

Our study has limitations. At our center, we administered tPA therapy to a larger number of patients than we report here. Patients had to be excluded from the study if no pretreatment TCD was performed, if no proximal occlusion was found on pretreatment TCD, if no windows for transcranial insonation were present, or if the patient was unavailable for follow-up (overall rate, 17%). Also, thrombolysis of occlusions at locations other than the proximal M1 or M2 MCA or treatment of patients with lacunar syndromes may yield different results for ER and long-term follow-up.

However, the present study provides data associating early recanalization and DR with long-term outcome. If confirmed in larger studies, DR during or shortly after intravenous tPA therapy may prove a feasible goal of systemic vascular rescue therapies. Conversely, the persistence of a proximal arterial occlusion without signs of early, and at least partial, recanalization should be viewed as a poor prognostic sign, and these patients may be considered more suitable for intervention procedures in the future.\(^18\)

In conclusion, DR or ER after early recanalization is sustained at 3 months in most patients (75%) in our study. Although the NINDS rt-PA Stroke Study did not show a difference in early improvement for the primary end points, our results parallel the posthoc analysis\(^13\) suggesting that ER might have occurred in this trial during tPA treatment. Complete or partial recanalization achieved early after tPA bolus often leads to better outcome at 3 months after stroke, and fewer patients achieve good long-term outcome without early recanalization.

**References**


Is the Benefit of Early Recanalization Sustained at 3 Months?: A Prospective Cohort Study
Lise A. Labiche, Fahmi Al-Senani, Anne W. Wojner, James C. Grotta, Marc Malkoff and Andrei V. Alexandrov

Stroke. 2003;34:695-698; originally published online February 13, 2003;
doi: 10.1161/01.STR.0000055940.00316.6B
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/34/3/695

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/