Thrombolysis in Young Adults With Ischemic Stroke

Jukka Putaala, MD; Tiina M. Metso, MD; Antti J. Metso, MD, PhD; Elina Mäkelä, MD; Elena Haapaniemi, MD, PhD; Oili Salonen, MD, PhD; Markku Kaste, MD, PhD; Turgut Tatlisumak, MD, PhD

Background and Purpose—No exclusive systematic data exist on the safety and outcomes of thrombolytic treatment in young patients with ischemic stroke.

Methods—We evaluated all 48 patients aged 16 to 49 years with hemispheric ischemic stroke treated with intravenous alteplase in Helsinki University Central Hospital from 1994 to 2007. For comparison of outcome, we selected, blinded to outcome data, 96 control subjects (1:2) with ischemic stroke not treated with alteplase matched by age, gender, and admission stroke severity (National Institutes of Health Stroke Scale). We selected similarly 96 older alteplase-treated gender and arrival National Institutes of Health Stroke Scale score-matched patients (aged, 50 to 79 years) for comparison of outcome and hemorrhage rate. A 3-month favorable outcome was defined as modified Rankin Scale score of 0 to 1. Symptomatic intracerebral hemorrhage was defined according to the Safe Implementation of Thrombolysis in Stroke Project Study.

Results—Young alteplase-treated patients (67% males; mean age, 38.8 ± 9.1 years) more often recovered completely (27% versus 10%, P = 0.010) and achieved a favorable outcome (40% versus 22%, P = 0.025) compared with their age-matched control subjects not treated with alteplase. In alteplase-treated patients, unfavorable outcome was more frequent in males and in those with carotid artery dissection. We observed no difference in outcome between cases and older control subjects treated with alteplase. However, none of the cases had symptomatic intracerebral hemorrhage versus 3 (3%) in the older control group (P = 0.551). Mortality rate was 2% (P = 0.552) in age-matched control subjects and 7% (P = 0.095) among older control subjects, whereas none of the case patients died during the 3-month follow-up.

Conclusions—Young adults with acute hemispheric ischemic stroke benefited from intravenous thrombolysis with good safety. (Stroke. 2009;40:2085-2091.)

Key Words: cerebral infarction ■ safety ■ stroke in young adults ■ thrombolytic therapy ■ treatment outcome

Stroke in young adults may have devastating consequences with respect to quality of life and work ability. Although it is universally well recognized that they have better chances of surviving a stroke and achieve better recovery than older individuals, young adults often have neuropsychological or social sequel, and a substantial proportion of them are not able to return to work.1,2 Intravenous thrombolysis with alteplase (recombinant tissue plasminogen activator) given within 4.5 hours of onset of ischemic stroke improves outcome3-6 and it is widely accepted as a first-line treatment.

A subgroup analysis of National Institute of Neurological Disorders and Stroke (NINDS) trials suggested that younger patients (≤60 years) benefit more from thrombolysis when adjusted for stroke severity.7 Recently presented observational data from the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST) demonstrated that patients aged ≤45 years make better recovery with a lower rate of symptomatic intracranial hemorrhages (SICH) compared with older ones.8 The SITS-MOST data did not include a control group adjusted for age, however. Because of the generally better recovery as well as different risk factors and etiologic spectrum in younger patients, the safety and efficacy of intravenous alteplase are difficult to predict, and positive effects may remain modest. Therefore, we decided to investigate whether young patients benefit from thrombolysis compared with control subjects, matched by age and adjusted for stroke severity, but who were not treated with alteplase.

Patients and Methods

This study was approved by the local ethics committee and carried out at the Department of Neurology, Helsinki University Central Hospital. Our center serves as the only neurological emergency unit for a population of 1.5 million. We reviewed all medical records of consecutive patients aged <50 years treated with alteplase for acute hemispheric ischemic stroke from 1994 to 2007. Because we use a different protocol for patients with vertebrobasilar occlusion allowing treatment delays of up to 48 hours from symptom onset,9 these were excluded from the present study.
The first 2 young patients were treated with alteplase according to the protocols of the European–Australasian Cooperative Acute Stroke Study (ECASS) and ECASS II trials.10,11 The rest were evaluated and openly treated according to our institutional protocol,12 which is a modification of the American Heart Association guidelines13 with respect to the following main points: we have allowed treatment between 3 and 4.5 hours from symptom onset in the absence of CT-hypodensity of more than one third of the middle cerebral artery territory and considered thrombolysis in patients with mild or rapidly improving symptoms in the presence of a large perfusion deficit. We also have considered thrombolysis in patients who have very severe symptoms, a large visualized ischemic core, or unknown time of stroke onset in the presence of large salvageable penumbra visualized with perfusion techniques.

