Safety of routine IV thrombolysis between 3 and 4.5 h after ischemic stroke

M. Uyttenboogaart a,⁎, P.C.A.J. Vroomen a, R.E. Stewart b, J. De Keyser a, G.J. Luijckx a

a Department of Neurology, University Medical Center Groningen, Hanzeplein 1, 9700 RB Groningen, The Netherlands
b Department of Health Sciences, University Medical Center Groningen, University of Groningen, The Netherlands

Received 14 April 2006; received in revised form 6 December 2006; accepted 11 December 2006
Available online 25 January 2007

Abstract

Background: The administration of tissue plasminogen activator (t-PA) has been proven effective for ischemic stroke within 3 h after onset. A pooled-analysis of six trials showed that intravenous t-PA still improves outcome when given between 3 to 4.5 h after stroke onset. On the basis of this pooled analysis, t-PA was also routinely offered to our patients between 3–4.5 h. We report the safety and clinical features of this group together with the features of the group given t-PA within 3 h.

Methods: Prospectively patient characteristics, stroke severity, stroke subtype, incidence of symptomatic intracerebral hemorrhage (SICH), in-hospital mortality, and 3-months modified Rankin Scale scores (mRS) were registered. Data was analyzed separately for patients treated within 3 h (early group) and those treated between 3–4.5 h (late group).

Results: Among 176 patients who underwent intravenous thrombolysis, 101 were treated in the early group and 75 in the late group. Six (5.9%; 95% CI 2.8%–12.3%) patients in the early group and 4 (5.3%; 95% CI 2.2%–12.9%) in the late group developed SICH (p = 1.0). In the early group 13 (12.9%; 95% CI 7.7%–20.8%) patients died within 7 days after admission, compared to 5 (6.7%; 95% CI 3.0%–14.7%) in the late group (p = 0.179). In the early group 44 (43.6%; 95% CI 43.3%–53.3%) were independent (mRS ≤ 2) at three months, compared to 36 (48.0%; 95% CI 37.0%–59.1%) in the late group (p = 0.559).

Conclusion: Our data show no trend of decreased safety of thrombolysis beyond 3 h. Due to a small sample size a harmful effect cannot be excluded but seems unlikely.

© 2006 Elsevier B.V. All rights reserved.

Keywords: Safety; Stroke; Thrombolysis; Time window

1. Introduction

The rationale for thrombolytic therapy in acute ischemic stroke is based on the concept that early reperfusion may salvage ischemic brain-tissue. The National Institute of Neurological Disorders and Stroke (NINDS) study showed that treatment with intravenous tissue plasminogen activator (t-PA) was effective within 3 h after onset of ischemic stroke [1]. Two other trials with intravenous t-PA, the European Cooperative Acute Stroke Study (ECASS)-I and ECASS-II [2,3], which had a time window of 6 h, yielded less convincing results. The Alteplase ThromboLysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trial[4], failed to show a beneficial effect of t-PA administration within a 3–5 h time window.

Thrombolysis with t-PA has become standard treatment for eligible patients with an ischemic stroke within 3 h after onset of symptoms. Unfortunately, many patients still arrive at the hospital beyond the 3 h time window[5–8]. Extending the time window would allow more ischemic stroke patients to benefit from intravenous t-PA treatment. A pooled analysis of individual-patient data showed that t-PA given between 3 and 4.5 h after stroke onset is still effective, without an increased risk of hemorrhage[9]. We decided that based on the evidence of this pooled analysis, thrombolysis...
could be offered to patients off-license in the 3–4.5 h interval. However, concerns exist about the safety of this procedure beyond 3 h in daily clinical practice. In this paper, we aim to describe our experiences with thrombolysis in the 3–4.5 h time window (late group) in daily clinical practice and to compare these with our experiences for treatment within 3 h (early group).

