ABSTRACT

**Background:** Awaiting the European approval of thrombolysis, we introduced thrombolysis as a routine treatment for selected patients with acute ischaemic stroke in 1998. Our aim was to assess the feasibility, clinical effectiveness and safety of intravenous thrombolysis with tissue plasminogen activator in patients with acute ischaemic stroke treated in an acute stroke unit.

**Methods:** All patients admitted within 3 h after an acute ischaemic stroke, were considered for thrombolysis. From 1998 to 2002 (52 months) 58 patients were treated. Results from 55 patients with middle cerebral artery ischaemia are presented.

**Results:** Admission delay remained unchanged (median 75 minutes), whereas in-hospital delay (“door to needle time”) was reduced from median 105 to 84 minutes during the study (p=0.002).

16 patients (39%) demonstrated dramatic clinical improvement within two hours and 33 patients (60%) demonstrated a substantial clinical improvement within 24 hours. 11 patients did not improve, 8 patients deteriorated during the first 24 hours. Five patients (9.1%) developed intracerebral haemorrhage, two (1.8%) were symptomatic. At follow-up after 3 months, 27 patients (59%) had achieved independence [modified Rankin Scale (mRS) 0-2], 11 (24%) had an unfavourable outcome (mRS 3-5) and 8 patients (17%) had died. One of the patients died due to a treatment complication (brain stem haematoma) after 17 days.

**Conclusions:** This open treatment study suggests that thrombolysis is feasible and may be administered relatively safely in an acute stroke unit without intensive care facilities. The clinical effect and safety were similar to results in randomised studies and other clinical series.
INTRODUCTION

Intravenous thrombolytic therapy with recombinant tissue plasminogen activator (tPA) is a highly effective treatment for selected patients with acute ischaemic stroke.\(^1\) The benefits are substantial when given within 3 hours of stroke onset. Its use may, however, be limited by delay in hospital admission. The treatment carries an increased risk of intracerebral haemorrhage\(^2\) and treatment with tPA in clinical routine may result in greater risk and lesser benefit than under the optimal conditions of controlled trials. To minimise the risks of thrombolytic therapy, patients should be carefully selected and treated following a strict protocol.\(^3,4\)

PATIENTS AND METHODS

All patients with acute ischaemic stroke admitted within the first 3 h after stroke onset were considered for thrombolytic therapy. Inclusion and exclusion criteria for thrombolytic treatment were mainly based on the National Institute of Neurological Disorders and Stroke (NINDS) study\(^5\). In addition, severely impaired consciousness (coma or stupor) and/or hypodensity of more than 1/3 of the middle cerebral artery (MCA) territory on the initial computed tomography (CT) were considered as exclusion criteria.\(^6,7\) Patients admitted to the hospital with acute stroke were first examined clinically in the emergency department, with focus on consciousness, language and motor deficits. An emergency CT examination was performed and was immediately assessed according to a standardised evaluation of early ischaemic changes.\(^8\) In the stroke unit, neurological deficits were assessed using the National Institute of Health Stroke Scale (NIHSS). The presumed vascular occlusion (proximal MCA\(^1\) or distal MCA\(^2\) occlusion, lacunar infarct, anterior or posterior cerebral artery infarct) was defined on the basis of the neurological examination and according to the OCSP classification.\(^9\) Patients received 0.9 mg/kg recombinant tPA (alteplase; Actilyse\(^\oplus\), Boehringer Ingelheim), 10% as a bolus and 90% as a continuous intravenous infusion over 60 min. Aspirin and heparin were not given during the first 24 hours after thrombolytic treatment.

