Thrombolysis in Patients With Marked Clinical Fluctuations in Neurologic Status Due to Cerebral Ischemia

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Background: It is unclear whether thrombolysis benefits patients with fluctuating neurologic symptoms.

Objective: To evaluate the clinical course of patients with acute stroke who presented with marked fluctuations in neurologic status and received thrombolytic therapy.

Design: Prospective analysis.

Setting: London Health Science Centre University Hospital, London.

Patients: We prospectively identified patients who were treated with intravenous or intra-arterial recombinant tissue plasminogen activator between January 1, 2004, and January 1, 2006. For this analysis, we chose patients who had marked fluctuation in neurologic status at presentation and who received thrombolytic therapy.

Main Outcome Measure: Fluctuation of neurologic deficits, defined as a 4-point or greater increase or decrease in the National Institutes of Health Stroke Scale (NIHSS) score.

Results: Among 127 patients, 13 (10.2%) had clinical fluctuations. Patients with fluctuations presented with a lower NIHSS score (median, 7; interquartile range, 10-17) compared with patients without fluctuations (median, 12; interquartile range, 10-17) (P < .001). Fluctuation of symptoms or signs ceased after thrombolysis. At 24 hours after stroke, the median NIHSS score was 2 (range, 1-12). All patients had favorable neurologic and functional outcomes at 3 months after thrombolysis (modified Rankin scale score, 0-2).

Conclusion: Thrombolysis may benefit patients with fluctuating symptoms or signs due to cerebral ischemia.

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Fluctuation in neurologic status in the immediate phase of cerebral ischemia is common. Up to 15% of patients with anterior circulation infarctions have an unstable course in the first 24 hours after stroke. For those who presented within the therapeutic time window, it is unclear whether they benefit from thrombolytic therapy. We report our experience with thrombolytic therapy in patients who presented with marked clinical fluctuation in neurologic status due to cerebral ischemia.

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The postthrombolytic diagnostic workup consisted of 12-lead electrocardiography, carotid ultrasonography NCCT and CTA, MRI and MRA, transthoracic echocardiography, transesophageal echocardiography, and 24-Holter monitoring whenever indicated. Stroke type was determined using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) trial criteria after the diagnostic workup was completed. Neurologic and
The acute ischemic stroke. Favorable outcome at 3 months was defined as an mRS score of 2 or less.

In the study, 127 patients received thrombolysis, of whom 13 (10.2%) had clinical fluctuations. Table 1 gives the baseline characteristics and outcomes of patients with and without fluctuations. Table 2 gives the detailed clinical presentations and outcomes of patients with fluctuations. No differences were found in age, sex, vascular risk factors, and time from symptom onset to rt-PA administration between patients who presented with and those who presented without clinical fluctuations (Table 1). The median baseline NIHSS score was lower in patients with fluctuations compared with patients without fluctuations (7 vs 12; \( P < .001 \)). The median number of fluctuations was 4, and the difference between the maximum and minimum NIHSS score ranged from 5 to 17 during fluctuations. The mean (SD) time from symptom onset to intravenous thrombolysis treatment was 171 (64) minutes (range, 80-300 minutes) in 12 patients with fluctuations. Intra-arterial rt-PA was initiated at 240 minutes in 1 patient with fluctuation who did not receive intravenous rt-PA.

Ten patients with fluctuations had anterior circulation stroke: 2 had lacunar stroke, 3 had tandem internal carotid artery and middle cerebral artery occlusions, 1 had a proximal middle cerebral artery occlusion, and 4 had possible middle cerebral artery branch occlusions. Three patients with fluctuations had basilar artery thrombosis. Follow-up cranial MRI or CT, performed 24 hours after the initial event, revealed ischemic infarction in all patients with fluctuation. One patient with fluctuation had asymptomatic petechial hemorrhage on follow-up MRI. The median 24-hour NIHSS score was 2 (range, 1-12). No patient with fluctuation died or had recurrent stroke during the 3-month follow-up. Patients with fluctuations had a more favorable outcome compared with patients with nonfluctuating symptoms at 90 days. Of the 13 patients with fluctuations, 13 (100.0%) had a favorable neurologic outcome compared with patients with nonfluctuating symptoms (7 vs 12; \( P < .001 \)).