For the comparison of outcome, we searched age-matched control subjects in a prespecified 1:2 design from the Helsinki Young Stroke Registry, which comprises all patients aged 15 to 49 with first-ever ischemic stroke treated with intravenous alteplase from January 1994 to May 2007.14 We matched the control subjects to the alteplase-treated patients by age, gender, and National Institute of Health Stroke Scale (NIHSS) score. Blinded to outcome data, we selected the first matching control patient for each case and subsequently reviewed the patient records. Those with general per-protocol contraindications for thrombolysis other than late arrival or unknown time of stroke onset were excluded, and the next matching control patient was selected. Furthermore, we sought to compare outcome and rate of hemorrhagic events with older control subjects (1:2) aged 50 to 79 years with hemispheric stroke and treated with alteplase. They were selected correspondingly from our prospective thrombolysis register and matched by gender and admission NIHSS score. All patients received standard stroke care and secondary prevention following generally accepted recommendations.13

Demographic characteristics, risk factors, time delay from stroke onset to hospital arrival, baseline NIHSS and Glasgow Coma Scale, circulation territory, and stroke etiology were registered for each case and age-matched control subject. If the exact stroke onset time was unknown, we registered the latest time point when the patient was normal. A 3-month follow-up evaluation for survived patients included modified Rankin Scale (mRS) and was assessed for cases, age-matched control subjects, and older control subjects face to face (87%, 93%, and 85%, respectively) or by a telephone interview (13%, 7%, and 15%, respectively). Face-to-face assessment was done by neurologists at the outpatient clinic or by the treating personnel in case the patient was in a rehabilitation center. Telephone interviews were performed by stroke neurologists trained for the assessment of mRS. Additional clinical data registered for cases included blood glucose and blood pressure before thrombolysis as well as time delays from stroke onset to treatment.

For our 48 cases, 17 underwent CT angiography and one patient MRI and MR angiography with perfusion scan at admission. After the initial brain imaging, additional CT angiography of intracranial vessels, including a perfusion scan, were done in 12 patients before thrombolysis. One patient underwent additional MRI and MR angiography. Follow-up imaging using either CT or MRI was performed routinely after 22 to 36 hours (Day 1) from thrombolysis or earlier if the patient deteriorated. Older control subjects underwent routine imaging protocol, including follow-up imaging with either CT or MRI on Day 1. Because the gender and age and NIHSS score-matched control patients did not undergo routine follow-up imaging studies, the rate of hemorrhagic events was only compared with that of older control subjects.

All initial and follow-up CT and MRI studies of cases as well as initial and Day 1 imaging studies of alteplase-treated older control subjects were evaluated post hoc by senior neuroradiologist (O.S.) blinded to outcome data. The following neuroradiological data were recorded for cases: (1) early ischemic changes on CT or MRI at admission; (2) perfusion scan findings; (3) arterial occlusions on CT angiography or MR angiography; and (4) all intracerebral hemor- rhages (ICH) visualized after thrombolysis. For older control sub- jects, we registered ICHs on Day 1. ICHs were classified according to the criteria applied in the ECASS trials (Supplemental Table I, available online at http://stroke.ahajournals.org). If the ICH was associated with an overt clinical deterioration, NIHSS score was evaluated from the patient records at that moment. SICH was defined according to SITS-MOST4 as local or remote parenchymal hemor- rhage type 2 on the 22- to 36-hour posttreatment imaging combined with a neurological deterioration of >4 points on NIHSS from baseline stroke or from the lowest NIHSS value between baseline and 24 hours or leading to death.

Stroke subtype was classified by a pair of investigators (J.P. and E.M.) according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.15 The classification was based on review of all medical records. In case of discrepancy, a senior coauthor reviewed the records and the final categorization was based on consensus agreement of all coauthors. In case a NIHSS score was not available from the medical records, it was assessed by a single investigator (J.P.) based on the documented patient examination using a previ- ously published algorithm.16 Retrospective assessment of initial stroke severity with the NIHSS has been validated and shown to be reliable and unbiased.17

To allow comparisons between cases and control subjects, func- tional outcome was dichotomized in 3 groups as follows: mRS 0 (complete recovery) versus 1 to 6, 0 to 1 (favorable outcome) versus 2 to 6, and 0 to 2 (good functional outcome) versus 3 to 6. Pearson χ² and Fisher exact tests were used to compare categorical variables across groups. Student t test allowed comparisons of means and Mann–Whitney U test of ordinal variables. All statistical analyses used SPSS 15.0 for Microsoft Windows (SPSS Inc, Chicago, Ill). Two-sided values of P<0.05 were considered statistically significant.

