Ultraearly Thrombolysis in Acute Ischemic Stroke Is Associated With Better Outcome and Lower Mortality

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Background and Purpose—Pooled analysis of major placebo-controlled trials suggests that the earlier thrombolysis is given after ischemic stroke, the better the outcome. We report a single-center assessment of the effect of ultraearly thrombolysis on the outcome of our patients.

Methods—Between January 2003, and December 2008, a total of 878 patients with ischemic stroke received thrombolysis within 4.5 hours from the symptom onset at the Helsinki University Central Hospital. Using univariate methods and multivariable logistic regression, we assessed the association between onset-to-treatment time (OTT) and favorable 3-month outcome (modified Rankin Scale 0 to 2).

Results—Median age was 70.5 years, median OTT 115 minutes, and median National Institutes of Health Stroke Scale (NIHSS) on admission 9. After adjustment for baseline stroke severity, more patients with OTT <70 minutes had a favorable outcome than those with OTT ≥70 minutes. Specifically, OR of 5.15 (1.50 to 27.5) was for the patients with NIHSS 7 to 12, and 2.74 (1.26 to 5.90) for those with NIHSS ≥13. Of the patients with OTT ≤90 minutes, those with NIHSS 7 to 12 had an OR of 1.72 (1.00 to 2.96) for a favorable outcome, and those with NIHSS ≥13 had lower mortality than the ones with OTT >90 minutes (16.4% versus 29.5%; $P=0.01$). Multivariable model showed an association of better outcome with lower baseline glucose level, younger age, lower baseline NIHSS, and OTT <70 minutes.

Conclusions—Ultraearly thrombolysis was associated with better outcome of our patients with stroke with moderate or severe symptoms. The earlier the treatment was given, the higher the likelihood of favorable outcome. **(*Stroke*. 2010; 41:712-716.)**

Key Words: ischemic stroke ■ outcome ■ thrombolysis

Thrombolysis with intravenous alteplase is the only approved drug treatment for acute ischemic stroke in eligible patients. Ever since the pooled analysis[1] suggested and the results of the European Cooperative Acute Stroke Study (ECASS III)[2] together with Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Registry (SITS-ISTR)[3] confirmed the extension of the time window from within 3 up to 4.5 hours, it became essential to study the importance of onset-to-treatment time (OTT) on the outcome. Such an association was suggested in the reanalysis of the National Institute of Neurological Disorders and Stroke study[4] as well as in the pooled analysis.[1] In the latter, number needed to treat for favorable outcome was 14 for the patients treated within 270 minutes from the symptom onset, 7 for the patients with OTT <180 minutes, and 3 for those with OTT <90 minutes. This tallies with the increased benefit of the earlier treatment shown in the laboratory >2 decades ago.[5–7]

The severity of stroke on admission and the patient's age are known predictors of outcome from a number of studies on stroke thrombolysis.[1,8–10] The former has a confounding effect on the time of hospital arrival, because patients with more severe strokes tend to present faster.[1] An association among OTT, major neurological improvement (predefined change in National Institutes of Health Stroke Scale [NIHSS] score within 24 hour), and the effect on 3-month outcome was observed in some studies,[11] but not in all.[12] Experience with 450 patients treated in Cologne, Germany,[13] suggested OTT not to be predictive of outcome. On the contrary, recent multivariable analysis of the Combined Lysis Of Thrombus in Brain ischemia USing Transcranial ultrasound and systemic tPA (CLOTBUST) trial[10] identified age, complete recanalization, baseline NIHSS score, and OTT to be independent predictors of 3-month outcome. With a special emphasis on the ultraearly treatment, we investigated whether OTT is associated with favorable outcome in our large single-center consecutive stroke cohort treated with intravenous alteplase.