2. Methods

2.1. Protocol for t-PA treatment

Since the results of the pooled analysis of the NINDS, ECASS and ATLANTIS t-PA trials were communicated at the 27th International Stroke Conference in February 2002 (San Antonio, Texas), the time window for routine intravenous t-PA treatment in ischemic stroke patients in our clinic was extended to 4.5 h. As part of the thrombolysis protocol, informed consent was obtained from each patient or from his or her relative in case of patient’s inability, after explaining the off-license use of t-PA in case of treatment in the late group. A brain CT scan was performed prior to thrombolysis.

For patients presenting within 3 h of stroke onset, we adopted the NINDS study protocol. For patients in the late group, we used the ECASS II protocol. In specific, we excluded patients in the late group with early ischemic changes (EIC) exceeding one third of the middle cerebral artery (MCA) territory on the initial brain CT-scan. EIC were defined as effacement of cerebral sulci, loss of gray/white matter differentiation, and parenchymal hypodensity, according to the ECASS criteria [3]. In contrast to the ECASS II, we did not exclude patients older than 80 years.

Neurological deficit was recorded with the National Institute of Health Stroke Scale (NIHSS). Stroke-subtypes were defined into total anterior circulation infarcts (TACI), partial anterior circulation infarcts (PACI), lacunar infarcts (LACI) and posterior circulation infarcts (POCI) [10]. All patients underwent a routine blood investigation and electrocardiography. Patients were treated with intravenous

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early group (0–3 h)</th>
<th>Late group (3–4.5 h)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), years</td>
<td>68 (14)</td>
<td>66 (15)</td>
<td>0.473*</td>
</tr>
<tr>
<td>Male</td>
<td>51 (50)</td>
<td>45 (60)</td>
<td>0.210</td>
</tr>
<tr>
<td>Median NIHSS score (range)</td>
<td>14 (2–23)</td>
<td>12 (2–35)†</td>
<td>0.025*</td>
</tr>
<tr>
<td>Median OTT (range), min</td>
<td>150 (30–180)</td>
<td>220 (185–270)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Stroke-subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACI</td>
<td>42 (42)</td>
<td>18 (24)†</td>
<td>0.010</td>
</tr>
<tr>
<td>PACI</td>
<td>44 (44)</td>
<td>39 (53)†</td>
<td>0.215</td>
</tr>
<tr>
<td>LACI</td>
<td>13 (13)</td>
<td>13 (18)†</td>
<td>0.409</td>
</tr>
<tr>
<td>POCI</td>
<td>2 (2)</td>
<td>4 (5)†</td>
<td>0.404‡</td>
</tr>
<tr>
<td>Mean SBP (SD), mm Hg</td>
<td>153 (24)†</td>
<td>157 (24)†</td>
<td>0.185*</td>
</tr>
<tr>
<td>Mean DBP (SD), mm Hg</td>
<td>83 (14)†</td>
<td>86 (18)†</td>
<td>0.187*</td>
</tr>
<tr>
<td>Mean glucose (SD), mmol/l</td>
<td>6.2 (1.5)†</td>
<td>6.8 (2.5)†</td>
<td>0.519*</td>
</tr>
<tr>
<td>Computed tomography findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midline shift</td>
<td>2 (2)</td>
<td>0 (0)§</td>
<td>0.510‡</td>
</tr>
<tr>
<td>EIC</td>
<td>46 (46)</td>
<td>28 (38)§</td>
<td>0.344</td>
</tr>
<tr>
<td>EIC in more than 33% of MCA</td>
<td>7 (7)</td>
<td>3 (4)§</td>
<td>0.522‡</td>
</tr>
<tr>
<td>Dense artery sign</td>
<td>23 (23)</td>
<td>14 (19)§</td>
<td>0.567</td>
</tr>
<tr>
<td>Normal</td>
<td>29 (29)</td>
<td>29 (40)§</td>
<td>0.128</td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>47 (47)</td>
<td>34 (45)</td>
<td>0.874</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (11)</td>
<td>9 (12)</td>
<td>0.819</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>27 (27)†</td>
<td>21 (29)§</td>
<td>0.798</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>25 (25)</td>
<td>22 (29)§</td>
<td>0.430</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>12 (12)</td>
<td>16 (21)</td>
<td>0.090</td>
</tr>
<tr>
<td>Prior use of acetylsalicylic acid</td>
<td>29 (29)</td>
<td>19 (25)</td>
<td>0.619</td>
</tr>
</tbody>
</table>

Values are given in numbers (%) and p-values calculated with χ² test, unless otherwise indicated.

