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Routine thrombolysis with intravenous tissue plasminogen activator in acute ischaemic stroke patients aged 80 years or older: a single centre experience

SIR—Treatment with intravenous tissue plasminogen activator (t-PA) in acute ischaemic stroke has been shown to improve outcome [1]. Little is known regarding the safety and efficacy of this treatment in patients aged 80 years and older, because this age group was underrepresented in clinical trials [1–4]. The NINDS trial [1] was the only trial without age limit and only 7% ($n = 42$) of the included patients were older than 80 years. However, about 30% of admitted ischaemic stroke patients are older than 80 years [5].

A number of previous observational studies compared the outcome of t-PA treatment in patients older than 80 years with their younger counterparts [6–12], and a recent systematic review suggested that t-PA is safe in older patients, despite a higher 3-month mortality and a less favourable functional outcome [13].

In this study, we compared the safety and outcome of t-PA treatment in patients aged 80 years and older with their younger counterparts in a prospective cohort from the University Medical Center Groningen (UMCG). In contrast to most previous studies, we not only investigated the 3-month mortality but we also compared the early in-hospital mortality at 7 days between the two groups.

Methods

UMCG cohort

After participation in the European Cooperative Acute Stroke Study (ECASS) II, our centre started with t-PA treatment for eligible stroke patients and served as referral centre for regional community hospitals. An ongoing prospective registry of patients treated with t-PA was started in April 2002. This study analysed the period between April 2002 and January 2006. Inclusion and exclusion criteria were based on those of the NINDS trial.

Neurological deficit before start of t-PA treatment was recorded with the National Institute of Health Stroke Scale (NIHSS). All patients had a brain CT scan, blood investigation and electrocardiography. Baseline variables such as gender, age, vascular risk factors, serum glucose concentration and antiplatelet medication were recorded. Stroke-subtypes were defined into lacunar infarcts (LACI) and non-lacunar infarcts (total anterior circulation infarcts (TACI) and partial anterior circulation infarcts (PACI) and posterior circulation infarcts (POCI)) according to the Oxfordshire Community Stroke Project Classification [14].

Patients were treated with intravenous t-PA according to the NINDS protocol. After treatment, 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.

For the safety analysis, we defined the following outcome measures: incidence of symptomatic intracerebral haemorrhage (SICH), early in-hospital mortality within 7 days and 3-month mortality. SICH was defined as a neurological deterioration within 48 h following thrombolysis, with an intraparenchymal haematoma demonstrated by CT scan, which could explain the deterioration. Functional outcome was assessed after 3 months using the modified Rankin Scale (mRS). The mRS was divided into favourable outcome (mRS 0–1) and unfavourable outcome (mRS 2–6). Data were analysed separately in the young and old age groups and compared between both groups.

Statistical analysis

All statistical analyses were done using SPSS version 11.0. The Mann–Whitney U and the $t$-test were used for continuous and ordinal variables, and the $\chi^2$ test, or Fisher exact test, for dichotomous variables. Confidence intervals for proportions were calculated using Wilson’s method. For the functional outcome and 3-month mortality, a multivariate analysis was done to adjust for possible confounders: NIHSS score, time from onset until treatment, stroke subtype (lacunar versus non-lacunar) and blood glucose concentration.

Results

UMCG cohort

Baseline characteristics

Between April 2002 and January 2006, 1029 consecutive ischaemic stroke patients were admitted to our department, of whom 142 received t-PA treatment within 3 h after onset. All patients were independent (mRS 0–2) before admission. Of the 142 treated patients, 111 (78%) were younger than 80 years and 31 (22%) were 80 years or older. Baseline characteristics of both groups are summarised in the Table 1.

The median NIHSS tended to be higher in the older group (15, range 6–22 versus 13, range 2–23), although this did not reach a statistical significant difference ($P = 0.197$).

Older patients had a longer onset to treatment time (mean time 158 min versus 145 min in younger patients, $P = 0.022$) and were less likely to have a lacunar stroke (3% versus 19% in the younger group, $P = 0.046$).
Research letters