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Table 1. Baseline Characteristics (Medians) by OTT

Characteristic	OTT <70 Minutes (n=87)	OTT ≤90 Minutes (n=257)	All Patients (n=878)	*P* Value
Age, years	66.0*	69.0	70.5	<0.01*
NIHSS (score)	10	10†	9	<0.01†
Glucose, mmol/L	6.7	6.7	6.6	NS
SBP, mm Hg	152	152	155	NS
DBP, mm Hg	83	82	82	NS

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.
*Compared with patients with OTT ≥70 minutes
†Compared with patients with OTT >90 minutes.
NS indicates nonsignificant.

Materials and Methods

Patients

The baseline population included 926 consecutive patients with acute ischemic stroke treated with intravenous alteplase (0.9 mg/kg of body weight) at the Helsinki University Central Hospital between January 1, 2003, and December 31, 2008. All patients were prospectively included in the SITS-ISTR registry. In the analysis, we included all consecutive patients considered eligible for stroke thrombolysis and treated within the time window of 4.5 hours from symptom onset (n=878) and excluded 48 patients treated beyond this time window. Evaluated by stroke physicians, 3-month modified Rankin Scale (mRS) 0 to 2 represented favorable outcome. The mRS was based on the clinical charts in 14 (1.6%) patients due to missing data in the SITS-ISTR registry. Fifteen (1.7%) patients included in the analysis were not independent on admission; mRS was 3 (n=12) or 4 (n=3) before thrombolysis.

No follow-up data were available for 18 (2.1%) patients included in the analysis, of whom 5 were not permanent Finnish inhabitants, 6 were from other hospital districts in Finland (follow-up data not reported to Helsinki University Central Hospital), and 7 could not be contacted.

The medical ethics committee approved the study.

Statistical Analysis

Distributions of the continuous variables were studied and tested for normality. Univariate comparison of subgroups with favorable or poor outcome was performed with Student *t* test or Mann–Whitney *U* test for continuous variables and with Pearson χ^2 test for discrete variables. For multivariate analysis of the effect of OTT, a model of backward logistic regression for favorable outcome was constructed including potential confounders as identified by univariate analysis ($P \leq 0.20$) and previous studies, incorporating 2-way interactions tested with logistic regression into the model, after testing for the linearity of log odds for the variables to be included. The effect of time was analyzed both by applying OTT as a continuous variable and also using a dichotomous variable for belonging in the ultraearly subgroup (defined as the 10th percentile and representing OTT <70 minutes). The other OTT cutoff value of 90 minutes was chosen in accordance to the pooled analysis.[1] ORs for outcome were determined with likelihood ratio tests and logistic regression. The population was divided into tertiles by stroke severity (mild: NIHSS ≤6, moderate: NIHSS 7 to 12, severe: NIHSS ≥13). Cox regression adjusting for NIHSS at baseline was used to calculate hazard ratios for death as well as the predicting value of OTT.

Table 2. Premorbidity and Baseline Characteristics by 3-Month Outcome

Characteristic	mRS 0–2, No. (%)	mRS 3–6, No. (%)	*P* Value
Chronic heart failure	33 (6.8%)	74 (19.0%)	<0.001
Atrial fibrillation	128 (26.1%)	132 (33.9%)	0.03
Diabetes	56 (11.5%)	61 (15.7%)	0.07
Age, years	64.9	72.1	<0.00001
NIHSS (scale)	7.9	13.8	<0.00001
Glucose, mmol/L	6.9	7.6	<0.0001
SBP, mm Hg	154	155	0.58
DBP, mm Hg	83	80	0.02

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

Table 3. OR for a Favorable 3-Month Outcome by OTT

OTT, Minutes	mRS 0–2, No. (%)	mRS 3–6, No. (%)	OR (95% CI)	*P* Value (χ^2)
<70	59 (67.8%)	28 (32.2%)	1.77 (1.08–2.95)	0.016
≥70	430 (54.4%)	361 (45.6%)		
≤90	149 (58.0%)	108 (42.0%)	1.14 (0.84–1.55)	0.38
>90	340 (54.8%)	281 (45.2%)		