* Mann–Whitney U test, † 1 missing value, § Fisher exact test, ¶ 2 missing values.

SD = standard deviation, NIHSS = NIH stroke scale, OTT = onset to treatment time, TACI/PACI = total/partial anterior circulation infarcts, LACI = lacunar infarcts, POCI = posterior circulation infarcts, SBP/DBP = systolic/diastolic blood pressure, EIC = early ischemic changes, MCA = middle cerebral artery, TIA = transient ischemic attack.

Hypertension was defined as a self-reported history of hypertension or use of anti-hypertensive medications, or a blood pressure consistently measured above 140/90 m Hg.

Diabetes was defined as a self-reported history of diabetes, or use of medications for diabetes, or an elevated fasting blood glucose >7.1 mmol/l.

Hyperlipidaemia was defined as a self-reported history of hyperlipidaemia or use of medications against hyperlipidaemia, or a serum cholesterol >6.5 mmol/l or a serum LDL >3.5 mmol/l.
alteplase 0.9 mg/kg to a maximum of 90 mg. Ten percent of the total dose was given as a bolus in 1–2 min and the remaining 90% was given in the next hour. Patients were monitored in a stroke unit, where early rehabilitation was started by a multidisciplinary team. We did not routinely perform a brain CT scan after each thrombolysis. Before the initial brain CT scan, the radiologist was informed about affected side of neurological deficit, but was unaware of the onset to treatment time. All initial brain CT scans were reassessed for this study with the assessor blinded for the outcome of thrombolysis.

2.2. Outcome measures

For the safety analysis, we defined the following outcome measures: incidence of symptomatic intracerebral hemorrhage (SICH) and early in-hospital mortality within 7 days. SICH was defined as a neurological deterioration (NIHSS increment ≥ 4 points) within 48 h following thrombolysis with an intraparenchymal hematoma demonstrated by brain CT scan. The modified Rankin Scale (mRS) score at 3 months was assessed with a structured interview [11] by a trained stroke nurse. The mRS was dichotomized into 0 (favorable outcome) and 3–6 (unfavorable outcome). Data were analyzed separately in the early and late group and compared between both groups.

2.3. Statistical analysis

All statistical analyses were done using SPSS version 11.0. The Mann–Whitney U test was used for continuous and ordinal variables, and the χ2 test or Fisher exact test for dichotomous variables. Predictors for unfavorable outcome were obtained with a univariate analysis and a multivariate analysis using a logistic regression approach. A threshold of p<0.2 was chosen to select variables from the univariate analysis for the logistic regression model, except for “onset to treatment time” (OTT), which was included regardless of the p-value.

### 3. Results

#### 3.1. Baseline characteristics

Between April 2002 and April 2005, 826 consecutive ischemic stroke patients were admitted to our department, of whom 176 (21%) received t-PA treatment. Baseline characteristics for the early and late group are presented in Table 1. In 57% of the patients treatment was started within 3 h. Patients in the early group had a significantly higher NIHSS score and a higher frequency of TACI compared with patients in the late group. Three patients (4.1%) in the late group had EIC in more than one-third of the MCA territory, when the CT scans were reassessed. These were considered protocol violations.

