Early Dramatic Recovery During Intravenous Tissue Plasminogen Activator Infusion

Clinical Pattern and Outcome in Acute Middle Cerebral Artery Stroke

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Background and Purpose—Acute-stroke patients receiving standard intravenous tissue plasminogen activator (tPA) have been noted to experience early dramatic recoveries. The prevalence, clinical characteristics, and outcome of patients experiencing dramatic recovery is not well described.

Methods—We prospectively studied all patients presenting with acute middle cerebral artery (MCA) stroke syndromes and transcranial Doppler (TCD) evidence of an MCA obstruction. All patients received intravenous tPA per the National Institute of Neurological and Communicative Disorders and Stroke protocol, with serial National Institutes of Health Stroke Scale (NIHSS) scores and continuous TCD monitoring. Dramatic recovery was defined as an improvement of ≥10 NIHSS points or a decrease to an NIHSS score of ≤3 by the end of infusion. Outcome at the end of infusion, at 24 hours, and at long-term follow-up were obtained. The timing and pattern of deficit recovery during dramatic recovery was also studied.

Results—Dramatic recovery occurred in 22% of all patients. Compared with patients who did not experience dramatic recovery, those patients who did had significantly lower end-infusion NIHSS (median 2 and range 0 to 16 for dramatic-recovery patients versus median 17 and range 6 to 35 for non–dramatic-recovery patients, \( P<0.01 \)) and 24-hour NIHSS (median 2 and range 0 to 16 for dramatic-recovery patients versus median 13 and range 2 to 35 for non–dramatic-recovery patients, \( P<0.01 \)). A long-term modified Rankin Score benefit was noted (median 1 and range 0 to 6 for dramatic-recovery patients versus median 4 and range 0 to 6 for non–dramatic-recovery patients, \( P<0.01 \)). Baseline clinical characteristics were similar. The only difference was improved TCD-determined flow values at the end of infusion (normal restoration of flow was 58% in dramatic-recovery patients versus 14% in non–dramatic-recovery patients, \( P<0.01 \)). A characteristic pattern of recovery of deficit was noted.

Conclusions—Early dramatic recovery in acute MCA stroke patients treated with intravenous tPA is relatively frequent. The benefit of dramatic recovery is maintained at 24 hours and over the long term. TCD monitoring suggests that dramatic recovery is a result of early restoration of MCA flow during the tPA infusion. The consistent pattern of early clinical recovery may help explain the mechanisms by which thrombolysis improves outcome and could suggest targets for enhancing the therapeutic effect of intravenous tPA. (Stroke. 2002;33:1301-1307.)

Key Words: recovery of function ■ thrombolytic therapy ■ ultrasonography

Resolution of chest pain and improvement on ECG are often observed during or shortly after successful intravenous thrombolytic therapy for myocardial infarction. When intravenous tissue plasminogen activator (IV-tPA) was applied to treat ischemic stroke, the National Institute of Neurological and Communicative Disorders and Stroke (NINDS) rt-PA Stroke Study reported a lack of significant early neurological improvement at 24 hours after treatment, whereas benefit from thrombolysis was noted at 90 days.\(^1\) However, there have been reports of early dramatic recovery associated with recanalization by transcranial Doppler (TCD) and angiography.\(^2,3\) Characteristics of patients who experience dramatic recovery (dramatic-recovery patients) and the mechanisms of recovery are not well described, especially for those patients who have an ultra-early recovery during IV-tPA infusion.

A post hoc analysis of the NINDS trial suggested that an early benefit might have occurred in some patients depending on how dramatic recovery is defined.\(^4\) Furthermore, it is not clear whether the early dramatic recovery in the NINDS trial was maintained at 90 days. It is possible that at long-term follow-up, those who did not experience this dramatic recov-
ery (non–dramatic-recovery group) may “catch up” with the dramatic-recovery patients in terms of reduction of the neurological deficit.

We have observed a stereotypical time course and pattern of deficit recovery when early dramatic recovery occurs in patients with acute middle cerebral artery (MCA) stroke syndromes.² This consistent pattern of early clinical recovery, previously published as anecdotal case reports,³ may provide a clue to the mechanisms by which thrombolysis improves outcome and could represent a target for the enhancement of therapeutic effect.

We set out to capture the frequency, characteristics, flow dynamics, and clinical course of patients with acute MCA stroke syndromes who experienced dramatic recovery during IV-tPA infusion compared with non–dramatic-recovery patients.