Results

Median age was 70.5 years (interquartile range, 17) and mean age 68.1 years (range, 16 to 93 years). There were 399 (45.4%) females. Median baseline NIHSS was 9 and mean 10.5. Basilar artery occlusion was present in 28 (3.2%) patients, whereas hemispheric and the rest of the posterior fossa strokes comprised 850 (96.8%) of all strokes. Median OTT was 115 minutes (interquartile range, 64). Of the 878 patients, 257 (29%) had OTT ≤90 minutes and 87 (10%) had OTT <70 minutes. Age and baseline NIHSS differed when patients were divided by OTT (Table 1). Premorbidity and baseline characteristics by dichotomized 3-month mRS are shown in Table 2.

The overall rate of symptomatic intracerebral hemorrhage rate was 19 (2.2%) according to SITS criteria.[14] There were 3 (3.4%) patients with symptomatic intracerebral hemorrhage in those with OTT <70 minutes compared with 16 (2.0%) in the rest of the population. The

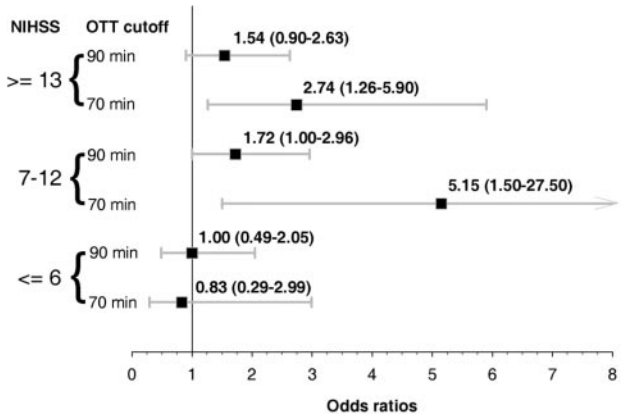

Figure 1. ORs for favorable 3-month outcome by OTT and adjusted for baseline NIHSS. The figure shows ORs for favorable outcome (mRS 0 to 2) for patients with OTT <70 minutes compared with OTT ≥70 minutes (OTT cutoff value 70). Furthermore, the odds for OTT cutoff 90 minutes are shown.

Table 4. Backward Logistic Regression of Predictors of Favorable Outcome

Predictor	OR (95% CI)	*P* Value
Baseline NIHSS	0.83 (0.78–0.85)	<0.0001
Age	0.96 (0.94–0.97)	<0.0001
Baseline glucose	0.88 (0.82–0.94)	<0.0001
OTT	0.99 (0.99–1.00)	0.022
OTT as a binary variable		
OTT <70 minutes	2.20 (1.24–3.90)	0.007

symptomatic intracerebral hemorrhage rate did not differ between OTT quartiles either. There were 2 (0.4%) patients with symptomatic intracerebral hemorrhage in those with a favorable 3-month outcome (mRS 0 to 2) and 17 (4.4%) in those with a poor 3-month outcome (mRS 3 to 6; $P<0.001$).

Higher proportion of patients with OTT <70 minutes had a favorable outcome than those with OTT ≥70 minutes (Table 3). Those with moderate or severe stroke had the highest likelihood of favorable outcome (Figure 1) if treated within 70 minutes from the onset of symptoms. Patients with OTT ≤90 minutes improved by an average of 4 NIHSS points within 24 hours and by an average of 6 points within 1 week of symptom onset. Those with OTT <70 minutes improved by 5 and 6 points, respectively, which is better than the improvement seen in all patients (4 points [$P<0.02$] and 5 points [$P<0.01$], respectively). Several parameters were associated with a favorable outcome (Table 4).

Overall, death rates by OTT did not differ in the whole series (Table 5). Death rate adjusted for baseline NIHSS was associated with lower 3-month mortality in patients with the most severe strokes (NIHSS ≥13) treated early (OTT ≤90 minutes), and there was a trend toward lower mortality of such patients treated ultraearly (OTT <70 minutes; Table 5).