#### 3.2. Outcome

SICH occurred in the early group in 6 patients (5.9%; 95% CI 2.8%–12.3%), of whom 4 died, and in the late group in 4 patients (5.3%; 95% CI 2.2%–12.9%), of whom 3 died (p = 1.0). Presence of EIC in more than one-third of the MCA territory in the late group was associated with SICH: 2 of the 3 patients with EIC in more than one-third of

### Table 2. Predictors for unfavorable outcome after thrombolysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Favorable outcome (n=80)</th>
<th>Unfavorable outcome (n=96)</th>
<th>Unadjusted OR</th>
<th>p</th>
<th>Adjusted OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>44 (55)</td>
<td>52 (54)</td>
<td>0.97 (0.53–1.76)</td>
<td>0.912</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 80 years</td>
<td>9 (11)</td>
<td>33 (34)</td>
<td>4.13 (1.84–9.30)</td>
<td>&lt;0.001</td>
<td>6.05 (2.39–15.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NIHSS score &gt;13</td>
<td>12 (29)</td>
<td>59 (62)*</td>
<td>4.06 (2.15–7.68)</td>
<td>&lt;0.001</td>
<td>3.80 (1.74–8.31)</td>
<td>0.001</td>
</tr>
<tr>
<td>OTT ≥ 3 h</td>
<td>36 (45)</td>
<td>39 (41)</td>
<td>0.84 (0.46–1.52)</td>
<td>0.559</td>
<td>1.13 (0.53–2.41)</td>
<td>0.753</td>
</tr>
<tr>
<td>Mean glucose (SD). mmol/l†</td>
<td>6.3 (2)</td>
<td>6.6 (2)*</td>
<td>–</td>
<td>0.196</td>
<td>1.10 (0.91–1.32)</td>
<td>0.324</td>
</tr>
<tr>
<td>Mean SBP (SD). mm Hg</td>
<td>154.0 (23)</td>
<td>155.6 (28)*</td>
<td>–</td>
<td>0.832</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean DBP (SD). mm Hg†</td>
<td>86.5 (16)</td>
<td>82.3 (16)*</td>
<td>–</td>
<td>0.087</td>
<td>0.99 (0.97–1.01)</td>
<td>0.377</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (10)</td>
<td>12 (13)</td>
<td>1.29 (0.50–3.32)</td>
<td>0.603</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>34 (43)</td>
<td>47 (49)</td>
<td>1.30 (0.71–2.36)</td>
<td>0.392</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>21 (26)*</td>
<td>26 (27)*</td>
<td>1.04 (0.53–2.04)</td>
<td>0.907</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>17 (21)</td>
<td>11 (11)</td>
<td>0.48 (0.21–1.10)</td>
<td>0.077</td>
<td>0.62 (0.23–1.67)</td>
<td>0.347</td>
</tr>
<tr>
<td>Non-lacunar stroke</td>
<td>61 (77)*</td>
<td>88 (92)</td>
<td>3.25 (1.33–7.94)</td>
<td>0.007</td>
<td>1.80 (0.60–5.41)</td>
<td>0.295</td>
</tr>
<tr>
<td>EIC on CT scan</td>
<td>24 (30)</td>
<td>50 (53)*</td>
<td>2.65 (1.42–4.96)</td>
<td>0.002</td>
<td>2.69 (1.08–6.70)</td>
<td>0.034</td>
</tr>
<tr>
<td>Dense artery sign</td>
<td>13 (16)</td>
<td>24 (26)*</td>
<td>1.77 (0.83–3.75)</td>
<td>0.136</td>
<td>1.44 (0.55–3.81)</td>
<td>0.459</td>
</tr>
<tr>
<td>Normal CT scan</td>
<td>33 (41)</td>
<td>25 (27)*</td>
<td>0.52 (0.27–0.98)</td>
<td>0.041</td>
<td>1.80 (0.66–4.91)</td>
<td>0.248</td>
</tr>
</tbody>
</table>

Values are expressed as numbers (%) unless otherwise indicated. * 1 missing value. † entered as a continuous variable in the logistic regression model. ‡ 2 missing values.