**Subjects and Methods**

We prospectively studied consecutive patients who experienced acute MCA stroke syndromes, had terminal internal carotid artery (ICA) or first-segment (M1) or second-segment (M2) MCA occlusion documented on baseline TCD, and received IV-PA therapy according to published guidelines.⁴ Patients who were entered into other treatment-based research protocols, including intravenous thrombolysis, or those who did not have a TCD were excluded. At our center, TCD is performed in most patients at bedside in the emergency room to identify and localize the offending occlusion and to monitor clot lysis when it occurs. The technique and accuracy of TCD screening for arterial occlusion in acute stroke have been previously published.⁷

Dramatic recovery was defined as an improvement of ≥10 National Institutes of Health Stroke Scale (NIHSS) points or an improvement to ≤3 NIHSS points at the end of the hour-long infusion,² ⁴ All patients had bedside serial or continuous TCD monitoring and received a baseline and end-of-infusion Thrombolysis in Brain Ischemia (TIBI) scale score.⁵ The TIBI scale is a TCD tool that defines the degree of flow in acute arterial obstruction similar to the concept of the Thrombolysis in Myocardial Ischemia (TIMI) flow-grading system for angiography. The TIBI system was validated against cerebral angiography in patients receiving thrombolysis: a TIBI score of 0 to 1 indicates complete lack of flow; a score of 2 to 3 indicates partial occlusion; and a score of 4 to 5 indicates complete recanalization with sensitivity of 91% and specificity of 93% for the MCA.⁵ We have previously published our inclusion methods and prospectively validated our TCD criteria for the diagnosis of occlusion and recanalization.⁷ The TCD was interpreted by an attending level–experienced neurosonologist.

A member of our stroke team not involved in TCD and certified in the use of NIHSS performed NIHSS scoring at baseline, at the end of infusion, and at 24 hours. A long-term modified Rankin Score (mRS) was obtained through outpatient visit or directed telephone interviews. Death was ranked as an mRS of 6.

The pattern and timing of clinical response and recovery of neurological deficits were recorded by additional NIHSS scoring during infusion, and the pattern and sequence of recovering signs were determined by analysis of the subcomponents of the NIHSS. A fellowship level stroke neurologist monitored the patient during infusion. As improvements in baseline deficits of the subcomponents of the NIHSS were observed, the ranked order of deficit recovery was noted. Exact timing of the recovery of deficits was not recorded. At the end of infusion, a complete NIHSS was recorded. Deficit recovery was ranked as “none” if no change had occurred in the NIHSS subcomponent, “partial” if there was ≥1 point change but deficit remaining at the end of infusion, and “complete” if the score resolved to 0 in that subcomponent.

Statistical methods included mean, SD, and Student t test for parametric measures. A χ² analysis (3×4 χ², 57 df) was used to compare TCD-determined degree of flow restoration. For nonparametric measures (NIHSS and mRS), median, range, and the Wilcoxon 2-sample test were used to determine significance.

**Results**

From September 1998 through June 2000, 53 of 123 IV-tPA–treated patients were identified as meeting inclusion criteria. The location of arterial occlusion in this group was terminal ICA in 14 (26%) patients, M1 MCA in 28 (53%) patients, and M2 MCA in 11 (21%) patients. Dramatic recovery was observed in 12 (22%) of 53 patients. Location of arterial lesions in the dramatic-recovery group was as follows: terminal ICA in 3 (25%) patients, M1 MCA in 7 (58%) patients, and M2 MCA in 2 (17%) patients. The location of arterial lesion in the non–dramatic-recovery group (n=41) was as follows: terminal ICA in 11 (27%) patients, M1 MCA in 21 (51%) patients, and M2 MCA in 9 (22%) patients. The dramatic-recovery group and non–dramatic-recovery group were equivalent in age (68±17 years for dramatic-recovery group versus 70±15 years for non–dramatic-recovery group, P=0.75 [not significant]) and baseline NIHSS score (Table). The time to bolus showed a nonsignificant trend toward earlier treatment in the dramatic-recovery group (114±44 minutes for the dramatic-recovery group versus 127±30 minutes for the non–dramatic recovery group, P=0.24 [not significant]). There was no noted difference in CT scan characteristics (data not shown). The etiology of stroke in the dramatic-recovery group was cardioembolism in 8 (67%) of 12 patients, large-vessel arteriosclerosis in 3 (25%) of 12 patients, and undetermined in 1 (8%) of 12 patients. In the non–dramatic-recovery group, the etiology of stroke was cardioembolism in 21 (51%) of 41 patients, large-vessel atherosclerosis in 8 (20%) of 41 patients, arterial dissection in 2 (5%) of 41 patients, and undetermined in 10 (24%) of 41 patients.

