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Poor Outcomes in Patients Who Do Not Receive Intravenous Tissue Plasminogen Activator Because of Mild or Improving Ischemic Stroke

Eric E. Smith, MD, FRCPC; Abdul R. Abdullah, MD; Iva Petkovska, MD; Eric Rosenthal, MD; Walter J. Koroshetz, MD; Lee H. Schwamm, MD

Background and Purpose—Some patients with mild or improving ischemic stroke symptoms do not receive intravenous tissue plasminogen activator (tPA) because they look “too good to treat” (TGT); however, some have poor outcomes.

Methods—We retrospectively analyzed data from a prospective single-center study between 2002 and 2004. TGT patients were those arriving within 3 hours of symptom onset and not treated with intravenous tPA solely because of mild or improving symptoms.

Results—Of 128 patients presenting within 3 hours, 41 (34%) were not given tPA because of mild or improving stroke. Of the TGT patients, 11 of 41 (27%) died or were not discharged home because of neurological worsening (n=6) or persistent “mild” neurological deficit (n=5). No single variable at presentation was associated with death or lack of home discharge. There were 10 of 41 TGT patients (24%) who had ≥ 4 -point improvement in National Institutes of Health Stroke Scale score before tPA decision; these patients were more likely to have subsequent neurological worsening (relative risk, 4.1, 95% CI, 1.1 to 15.4; $P=0.05$).

Conclusion—A substantial minority of patients deemed too good for intravenous tPA were unable to be discharged home. A re-evaluation of the stroke severity criteria for tPA eligibility may be indicated. (*Stroke*. 2005;36:2497-2499.)

Key Words: angiography ■ computed tomography ■ outcome ■ stroke, acute ■ tissue plasminogen activator

In ischemic stroke patients with mild symptoms and perceived excellent prognosis, some physicians decide against intravenous tissue plasminogen activator (tPA) administration because of the risk of hemorrhage. Previous studies suggest that 29% to 43% of ischemic stroke patients arriving within 3 hours are not treated with tPA solely because of mild or improving symptoms.¹⁻⁴ In a single study, 32% of such patients died or could not be discharged home, calling into question the decision not to treat.¹

Materials and Methods

We analyzed 431 consecutive ischemic stroke discharges collected at our institution as part of the Paul Coverdell National Acute Stroke Registry Pilot Prototype (March 1, 2002, to July 31, 2002) and the Get With the Guidelines Stroke Pilot (January 1, 2003, to March 31, 2004). For those who arrived within 3 hours of symptoms but were not treated with intravenous tPA, the reason for exclusion was assigned retrospectively by a study physician on the basis of chart documentation by the treating vascular neurologist. The reason for exclusion was documented in 67 of 71 (94%) cases. We selected those patients who did not receive intravenous tPA solely because of mild or improving stroke (patients who were “too good to treat” [TGT]).

All TGT patients underwent nonenhanced computed tomography scan followed by computed tomography angiography (89%), magnetic resonance angiography (10%), or catheter angiography (1%).

By protocol, vascular imaging was not allowed to delay intravenous tPA administration. Vascular occlusion was defined as a partial or complete arterial-filling defect attributed to thrombus. Stroke pathophysiology was assigned using modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria,⁷ grouping patients with cardioembolism and cryptogenic embolism into 1 category called proximal-source embolism.

We defined early rapid improvement (RI) as a ≥ 4 -point National Institutes of Health Stroke Scale (NIHSS) score improvement from time of initial evaluation to time of tPA decision,⁵ and neurological worsening as a ≥ 2 -point worsening in NIHSS score from time of tPA decision to time of hospital discharge.⁶ The primary outcome was the proportion of patients unable to be discharged home.

Analysis of proportions was by Fisher exact test, whereas continuous variables were analyzed by *t* test or Wilcoxon rank sum test as appropriate. A logistic regression model was used to identify factors associated with the decision to withhold tPA.

Results

In 71 ischemic stroke patients with symptom duration of < 3 hours, TGT was the most common reason for exclusion from intravenous tPA treatment (41 of 71; 58%). NIHSS score improved ≥ 1 point from emergency department arrival to tPA decision time in 21 of 41 TGT patients (51%), and in those patients, the median NIHSS score decreased from 5 (range 2 to 21) to 3 (range 0 to 5). Stable mild stroke symptoms were

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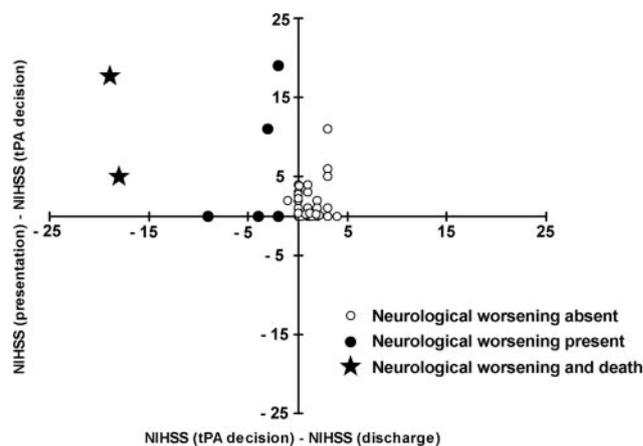
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observed in 20 of 41 TGT patients (49%), with median NIHSS score of 3 (range 0 to 5). TGT patients were less likely than tPA-treated patients to have vascular occlusion (8 of 41 versus 38 of 50; $P<0.001$) and more likely to have strokes attributable to small vessel infarction (10 of 41 versus 3 of 50; $P=0.02$). Vascular occlusion was visualized in 8 TGT patients: middle cerebral artery (MCA) M1 (4), MCA M2 branch (1), terminal internal carotid artery (ICA; 1), posterior cerebral artery P2 branch (1), and vertebral artery (1). In a logistic regression model including the variables RI, NIHSS score at the time of tPA decision, and the presence of vascular occlusion, the only independent predictor of the decision to withhold tPA was NIHSS score at the time of tPA decision.