OR = Odds ratio (95% CI). SD = standard deviation. NIHSS = NIH stroke scale. OTT = onset to treatment time. SBP = systolic blood pressure. DBP = diastolic blood pressure. EIC = early ischemic changes.

Hypertension was defined as a self-reported history of hypertension or use of anti-hypertensive medications, or a blood pressure consistently measured above 140/90 mm Hg.

Diabetes was defined as a self-reported history of diabetes, or use of medications for diabetes, or an elevated fasting blood glucose > 7.1 mmol/l.

Stroke subtype was dichotomized into lacunar (LACI) and non-lacunar stroke (TACI, PACI, POCI), according to the Oxfordshire classification [10].
the MCA territory developed SICH, compared with 2 out of
the remaining 70 patients (p=0.007). In the early group, however, the presence of EIC in more than one-third of
the MCA territory was not associated with SICH (0/7 versus 6/
94, p=1.0). Multivariate analysis showed that, after
adjustment for age, gender, NIHSS, EIC, glucose concen-
tration and stroke subtype, treatment in the late group was
not associated with SICH (OR 1.03; 95% CI 0.26–4.02).

The early in-hospital mortality rate was 12.9% (95% CI
7.7%–20.8%; n=13) in the early group and 6.7% (95% CI
3.0%–14.7%; n=5) in the late group (p=0.179). Variables
associated with early in-hospital mortality in the whole
group in an univariate analysis were: EIC (12/74 versus 6/
3.0%; p=0.001), NIHSS score (14/82 versus 4/93, p=0.006) and TACI (13/56 versus 5/
20, p<0.001).

The baseline NIHSS and frequency of TACI were
different in early and late groups. However, when adjusted
for NIHSS score and frequency of TACI, treatment in the late
group did not predict SICH (OR 0.98; 95% CI 0.26 to 3.73)
or early death (OR 0.63; 95% CI 0.19 to 2.13).

Forty-four (43.6%; 95% CI 43.3%–53.3%) patients in the
early group and 36 (48.0%; 95% CI 37.0%–59.1%) patients in the late group were independent (mRS ≤2) at 3 months
(p=0.559). Very favorable outcome (mRS ≤1) was also not
different between the early and late group: 28 (27.7%; 95%
CI 19.3%–37.5%) versus 25 (33.3%; 95% CI 22.9%–
45.2%), respectively (p=0.422).

Twenty (19.8%; 95% CI 12.5%–28.9%) patients treated
in the early group were dead after 3 months, compared to 10
(13.3% 95%; CI 6.6%–23.2%) in the late group (p=0.259).
Of the variables associated with unfavorable outcome in the
univariate analysis (Table 2), three predicted outcome in a
multivariate analysis: NIHSS score >13, age ≥80 years and
presence of EIC.

4. Discussion

This paper reports our experiences with the routine
administration of thrombolysis with t-PA between 3 and
4.5 h after stroke onset. We found no difference in the occurrence of SICH and early in-hospital mortality between
the sub-3 h and 3–4.5 h groups. We observed a similar
incidence of SICH (5.7%) and early in-hospital mortality
(9.7%) in thrombolysis up to 4.5 h as were reported in the
NINDS study [1] and other t-PA registries [7,12–19], where
most patients were treated within 3 h. In the ATLANTIS trial
[4], 7.0% of the t-PA treated patients in the 3–5 h time
window had a SICH, compared to 5.3% in our cohort.

In patients treated beyond 3 h, the presence of EIC more
than one-third of MCA territory was associated with the
development of SICH. Although the numbers are low, these
findings again suggest that t-PA should not be used beyond
3 h in patients who show EIC more than one-third of the
MCA territory. Within 3 h, major EIC changes were not
associated with an increased risk of SICH. This is consistent
with the observation from Patel et al, who found no increased
risk of intracerebral hemorrhage in patients with EIC treated
within 3 h after onset [20]. This finding, however, was not
confirmed by Tanne et al. [21].