Discussion

Our results show that ultraearly thrombolysis (OTT <70 minutes) is associated with higher likelihood of a favorable 3-month outcome (Table 3). Those with moderate baseline symptoms (NIHSS 7 to 12) had more than 5-fold and those with severe strokes (NIHSS ≥13) almost 3-fold higher likelihood of favorable outcome if treated ultraearly compared with the rest of the patients (Figure 1). Higher likelihood of good recovery was still evident in patients with moderate strokes treated within 90 minutes (Figure 1). These results confirm that the earlier thrombolysis is given, the better the outcome of patients, as was suggested by the NIHSS Recombinant Tissue Plasminogen Activator study[4] and the pooled analysis.[1]

Another important finding was reduced 3-month mortality in patients with severe stroke treated within 90 minutes and a trend toward lower mortality in similar patients treated within 70 minutes (Table 5). The smaller number of patients in the latter group may explain the observed trend instead of a significant difference. We wonder why this was the case only for the most severe strokes (NIHSS ≥13). Baseline stroke severity is known to be associated with 30-day mortality.[15] Patients with mild or moderate acute stroke do not usually die. Our results show that rapid treatment of patients with severe strokes improves the likelihood of survival. Greater improvement of NIHSS at 24 hours and 1 week after symptom onset in the patients treated early supports such a possibility. The results reveal how important it is to shorten the OTT to minimum.

As expected, the backward logistic regression retained baseline stroke severity (NIHSS score) and age as independent predictors of favorable 3-month outcome (Table 4). The other independent predictors were baseline glucose and OTT. Baseline glucose was associated with outcome in the SITS-ISTR registry (unpublished data) and the effect of early treatment is known to improve the outcome.[1,4] In the present study, when time to treatment was used as a binary variable, ultraearly treatment within 70 minutes was associated with the highest likelihood of a favorable outcome (Table 4).

Apart from the lower age (66.0 versus 70.5 years, $P<0.01$) and a slight male predominance (58 of 87 [67%] versus 421 of 791 [53%], $P=0.02$), the ultraearly subpopulation did not differ from the rest of the population in terms of the risk factor profile or baseline variables (Table 1). A history of chronic heart failure or atrial fibrillation was associated with a poor outcome ($P<0.001$ and $P=0.03$, respectively; Table 2). This observation was not unexpected. A history of diabetes showed a trend toward a poorer functional outcome (Table 2), an observation well known among clinicians.

Summary

Ultraearly thrombolysis after acute ischemic stroke was associated with better outcome and lower mortality. All

Table 5. Mortality at 3 Months

OTT, Minutes	Survived, No. (%)	Dead, No. (%)	HR (95% CI) *P* Value	Baseline NIHSS	Survived, No. (%)	Dead, No. (%)	*P* Value
<70	80 (92%)	7 (8%)	0.63 (0.28–1.39)	≥13	32 (86.5%)	5 (13.5%)	0.09
≥70	694 (87.7%)	97 (12.3%)	0.31		196 (73.4%)	71 (26.6%)	
≤90	232 (90.3%)	25 (9.7%)	0.74 (0.46–1.19)	≥13	87 (83.6%)	17 (16.4%)	0.01
>90	542 (87.3%)	79 (12.7%)	0.25		141 (70.5%)	59 (29.5%)	

Left side of the table shows overall mortality by OTT and the right side shows mortality by OTT for patients with most severe strokes. HR indicates hazard ratio.