**Results**

Between February 1994 and December 2007, we identified 48 patients aged 16 to 49 years with hemispheric stroke treated with intravenous alteplase. Demographic data, clinical features, time delays, and etiology of cases and age-matched control subjects (n=96) are presented in Table 1. Except for more frequent heavy drinking among control subjects, risk factors did not differ between the 2 groups. Etiology by TOAST classification was similar. As expected, onset-to- door time was higher, and the proportion of those with unknown exact stroke onset time was larger in age-matched control subjects. Older control subjects (n=96; mean age, 68±7.8 years) had similar NIHSS score on admission (median, 7; mean, 9.0±4.9; range, 1 to 22; P=0.934) as did cases, arrived at the hospital in (median) 1 hour 15 minutes (P=0.458), and were treated 2 hours 10 minutes after stroke onset (P=0.493).

Dense media sign on CT was detected in 14 (29%) cases, and 12 (25%) had early ischemic CT changes. Of the 14 (29%) patients who underwent CT angiography or MR angiography, 8 (57%) had artery occlusion. Of the 11 (23%) patients who underwent perfusion scan before thrombolysis (MR angiography in one and CT angiography in 10 patients), the decision whether to give alteplase was based directly on the results of the perfusion scan in 3 patients: one had severe symptoms and a large infarct core, but clearly larger penum- bra, and was treated 6 hours 15 minutes after stroke onset; one had rapidly improving symptoms; and the one scanned with MR angiography had very mild symptoms but consid- erable perfusion deficit. All of our young patients received a full dose of alteplase, and none experienced overt adverse drug effects or major extracranial bleedings. In a 16-year-old boy, mechanical thrombectomy was successfully performed with a MERCI device18 after thrombolysis had failed. An-
other 46-year-old man with severe brain swelling underwent hemicraniectomy 6 days from admission.

The comparisons of dichotomized outcome scores are presented in Figure 1, and proportions of each subgroup of mRS of cases and both control groups in Figure 2. At 3 months, 13 (27%) cases had fully recovered (mRS 0), a proportion significantly larger compared with age-matched control patients not treated with alteplase (n=10; 10%; \( P=0.010 \)). Favorable outcome, mRS 0 to 1, was achieved by 19 (40%) cases and 21 (22%) age-matched control subjects
The effect was observed also in those with good functional outcome (mRS 0 to 2). The proportions of dichotomized 3-month outcome scores did not differ significantly between cases and older alteplase-treated control subjects. However, none of our young patients died or were severely disabled (mRS 5 or 6) at 3 months (Figure 2). Mortality rate among age-matched control subjects was 2% ($P=0.552$) and in older control subjects 7% ($P=0.095$).

Cerebral parenchymal hemorrhage without clinical deterioration occurred in one (2%) case patient receiving low-molecular-weight heparin 3 days after thrombolysis (Supplemental Table I). None of the case patients had SICH. A total of 19 (20%) older alteplase-treated controls had ICH within 36 hours after thrombolysis, and of these, 3 patients with parenchymal hemorrhage type 2 had ≥4-point increases on NIHSS (range, 8 to 16). Thus, 3% of the older control subjects had SICH. The differences of the rates of any ICH within 36 hours or SICH between cases and older control subjects were not significant ($P=0.444$ and $P=0.551$, respectively), however.

We observed a nonsignificant trend toward better outcome among patients with undetermined etiology (Table 2). Unfavorable outcome was more frequent in males, among those with early ischemic changes or dense media sign on CT as well as in patients with stroke of other determined etiology. The other determined subgroup consisted mainly of patients undergoing carotid artery dissection (mean age, 38±7.3 years; median NIHSS score, 10.5; median onset-to-needle time, 2 hours 8 minutes) who were mostly males (10 of 12 [83%]) and had an unfavorable outcome, because only one of them (8%) achieved mRS <2 at 3 months. However, 8 (67%) of the dissection patients scored 0 to 2 and none >4 on mRS. A 27-year-old woman with hemorrhagic infarct associated with clinical deterioration of 5 points on NIHSS had dissection (Supplemental Table I).