A substantial number of ischemic stroke patients may
benefit from intravenous t-PA treatment by extending the
time window to 4.5 h. In our cohort, about 1 in 5 of all
admitted ischemic stroke patients were treated with t-PA,
which is a higher proportion than reported in previous
studies [7,13,15,16,18].

Our study is not suited and was not intended to compare
effectiveness because the lack of a placebo group. However,
the pooled trial data from the six pivotal randomized
placebo-controlled t-PA trials suggest some effectiveness
after 3 h; the odds of a favorable outcome decreased from 2.8
(95% CI 1.8–4.5) for treatment within 0 to 1.5 h, 1.5 (95%
CI, 1.1–2.2) for treatment between 1.5 and 3 h and 1.4 (95%
CI, 1.1–1.9) between 3 and 4.5 h. After 4.5 h the lower limits
of the 95% CI for the odds of a favorable outcome cross 1.0
and the benefit of therapy become small and lack
significance [9].

Older age, higher NIHSS score, and presence of EIC on
the CT scan were independent predictors of unfavorable
outcome, which is in accordance with previous reports.
[14,22] The incidence of EIC the early and late group
together (42%) was higher compared to the NINDS (31%)
[20] but comparable with the ECASS I (43%) [23].

The present study has limitations. Firstly, the small
sample size has led to wide confidence intervals around the
point estimates. No trend towards increased risk of
thrombolysis beyond 3 h was found, however. Secondly,
safety and outcome data may be biased because of a lack of a
placebo–controlled design. Even though some significant
imbalance (NIHSS, number of TACI) between the two
cohorts were corrected for, this does not serve to exclude all
relevant bias. Thirdly, the results were obtained from a
single-center that serves as regional stroke reference center.
Since safety and efficacy of thrombolysis depends much on
the experience of a given center [24], our result may have a
limited generalizability. Fourthly, we performed no routine
brain CT scans after thrombolysis, therefore we could not
study the incidence of asymptomatic intracerebral hemor-
raghes in the early and late group.

The safety of thrombolytic therapy for stroke in daily
practice in Europe has been monitored in the Safe
Implementation of Thrombolysis in Stroke Monitoring
Study (SITS-MOST), but this registry, in which we
participate, concerns only stroke patients that are treated
within 3 h. Therefore more studies are required that
investigate the safety and efficacy of t-PA beyond 3 h with
stratification for stroke severity. The results of this study are
an extra argument to participate in further studies because the
results of our study suggest that thrombolysis between 3 and
4.5 h is safe. The ECASS III, an ongoing double blind
randomized placebo–controlled trial, investigates the
efficacy and safety of t-PA in the 3–4.5 h time window. The Third International Stroke Trial (IST-3) is another ongoing trial, which includes patients from 0–6 h after stroke onset. The role of perfusion and diffusion weighted imaging on magnetic resonance imaging (MRI) for selecting eligible stroke patients for t-PA, is investigated in Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET). The Desmoteplase in Acute Ischemic Stroke Trial II (DIAS II), investigates the efficacy and safety of desmoteplase in acute stroke and selects patients on the basis of perfusion/diffusion mismatch on brain MRI/CT imaging.

In summary, efforts should be continued to treat eligible stroke patients with t-PA as soon as possible, but some patients will continue to arrive beyond the recommended 3 h time window. Based on the pooled-analysis, these patients could still benefit from intravenous t-PA when given before 4.5 h. Our study suggests that in a routine clinical setting, intravenous t-PA treatment between 3 and 4.5 h has a safety profile comparable with treatment within 3 h, but strict adherence to the ECASS II, especially with regard to the presence of EIC on brain CT, criteria and treatment by an experienced acute stroke team is mandatory.

Acknowledgements

This study was supported by a grant from the Catharina Heerdt Foundation. We thank Coby Bolwijn for the assessment of the modified Rankin Scale scores.

References