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outcome (mRS score, ≤2) compared with 68 of 114 patients (59.6%) without fluctuations (P = .004).

COMMENT

Of patients receiving thrombolytic therapy, 10.2% had clinical fluctuations during the immediate stage of stroke. Patients with fluctuations presented with a lower baseline NIHSS score and had a more favorable outcome at 90 days after stroke compared with patients with non-fluctuating symptoms. Neurologic and functional recovery was favorable at 3 months in all patients. Most patients with fluctuations (10 of 13 patients) had had large-artery occlusions.

The incidence of fluctuations within the first 6 hours after symptom onset in patients with acute ischemic stroke is unclear. The proportion of patients with fluctuating deficits in our study is consistent with that in other studies. O’Connor et al3 showed improvement of deficit in 14% of patients during the immediate stage of stroke. In a transcranial Doppler study, a deterioration (defined as an NIHSS score of ≥4) occurred in 16% of patients who presented with a spontaneously resolving deficit (defined as an NIHSS score of <4 within the 6 hours after symptom onset). The presence of large-vessel occlusion regardless of the cause was strongly associated with spontaneous early deterioration, followed by improvement in patients who did not receive rt-PA.4

Fluctuating deficits in the immediate phase of ischemic stroke may be related to several mechanisms. Spontaneous recanalization of the vessel and the presence of sufficient compensatory brain collateral flow are potential causes. In contrast to spontaneous improvement, spontaneous deterioration may be due to propagation of the thrombus, decrease in collateral flow, or subsequent thrombosis in a partially recanalized vessel. Progressive evolution of the infarct core may also cause progression during the acute stroke.

Of the 13 patients with lacunar syndromes, 2 presented with motor fluctuations during their emergency. Donnan et al2 initially described the term as capsular warning syndrome and defined it as multiple stereotypic transient ischemic attacks (TIAs) preceding capsular infarction. Several different hypotheses were proposed to explain the repetitive nature of presentation of patients preceding lacunar infarctions. Small penetrating vessel disease due to lipohyalinotic or atheromatous disease and superimposed thrombus may play a role in the mechanism of crescendo TIAs that occur during lacunar infarctions. Recanalization of occluded penetrating arteries after thrombolysis may prevent further evolution of the lacunar infarct. This procedure may have led to cessation of fluctuations and subsequent neurologic improvement in our 2 patients with lacunar infarctions. On the other hand, hemodynamic factors, such as excessive reduction in blood pressure or systemic hemorheologic changes in the blood, may lead to hypoperfusion in the territories of deep penetrating arteries and, hence, contribute to stereotyped clinical fluctuations in these patients. Optimization of blood volume and blood pressure may prevent expansion of infarction.

Patients who had clinical fluctuations may fit into the conventional definition of crescendo TIAs. However, in our study, all patients with fluctuations ended up with radiologically proved cerebral infarction. Despite this, remarkably good neurologic outcome was observed after thrombolysis in all patients at 3 months. Coutts et al8 demonstrated that patients with a minor stroke and a TIA with a lesion on diffusion-weighted imaging and a large-artery stenosis had a 32% chance of disease recurrence within 90 days vs an 11% risk with diffusion-weighted imaging abnormalities alone. Our patients did not have any recurrent stroke or TIA within 90 days after acute stroke.

During the immediate phase of the ischemic event, clinical fluctuations may be an indicator of plaque or thrombus instability. Therefore, early investigation, such as CTA and MRA and/or MRI and CT perfusion study, may be useful in determining the extent of ischemia in patients with clinical fluctuations. Several limitations apply to our study. The present study only included a few patients. In addition, we did not collect information about patients with fluctuations who did not receive thrombolytic therapy. Our observation suggests that withholding or delaying thrombolytic therapy in patients with fluctuations is not warranted.

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REFERENCES