At the end of infusion, the dramatic-recovery group showed a significant improvement in NIHSS (Table). This difference was still seen at 24 hours. Dramatic-recovery patients had continued mRS benefit at long-term follow-up (Table). Follow-up occurred at 1.6±1.7 months. (For patients who died, the date of death was considered time to follow-up.)

The extent of MCA occlusion by TCD criteria was equivalent at baseline (Figure 1). At the end of infusion, complete restoration of normalized flow was significantly improved in the dramatic-recovery group (Figure 1).

There was a consistent pattern and time course of recovery observed during the infusion (Figure 2). Certain deficits were recovered early during infusion, and there was a complete...
Dramatic recovery during IV-tPA infusion occurred in 22% of all patients with acute MCA syndrome and terminal ICA, M1, or M2 occlusion documented by TCD. This is similar to a previous report of consecutive patients treated with tPA previously reported by our center.2 The present study focused only on MCA strokes; it reports 24-hour and long-term outcome and describes the clinical pattern of recovery. The improved outcome of dramatic recovery was sustained at 24 hours and appears to be sustained at long-term follow-up. The present study revealed that dramatic recovery in acute MCA stroke syndromes followed a consistent clinical pattern and time course of symptom resolution and was related to restoration of flow by TCD criteria.

At baseline, our cohort was more severely affected than the NINDS trial participants by 3 to 4 NIHSS points (median NIHSS 18), consistent with the notion that MCA distribution strokes with arterial occlusion observed on TCD are at the severe end of the clinical spectrum.1 The dramatic-recovery group characteristics were similar to the non–dramatic-recovery group at baseline (Table), and these groups had a similar baseline degree of arterial occlusion (Figure 1).

It was not possible to predict which patients would experience a dramatic recovery. Although there was a nonsignificant trend toward earlier treatment in the dramatic-recovery group, the only difference noted was the improvement of TIBI flow grades at the end of infusion (Figure 1). This suggests that dramatic recovery is the consequence of flow restoration. Previous reports suggest that early recanalization occurs in 30% of all IV-tPA–treated patients and precedes dramatic recovery.2,3,8

Patients who experience dramatic recovery have a significantly better outcome. At 24 hours, their stroke tended to be mild with a median NIHSS of 2 (range 0 to 16). The non–dramatic-recovery group remained severely affected at 24 hours (median NIHSS 13, range 2 to 35; P < 0.01). Most important, at long-term follow-up, the average dramatic-recovery patient had recovered to relative independence with a median mRS of 1 (range 0 to 6). Conversely, the non–dramatic-recovery patient tended to be significantly disabled at follow-up (mRS 4, range 0 to 6; P < 0.01), as shown on the Table.

A surprising observation is that there was only minimal improvement of the NIHSS in the dramatic-recovery and non–dramatic-recovery groups between end infusion and 24 hours (Table). This suggests that when strokes are due to a terminal ICA, M1 MCA, or M2 MCA occlusion, most early improvement is related to immediate restoration of flow that occurs during the tPA infusion. We did not monitor NIHSS after 24 hours, but in the NINDS trial, substantial improvement in the NIHSS occurred between 24 hours and 3 months. However, because the difference between our dramatic-recovery and non–dramatic-recovery patients was still present in mRS at follow-up and because non–dramatic-recovery patients had poor long-term mRS, it is likely that such delayed improvement was not substantial in the non–dramatic-recovery group. This confirms that the best chance for recovery in severely affected stroke patients with MCA occlusion is to get the artery open rapidly.
Therefore, our results reinforce recent data supporting the importance of speeding thrombolysis by earlier treatment. Furthermore, ultrasound-enhanced thrombolysis may shorten the time required for early recanalization. In patients with persisting occlusion and lack of clinical recovery, the role of intravenous therapy followed by intra-arterial techniques may also improve outcome. Because recanalization during the IV-tPA infusion appears to be correlated with good outcome, it is conceivable that halting the IV-tPA infusion when recanalization is detected by TCD could potentially result in a lesser total dose of tPA and a decreased rate of intracerebral hemorrhage.

The consistent time course and pattern of dramatic recovery is intriguing. Certain deficits were recovered earlier than others in a predictable pattern. We also noted that the deficits that tended to recover earlier tended to recover completely (Figure 2). These patients all had MCA syndromes with TCD-confirmed occlusions. Only 2 of 12 dramatic-recovery patients had occlusion of the terminal ICA. All others had patent anterior cerebral arteries (ACAs) by TCD criteria. As the clot lysed, a stepwise return of flow from the proximal to distal MCA is observed, leading to TIBI flow grade improvement. This predictable event suggests 2 alternative theories as to the mechanism of early dramatic recovery.