Clinical assessment with the NIHSS was repeated after 2 and 24 hours. Cerebral CT examination was repeated after 22-36 h. Haemorrhagic transformation on CT was defined according to the ECASS studies as either haemorrhagic infarction or parenchymal haematoma.\(^6,7\) A symptomatic haemorrhage was defined as a parenchymal haematoma with a clinical deterioration of \(\geq 4\) NIHSS points. An early dramatic recovery related to
Thomassen

Thrombolysis was defined as an improvement of ≥10 NIHSS points or a decrease to NIHSS score of ≤3 two hours after the end of infusion.10 A substantial clinical improvement probably related to thrombolysis was defined as an improvement of ≥4 points on the NIHSS 24 hours after treatment.

Final outcome was assessed by a telephone interview using the modified Rankin Scale (mRS; grade 0-6). Favourable outcome was defined as mRS grade 0-2, i.e. independence. If there was uncertainty about the mRS outcome group, the patient was placed in the lower (worse) of the two possible groups. For practical reasons, final assessment of the first 7 patients was carried out at 6 months. We therefore report outcome for the next 46 patients who have a follow up at 3 months, including all patients that died during the study period.

To assess possible changes in patient admission, stroke severity, or outcome over time, we analysed the data from the first two years vs. the last two years of the study.

**RESULTS**

From May 1998 to oktober 2002, thrombolytic treatment was administered to 58 acute stroke patients, 34 men and 24 women who had a median age of 74 years (range 18-79 years). 55 patients had an ischaemic lesion in the MCA territory, two had a basilar artery thrombosis and one patient had a psychogenic hemiparesis. The treated patients represented approximately 3% of all patients with acute stroke admitted to our department during the study period. We present the results of the 55 patients with a MCA territory cerebral infarction.

17 patients were admitted with clinical signs and symptoms compatible with a left proximal MCA (MCA₁) occlusion and seven with a right MCA₁ occlusion. 19 patients clinically had a left distal MCA (MCA₂) occlusion with severe aphasia as the predominant symptom, five patients had right MCA₂ occlusions. Seven patients clinically had a lacunar infarction in the internal capsule. The patients had an average NIHSS score of 12 at the time of thrombolysis.
Six patients were in-patients at stroke onset; the remaining 49 patients had a median hospital admission delay of 65 min (range 25-150 min). Ten patients were examined with CT and/or MR. Among the remaining 39 patients examined only with CT, the total in-hospital delay before treatment was median 96 min (range 47-152 min) (table1).

Table 1: Delay from stroke onset to hospital admission and in-hospital delay for 39 patients treated with tPA. Time in minutes (median).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Delay</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset to admission</td>
<td>65</td>
<td>25 –150</td>
</tr>
<tr>
<td>Admission to treatment</td>
<td>96</td>
<td>47 – 152</td>
</tr>
<tr>
<td>• Admission to examination</td>
<td>5</td>
<td>0 - 35</td>
</tr>
<tr>
<td>• Examination to CT scan</td>
<td>30</td>
<td>6 – 100</td>
</tr>
<tr>
<td>• CT scan to stroke unit</td>
<td>28</td>
<td>15 – 110</td>
</tr>
<tr>
<td>• Stroke unit to treatment</td>
<td>19</td>
<td>2 – 70</td>
</tr>
<tr>
<td>Onset to treatment</td>
<td>165</td>
<td>44 – 244</td>
</tr>
</tbody>
</table>

Hospital admission delay, stroke severity (baseline NIHSS score), and outcome (mRS) was not significantly different among patients treated during the last two years of the study as compared to the first two years, whereas in-hospital delay was reduced from median 105 min to 84 min (p=0.002).

The patients (n=55) were treated median 165 min (range 44-244 min) after stroke onset. One patient received thrombolysis within 1 hour, 5 patient within 2 hours, and 38 patients (69%) received treatment within 3 hours. 11 patients (20%) were treated later than 3 hours (median 192 min, range 184-244 min) after stroke onset. The reason for delayed treatment was mostly incorrect initial information about stroke onset.