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>&lt;80 years</th>
<th>≥ 80 years</th>
<th>Group comparison</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, no. (%)</td>
<td>61 (55%)</td>
<td>12 (39%)</td>
<td></td>
<td>0.110</td>
</tr>
<tr>
<td>Age (y)</td>
<td>63.9 ± 13.0</td>
<td>83.6 ± 3.5</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>68 (29–79)</td>
<td>82 (80–91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS</td>
<td>12.7 ± 5.1</td>
<td>14.3 ± 4.6</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>13 (2–23)</td>
<td>15 (6–22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OTT (min.), mean ± SD</td>
<td>145.1 ± 30.7</td>
<td>157.8 ± 23.9</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td>Lacunar stroke</td>
<td>21 (19%)</td>
<td>1 (3%)</td>
<td>0.044</td>
<td></td>
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<tr>
<td>EIC on CT no. (%)</td>
<td>48 (43%)</td>
<td>12 (38%)</td>
<td>0.651</td>
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<td>Bloodpressure (mm Hg)</td>
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<tr>
<td>Systolic</td>
<td>152 ± 24</td>
<td>159 ± 26</td>
<td>0.195</td>
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<tr>
<td>Diastolic</td>
<td>83 ± 13</td>
<td>79 ± 15</td>
<td>0.125</td>
<td></td>
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<tr>
<td>Glucose level (mmol/l)</td>
<td>6.2 ± 1.5</td>
<td>6.4 ± 1.5</td>
<td>0.369</td>
<td></td>
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<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular risk factors no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>24 (21.6%)</td>
<td>12 (38.7%)</td>
<td>0.053</td>
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<tr>
<td>Hypertension</td>
<td>53 (48%)</td>
<td>12 (39%)</td>
<td>0.372</td>
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<tr>
<td>Diabetes</td>
<td>14 (13%)</td>
<td>3 (10%)</td>
<td>1.004</td>
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<tr>
<td>Hyperlipidaemia</td>
<td>31 (28%)</td>
<td>5 (10%)</td>
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<tr>
<td>Prior stroke</td>
<td>18 (16%)</td>
<td>3 (10%)</td>
<td>0.564</td>
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<tr>
<td>Current smoking</td>
<td>38 (34%)</td>
<td>5 (16%)</td>
<td>0.090</td>
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<td>Prior use of antiplatelets</td>
<td>32 (29%)</td>
<td>14 (45%)</td>
<td>0.086</td>
<td></td>
</tr>
</tbody>
</table>

OTT = onset to treatment time, EIC = early ischaemic changes
^χ2-test.
^b Mann–Whitney U-test.
^c T-test.
^d Fisher’s Exact Test.

Outcome

SICH occurred in four of the younger patients (3.6%; 95% CI 1.4–8.9) of which two were fatal, and in three of the older patients (9.7%; 95% CI 3.3–24.9) of which two were fatal (P = 0.176).

The in-hospital mortality at 7 days was 10.8% (95% CI 6.3–18.0, n = 12) in the younger group and 12.9% (95% CI 5.1–28.9, n = 4) in the older group (P = 0.751).

After 3 months, 12.6% (95% CI 7.7–20.1, n = 14) of the younger patients who died had died compared with 45.2% (95% CI 29.2–62.2, n = 14) of the older patients (P < 0.001). Of the ten older patients who died after 7 days and within 3 months, the cause of death was sequel to stroke (n = 3), cardiopulmonary failure (n = 5), and unknown (n = 2). After adjustment for confounders, age ≥ 80 years was independently associated with a higher mortality rate (OR 6.3; 95% CI 2.1–19.0).

The distribution of the mRS scores 3 months after treatment is presented in the Figure I. Five patients aged 80 years or older (16.1%; 95% CI 7.1–32.6) and 40 patients younger than 80 years (36.0%; 95% CI 27.7–45.3) had a favourable outcome (P = 0.004). After adjustment for confounders, a non-significant trend towards unfavourable outcome (mRS 2–6) was observed in the older patients (OR 2.6; 95% CI 0.8–8.7).

Discussion

The results of our study demonstrated that t-PA treatment in acute ischaemic stroke in patients aged 80 years or older, has a comparable safety profile with their younger counterparts.

The overall incidence of SICH (4.9%) in our cohort was similar to other studies [6–11, 15, 16], the systematic review from Engelter et al. [13] and the NINDS study [1]. In line with previous studies, the mortality rate at 3 months was significantly higher in the group of 80 years or older [7–10]. We also compared the early in-hospital mortality, which was not different between the two groups. This means that the high mortality rate at 3 months is not related to acute stroke therapy, but to factors that occur after hospital discharge. Frail, vulnerable elderly who had a stroke have a higher prevalence of comorbidity and are more susceptible to complications and other illnesses than younger patients.

A favourable outcome at 3 months after t-PA treatment was significantly less frequent in the older patients, but is in line with the natural course of ischaemic stroke in this age group, demonstrated by other studies [17]. Older patients may have had already a higher mRS score on admission, however, we did not thrombolise any patient with significant pre-existent disability. In our cohort, older patients had a longer onset to treatment time, which could have confounded the outcome after 3 months.

It is important to note that our and previous cohorts did not investigate the effectiveness of t-PA in the older patients. A randomised placebo controlled trial, the Third International Stroke Trial (IST-3), which also investigates the effectiveness of t-PA in patients older than 80 years, is ongoing.

Despite higher mortality and less favourable outcome in the very older patients treated with t-PA in acute stroke, the safety profile of treatment seems acceptable. At this moment, efficacy data are lacking, and therefore the decision to thrombolise older stroke patients should be made on an individual basis.

Key points

- Intravenous thrombolysis for acute ischaemic stroke patients aged 80 years or older seems safe with respect to the incidence of symptomatic intracerebral haemorrhage.
- The early in-hospital mortality rate after thrombolysis in older patients is comparable with younger patients, despite higher 3-month mortality in older patients.
- Older patients had less frequently a favourable outcome after 3 months compared to younger patients. This may be related to an increased vulnerability to complications and a higher prevalence of comorbidity in the elderly.
References


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