There were 11 TGT patients who were not discharged home (Table). Neurological worsening ($n=6$) or persistent neurological deficit ($n=5$) was the reason for inability to be discharged home, rather than any medical complication. Those with persistent neurological deficit had cognitive impairment ($n=1$), gait impairment attributable to hemiparesis ($n=2$), or ataxia ($n=2$). Premorbid disability was not related to lack of home discharge; the 2 patients with premorbid modified Rankin score of >0 were able to be discharged home. Care was withdrawn in 2 TGT patients resulting in death. Both had right ICA stenosis with embolism to the right MCA; each initially had RI but subsequently worsened with the development of large MCA territory infarctions.

NIHSS score changes in TGT patients from the time of arrival to the time of tPA decision and hospital discharge are graphed in the Figure. TGT patients with RI were more likely than those without RI to have vascular occlusion (5 of 10 versus 3 of 31; $P=0.01$) and strokes attributable to proximal-source embolism or large artery atherosclerosis (10 of 10



Changes in NIHSS score from presentation to time of intravenous tPA decision and time of hospital discharge in TGT patients. NIHSS score improvement from time of presentation to time of intravenous tPA decision is graphed on the y axis; NIHSS score improvement from time of intravenous tPA decision to time of hospital discharge is graphed on the x axis. The top left quadrant represents patients who had NIHSS score improvement before decision not to administer intravenous tPA, followed by NIHSS score deterioration during the hospital stay. Patients with neurological worsening (see text for definition) or death are represented by black circles and black stars, respectively.

versus 21 of 31; $P=0.05$). Five patients had RI and visualized vascular occlusion, including 3 whose vascular imaging was performed after they had improved clinically.

Neurological worsening after the decision to withhold tPA was seen in 7 TGT patients (Figure), 4 of whom had RI. In all cases, worsening was attributable to increased deficits referable to the same initial vascular territory rather than hemorrhagic transformation or recurrence in a new vascular territory. RI was the only feature that was associated with subsequent neurological worsening (relative risk, 4.1; 95% CI, 1.1 to 15.4; $P=0.05$). The 3 patients with neurological worsening without RI all had small vessel infarctions.

Characteristics of Patients Who Could Not Be Discharged Home After Decision to Withhold tPA

Characteristic	No Home Discharge (n=11)	Home Discharge (n=29)	P Value
	No. (%)	No. (%)	
Age, mean±SD	73.2±11.7	67.5±13.2	0.22
Female gender	7 (64)	10 (34)	0.15
Initial NIHSS score	5 [2, 13]	3 [2, 4]	0.15
NIHSS at tPA decision	2 [1, 4]	2 [1, 3]	0.44
RI	4 (36)	6 (21)	0.42
Vascular occlusion	4 (36)	4 (14)	0.18
Stroke etiology			
Proximal-source embolism	7 (63)	17 (59)	
Large artery	2 (18)	4 (14)	0.79
Small vessel	2 (18)	8 (28)	
Neurological worsening	6 (55)	1 (3)	<0.001
NIHSS score at discharge*	2 [2, 4]	1 [0, 1]	<0.001
Modified Rankin Scale score <1	1 (9)	24 (83)	<0.001

Continuous variables are median [interquartile range] unless otherwise noted. One patient was admitted from a nursing home and was excluded.

*Excluding 2 patients who died.

Discussion

We found that a substantial number of TGT patients were unable to be discharged home based on the degree of neurological disability (Table). We did not find any patient characteristics at the time of initial evaluation that predicted discharge destination (Table), although there was a trend for an association with visualized vascular occlusion ($P=0.18$) and NIHSS score at emergency department arrival ($P=0.15$).

RI appears to confer a risk of subsequent neurological worsening, consistent with data from clinical trials showing that patients with substantial early recovery⁸ or clinical transient ischemic attack⁹ were at greater risk of subsequent neurological deterioration. We note that 3 of 5 RI patients with visualized vascular occlusion had imaging performed after clinical improvement, suggesting that adequacy of collateral flow may be a critical factor in the clinical outcome in these patients. Despite the association of RI with neurological worsening, most RI patients (6 of 10) were still able to be discharged home (Table).

There are several limitations of this study. Blinded assignment of study variables was not performed because the

treating physicians had access to all clinical data when making decisions that could have influenced the outcome. We do not have longer-term outcomes for our cohort, leaving open the possibility that some patients who were dependent at hospital discharge recovered independence by 90 days; however, inability to go home at discharge is an important outcome for patients, families, and physicians. Finally, we note that this is a single-center study with a relatively small sample size.

Based on these data, a re-evaluation of the stroke severity criteria for intravenous tPA administration may be warranted. Future studies should account for the heterogeneity in the reasons why patients cannot be discharged home, and should consider incorporating an assessment of gait as a potential predictor of poor short-term outcomes. These studies are needed before recommending any alterations to current practice.

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