Five patients (9%) treated 44-192 min (median 180 min) after stroke onset suffered some haemorrhagic transformation of the infarct, but only one patient (1.8%) had a symptomatic intracerebral haemorrhage (SICH). This patient had a baseline NIHSS score 14, developed after 3 ½ hours a brain stem haematoma with severe deterioration (11 NIHSS points), and died on day 17.
Four patients (5.5%) died during the acute phase of their strokes. A 71-year-old woman developed a mesenterial thrombosis and died after 30 hours. A 53-year-old man died after 43 hours due to a malignant cerebral oedema. A 79-year-old woman died on day 17 due to complications following a brain stem haematoma, and a 75-year-old man died in a nursing home on day 8 due to non-bleeding complications following his stroke.

At follow-up after 3 months (n=46), 27 patients (59%) had achieved a favourable outcome with independence (mRS 0-2), 11 patients (24%) had an unfavourable outcome (mRS 3-5) and 8 patients (17%) had died (mRS 6).

Figure 1: Outcome after 3 months. mRS = Modified Rankin Scale. mRS 0-2 = favourable outcome (independence), mRS 3-5 = unfavourable outcome, mRS 6 = death.

<table>
<thead>
<tr>
<th></th>
<th>mRS 0-2</th>
<th>mRS 3-5</th>
<th>mRS 6</th>
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<tbody>
<tr>
<td>NINDS (n=312)</td>
<td>43</td>
<td>40</td>
<td>21</td>
</tr>
<tr>
<td>STARS (n=389)</td>
<td>43</td>
<td>44</td>
<td>13</td>
</tr>
<tr>
<td>Houston (n=30)</td>
<td>37</td>
<td>43</td>
<td>20</td>
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<tr>
<td>Cologne (n=100)</td>
<td>53</td>
<td>35</td>
<td>12</td>
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<tr>
<td>Calgary (n=68)</td>
<td>57</td>
<td>27</td>
<td>16</td>
</tr>
<tr>
<td>Bergen (n=46)</td>
<td>59</td>
<td>24</td>
<td>17</td>
</tr>
</tbody>
</table>

DISCUSSION

The findings of this clinical study suggest that thrombolytic treatment for acute ischaemic stroke is feasible and relatively safe in an acute stroke unit, which does not have intensive care facilities.

The median admission delay in this study (68 min) is comparable to other open prospective studies, which report admission delays of 57-68 min. The median in-hospital delay before treatment was significantly reduced during our study, but close to 90% of the patients were nevertheless treated more than 2 h after stroke. This emphasises the need for
continuous improvement and updating of the hospital routines so that the time to treatment can be maintained at a minimum.

The baseline stroke severity in the patients in this study (average NIHSS score 12, range 2-28) was slightly lower than in the NINDS study (average NIHSS score 14, range 2-37) \(^5\), and other open prospective studies.\(^{11-16}\) 39% of our patients showed a dramatic recovery within the first 2 hours after thrombolytic treatment, and 50% showed a substantial clinical improvement within 24 hours. These findings are compatible with an early tPA effect, but may also be due to early spontaneous recanalisation, which may occur in 25% of patients during the first 24 hours.\(^{17,18}\)

We found a favourable outcome (mRS 0-2) in 59% of the patients. This was similar to the NINDS study\(^5\) and phase IV studies of tPA\(^{11-16}\) (figure 1), which reported a favourable outcome at 3 months in 43-57% of treated patients.

The 9.1% rate of haemorrhagic transformation, and the 1.8% rate of symptomatic intracerebral haemorrhages in this study are also comparable to other phase IV studies of tPA, in which 4-14% of the patients developed some haemorrhagic transformation of the infarct.\(^{11-16}\)

The results of this study support the conclusion from several previous studies, that thrombolytic treatment with tPA for acute ischaemic stroke is feasible, and that the outcome and haemorrhagic complication rates found in the randomised trials may be reproduced in clinical practice.

**ACKNOWLEDGEMENTS**

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REFERENCES