The first of these models involves restoration of collateral flow during clot dissolution or clot migration to distal branches (Figure 3). The deficits that recover early (gaze deviation, leg strength, and sensory loss) are cortically represented in regions abutting border-zone perfusion with the ACA and posterior cerebral artery. Although there was no evidence of ACA involvement by TCD criteria in 10 of 12 patients, it is possible that the most proximal aspect of the thrombus was partially obstructing collateral channels. As the most proximal portion of the thrombus was lysed, collateral flow was restored. The regions in the border zone are reperfused first, followed by cortical regions located more centrally in the ischemic penumbra. In a typical M1 MCA occlusion, leg motor strength and language might be located in the core of this region, explaining the lack of early recovery.

The second model of dramatic recovery involves the small perforators originating from the M1 MCA and terminal ICA and supplying the internal capsule and thalamus (Figure 4). As the proximal region of the thrombus is lysed, flow is restored directly to the perforators that, in turn, restore function to the thalamus and internal capsule. The functional anatomy of the internal capsule is controversial and may be variable. In general, descending fibers from the frontal eye field are represented in the anterior limb and motor fibers are represented in the posterior limb of the internal capsule.

As the small perforators are restored (positive diastolic flow at the depths corresponding to the M1 MCA origin, TIBI grades 2 to 3), a stepwise return in function of anterior and posterior limbs of the internal capsule as well as the thalamus may occur. This could explain the clinical pattern of recovery (gaze, motor, and sensory) and why cortical functions such as language recovered later during the infusion. Based on clinical neuroanatomic correlation, the internal capsule would seem to recover function from a lateral to medial pattern. Although this is counterintuitive, the variable anatomy of the arterial supply to these regions and the significance of supply from terminal ICA and ACA perforators may further contribute to different patterns and time course of dramatic recovery.

Further characterization of the mechanism of dramatic recovery will require real-time serial regional cerebral perfusion measurements performed in a prospective and controlled manner. Ideally, serial or real-time perfusion and diffusion imaging would be performed by using MRI or xenon-CT techniques. Unfortunately, current cerebral perfusion techniques are often difficult to carry out in acute-stroke patients undergoing thrombolysis and have limited availability. Recent evidence suggests that transcranial color-coded duplex, contrast agents, and harmonic perfusion imaging can measure cerebral perfusion and may represent a feasible research tool.

Defining the mechanisms of recovery has several implications. If collateral flow is found to be contributory, techniques to increase collateral flow, such as avoiding hypotension, induced hypertension (in select cases), hyperoncotic intravascular volume expansion, may help recovery. With the small perforator model, mechanisms to augment clot dissolution, such ultrasound enhanced thrombolysis or combined intravenous and intra-arterial therapy, may prove effective in improving outcome.

The present study had several potential limitations. Patients were included only if they had a baseline TCD. This would exclude the $15\%$ of patients in whom TCD windows are not available. These patients tend to be elderly, to have renal failure–induced calcium disorders, or to be members of minorities, potentially skewing results. In addition, our cohort represents a nonrandomized select population. The actual incidence of dramatic recovery may be less prevalent in the general acute-stroke population. Also, the ranking and timing (but not the exact timing) of deficit recovery were noted. The exact timing of recovery would be useful in future applications and might allow clinicians to pick a specific time frame at which dramatic recovery could be expected and help to drive decisions as to when to become more aggressive with therapy. Finally, long-term follow-up was performed at different times for various patients, sometimes via the use of directed telephone interviews. Future studies investigating long-term outcome in a more controlled fashion are needed before drawing final conclusions.

In summation, dramatic recovery during IV-tPA infusion is a relatively frequent occurrence in patients with acute MCA strokes and occurs because of the early restoration of flow during tPA infusion. The benefit of dramatic recovery was maintained at 24 hours and appears to be maintained at long term. Recovery followed a consistent time course and clinical pattern that might help explain the mechanisms of recovery and provide targets to enhance the effect of IV-tPA therapy.

**Acknowledgments**

Drs Felberg, Okon, and Burgin and the University of Texas-Houston Medical School cerebrovascular fellowship were supported by National Institutes of Health (NIH) training grant T32-NS-07412. Dr El-Mitwalli was supported by an Egyptian Government grant for
Figure 3. Collateral flow model of dramatic recovery. Figure 3 is modified from Essentials of Clinical Neuroanatomy and Neurophysiology.11
Figure 4. Perforator model of dramatic recovery. Figure 4 is modified from Neuroanatomy: Text and Atlas.²⁰
postdoctoral studies. Dr Alexandrov was supported by an NIH 1-K-23-02229-01 Career Development Award.

References