**Discussion**

Our results suggest that young adults with acute ischemic stroke benefit from thrombolysis compared with their control patients not treated with alteplase, matched by age, gender, and initial stroke severity. More than one fourth of those treated with alteplase recovered completely, 40% were able to return to work, 82% reached good functional outcome, and none was bedridden or dead at 3 months follow-up. We could not demonstrate a difference on dichotomized mRS when compared with older alteplase-treated patients. However, none of the young patients died or had SICH.

Recently presented data on 18- to 45-year-old SITS-MOST patients, treated within a 3-hour time window, showed that 54% scored 0 to 1 and 76% 0 to 2 on 3-month mRS with a mortality rate of 5.5%. Except the mortality rate, these figures are comparable to ours. In this SITS-MOST analysis, those >45 years recovered clearly worse compared with younger patients. The higher upper age cutoff (50 years) may in part explain the fact that we did not find such a difference. The issue of whether younger age is truly associated with higher benefit from thrombolysis should possibly be further tested in randomized trials.

In the entire cohort of SITS-MOST and in pooled randomized, controlled trials, the proportion of those with favorable outcome (mRS 0 to 1) was similar to our series, approximately 40%. However, a considerably higher percent-
age of our patients achieved full recovery (mRS 0) or good functional outcome (mRS 0 to 2). The proportion of those with a score of 1 on mRS (13%) was smaller among our patients than in SITS-MOST (20%) and pooled randomized trials (23%), but in contrast, the percentage of patients scoring 2 on mRS (42%) was clearly higher in our series (16% in SITS-MOST and 7% in pooled randomized trials). These differences are likely explained by the fact that previous studies enrolled a high amount of persons who already had retired before the stroke. In those of working age, mRS 2 rather than mRS 1 is observed more frequently, probably because the residual symptoms deteriorate one’s working ability even if they are mild and otherwise would not affect their daily living. Favorable outcome, defined as mRS 0 to 1, may thus be more appropriate in trials enrolling patients of working age. This definition was also applied in the latest ECASS trial.\(^5\)

Our young patients had similar rates of hemorrhagic infarcts (HI1 or HI2), detected within 36 hours after thrombolysis, as did their older alteplase-treated control subjects. The difference of the rate of SICH was not significant, although by the applied definition of the SITS-MOST,\(^4\) none of our cases had a SICH, whereas the rate was 3% among older control subjects. The definitions of SICH have varied between randomized, controlled trials. According to the NINDS trials\(^1^9\) and Cochrane reviews,\(^2^0\) SICH (defined as any hemorrhage plus any neurological deterioration of \(\geq 1\) on NIHSS or that leads to death within 7 days) occurred in 3 (6%) of our case patients. In the ECASS and ECASS II trials,\(^1^0,1^1\) SICH was defined as any hemorrhage plus a neurological deterioration \(\geq 4\) on the NIHSS from baseline or from the lowest NIHSS value between baseline to 7 days or leading to death. ECASS III included an additional condition requiring that the bleeding was the predominant cause for deterioration.\(^5\) By the original ECASS definition, one (2%) of our cases had SICH, but not by the latest ECASS III definition because this patient probably deteriorated because of reasons other than hemorrhage. Hemorrhagic infarcts (HI1 or HI2) were frequent (23%) in our young patients, and they were often associated with early anticoagulation. Within 7 days from thrombolysis, 19% had these findings, akin to percentages in the ECASS II trial.\(^2^1\) Hemorrhagic infarcts are.
However, not that important clinically, because it was suggested that only parenchymal hemorrhage type 2 independently impairs prognosis. It remains unclear how many of these early or late hemorrhages were primarily due to direct complication of the thrombolytic agent, anticoagulants, or only natural evolution of the infarction. Concerning the different definitions, the overall rate of SICH in our young patients was lower than that seen in SITS-MOST and in pooled randomized, controlled trials and slightly higher than that in the younger subgroup of SITS-MOST. The etiologic spectrum of ischemic stroke in young adults is diverse and differs considerably from that of older patients. Cervical artery dissection is the most common solitary cause, but in more than one third, the exact etiology remains unknown. The NINDS trials reported that stroke subtype, defined before exhaustive diagnostic evaluation, does not affect response to intravenous thrombolysis. The relationship of the final stroke subtype obtained after complete diagnostic evaluation and response to thrombolysis was later analyzed in a retrospective study, presenting consistent data with those of the NINDS trials. Given the diversity of causes and the high frequency of arterial dissection and cryptogenic stroke in the young, these data may not be generalized to apply to all young adults. In these studies, the proportions of other determined etiology (TOAST 4) were only 1% to 4%. The NINDS trials did not report any patient with cryptogenic stroke, whereas Hsia and coworkers presented a percentage of 18%. Intravenous thrombolysis in patients with dissection was not particularly assessed in any randomized trial and data on this issue arise currently from nonrandomized studies involving 50 patients with internal carotid artery dissection with a median NIHSS score of 16 at admission (NIHSS score was not provided for 11 patients), mean age of 48 ± 10, and treatment time window ranging from 35 minutes to 7 hours. Of these 50 patients, 34% scored 0 to 1 and 48% 0 to 2 on mRS at 3 months, and mortality rate was 8%. In our young patients receiving thrombolysis, 25% had internal carotid artery dissection with less severe strokes and at a younger age than in the previous literature, but only one (8%) achieved a favorable outcome. However, 67% achieved MRS 0 to 2, and none was severely disabled or dead at follow-up. Despite this, carotid artery dissection was associated with worse outcome in our series overall. Because the patients undergoing dissection were mostly males, it likely explains the worse outcome among males as well. The observed trend toward better outcome in our patients with undetermined etiology may serve as another prognostic factor, but the small number of patients does not allow for firm conclusions. Nevertheless, in contrast to randomized trials having enrolled mainly older patients, stroke subtype seems to affect response to thrombolysis in young adults.