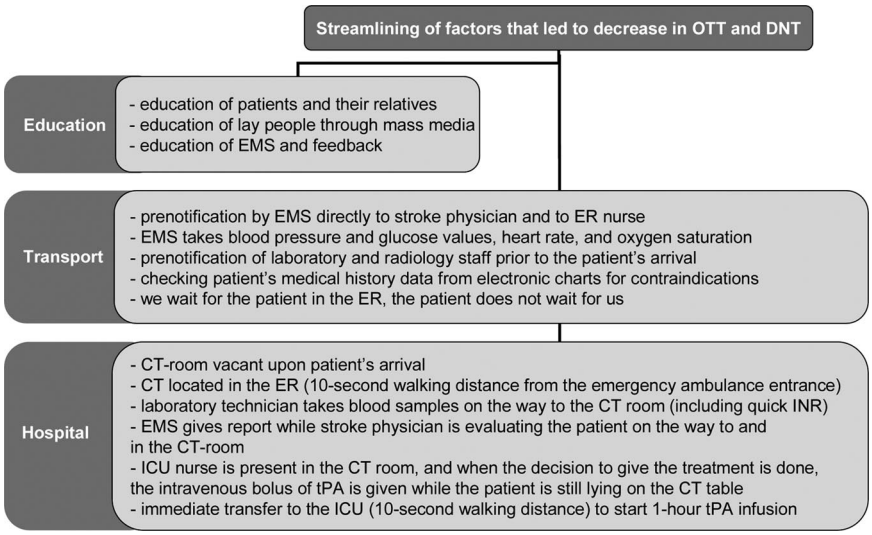

Figure 2. Streamlining of factors that led to decrease in OTT and door-to-needle time (DNT) in our institution. EMS, emergency medical services; ER, emergency room; INR, international normalized ratio; ICU, intensive care unit; tPA, tissue plasminogen activator.

efforts to shorten the time delay from onset to treatment are highly warranted. This is even more important in light of the recent extension of the time window to 4.5 hour.[2,3] A longer time window might be misinterpreted as to allow more time to prehospital and in-hospital practice. To this end, the Standard Treatment with Alteplase to Reverse Stroke Study (STARS) did report an alarming observation of inverse relationship between the onset-to-door time and the door-to-treatment time delays, meaning that patients arriving early after symptom onset were not evaluated as fast as patients arriving later.[16] Our results show that emergency stroke care must be optimized to provide fast patient access, immediate evaluation by a stroke physician, priority for imaging, rapid laboratory diagnostics, and fast treatment starting at the emergency room; this includes increased public awareness, effective emergency medical services, and streamlined in-hospital organization[17] (Figure 2). Minimizing prehospital and in-hospital delays makes ultraearly thrombolysis possible and this is a highly effective way to improve the outcome of patients with ischemic stroke. Although thrombolysis is effective up to 4.5 hours, we should do our very best to treat our patients with stroke as soon as possible.

Appendix

The Helsinki Stroke Thrombolysis Registry Group includes Artto Ville, Atula Sari, Curtze Sami, Häppölä Olli, Kaste Markku, Liebkind Ron, Lindsberg Perttu J, Meretoja Atte, Mustanoja Satu, Piironen Katja, Pitkäniemi Janne, Putaala Jukka, Rantanen Kirsi, Sairanen Tiina, Salonen Oili, Silvennoinen Heli, Soinne Lauri, Strbian Daniel, Tatlisumak Turgut, and Tiainen Marjaana.

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Disclosures

L.S. has received modest honoraria from Boehringer Ingelheim for speaking and consulting. T.S. received modest honoraria from Boehringer Ingelheim for speaking. T.T. has a research contract with Boehringer Ingelheim, Sanofi Aventis, Lundbeck, Mitsubishi Pharma, Schering Plough, Concentric Medical, and BrainsGate (significant); a grant from Boehringer Ingelheim (modest); and is on the advisory board/consultant of Boehringer Ingelheim, Mitsubishi Pharma, and BrainsGate (modest). M.K. has received honoraria and his travel expenses have been covered for participating in the Steering Committee meetings of ECASS III, DIAS-2, and DIAS-4 trials and for serving as a consultant for Boehringer Ingelheim, PAION AG, Forest Research Laboratories, Inc, and Lundbeck A/G (modest).

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