The pooled analysis of randomized, controlled trials suggested a potential benefit from thrombolysis beyond 3 hours, and the efficacy of intravenous alteplase in a 3- to 4.5-hour time window was recently demonstrated in the ECASS III trial. Our data, with a small patient number, did not show any trend toward worse outcome or higher bleeding rate among those young adults treated later than 3 hours from symptom onset (data not given). Certain other off-label situations are of interest when considering thrombolysis in the young. Case reports and limited experience on pregnant females receiving alteplase suggest that the treatment should not be withheld, but risks and benefits should be carefully assessed. The same holds true in case of menstruating females according to limited literature. We had no pregnant or menstruating females in our series and thus no experience in treating such patient groups. Only few case reports and single case series of children and adolescents receiving intravenous or intra-arterial thrombolysis for acute ischemic stroke have been published. Yet, according to the US Nationwide Inpatient Sample, thrombolytic therapy is currently being administered to children. Our youngest patients, aged 16 and 17 years, both received alteplase uneventfully.

The main restrictions of our study were the retrospective and nonrandomized design. The true efficacy of alteplase in this setting is difficult to assess. However, the use of historical control patients is justified, because conducting a randomized trial on the issue would be unethical or impossible at present. The age-matched control group was admitted to the hospital clearly later than thrombolysed patients, which might have had some influence on their outcomes per se. They also had more often unknown time of stroke onset, which may have affected the decision-making whether to give alteplase, particularly during the earliest years of the study period, because of unavailability of perfusion techniques. We also applied a predefined ratio for cases and control subjects (1:2), which might have affected the statistical significance of the results. This ratio was based on the estimates of the reasonable amount of control patients we were able to find with affordable effort through the strict matching process (age, gender, and admission NIHSS score). Gender and increasing age predict outcome also in young patients with stroke, and stroke severity measured by NIHSS is a reliable predictor of 3-month outcome. Therefore, matching cases and control subjects by these conditions was rational despite that it restricted the availability of proper control patients. Finally, because direct patient contact for outcome assessment is not always possible, we have assessed mRS also over the telephone. Telephone assessment is not yet validated in larger studies but is suggested to be reliable. In our study, the proportions of those with face-to-face or telephone measurement of mRS were closely similar between the groups, and the assessment was done by experienced raters.

**Conclusions**

Our results suggest an overall efficacy and good safety of thrombolysis in young adults. Further studies are needed to determine the prognostic factors in young adults and to assess in particular the true efficacy of thrombolysis in the circumstance of cervical artery dissection. Another future challenge is to evaluate the safety and efficacy of thrombolysis in children and young adolescents.

**Acknowledgments**

We are indebted to Marja Metso, RN, and Jaana Valkeapää, RN, for their dedication and technical support.
Sources of Funding

This work was supported by the Helsinki University Central Hospital, the University of Helsinki, and the Paà¨ivikki and Sakari Sohlberg Foundation.

Disclosures

None.

References


Thrombolysis in Young Adults With Ischemic Stroke
Jukka Putaala, Tiina M. Metso, Antti J. Metso, Elina Mäkelä, Elena Haapaniemi, Oili Salonen, Markku Kaste and Turgut Tatlisumak

Stroke. 2009;40:2085-2091; originally published online April 16, 2009;
doi: 10.1161/STROKEAHA.108.541185
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 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/40/6/2085

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/