Safety of intravenous thrombolysis for ischaemic stroke in Asian octogenarians and nonagenarians

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Abstract

Background: symptomatic intracerebral haemorrhage (ICH) is a major concern of intravenous thrombolysis (IVT) for ischaemic stroke. Asians are considered more vulnerable to ICH than non-Asians. Reports on safety of IVT for Asian octogenarians and nonagenarians are limited.

Aims: the aims of our study were to compare the safety of IVT between octogenarians and nonagenarians and between Asian and Western patients.

Methods: patients receiving IVT for ischaemic stroke were prospectively registered from four hospitals in Taiwan. Octogenarians and nonagenarians were recruited for analysis. The primary safety outcome measure was symptomatic ICH. The secondary outcome measure was 3-month mortality. We searched the literature on IVT for ischaemic stroke for comparison.

Results: from January 2007 to December 2012, a total of 186 (18.3%) ischaemic stroke patients aged 80 and older, including 166 octogenarians and 20 nonagenarians, were recruited from 1,018 patients receiving IVT. Nine (4.8%) of recruited patients had symptomatic ICH, all in the octogenarian group (5.4%). Three-month mortality was 14.1% in recruited patients and without difference between the two age groups (P = 0.558). The results were comparable with reports on Western octogenarians and nonagenarians in the literature.

Conclusion: octogenarians and nonagenarians receiving IVT have a similar safety outcome. Asian octogenarians and nonagenarians receiving IVT for ischaemic stroke are not at higher risk of symptomatic ICH and mortality than Western patients.

Keywords: acute ischaemic stroke, Asians, intracerebral haemorrhage, intravenous thrombolysis, older people

Introduction

Octogenarians and nonagenarians are particularly susceptible to stroke than younger (aged <80) individuals. Patients aged 80 and older are likely to have lower rates of positive outcomes following treatment than younger patients [1–5]. Some observational studies and meta-analyses indicate that very elderly patients might benefit and should not be routinely excluded from intravenous tissue-type plasminogen activator (t-PA) treatment [1, 2, 6]. Symptomatic intracerebral haemorrhage (SICH) is the major concern of intravenous thrombolysis (IVT) for ischaemic stroke. Reports suggest that Asians are more vulnerable to ICH than non-Asians [7, 8]. Safety of IVT in patients aged 80 and older is of importance in this World’s largest population with an increasing burden of stroke [9, 10].
The majority of studies reporting IVT in octogenarians and nonagenarians were from Caucasians. We undertook this study to assess the safety of IVT for stroke in octogenarians and nonagenarians from four hospitals in Taiwan and compare its safety between our and Western patients.

**Methods**

**Study population**

Changhua Christian Hospital (CCH), National Cheng Kung University Hospital (NCKUH), National Taiwan University Hospital (NTUH) and Chiayi Christian Hospital (CYCH) are high-volume hospitals of IVT without upper age limit in Taiwan. Patients were prospectively registered in the four hospitals according to the description of the Taiwan Stroke Registry [11]. All hospitals’ Institutional Review Boards approved the conduct of the registry.

The inclusion and exclusion criteria for IVT were similar to those of the SITS-MOST study, but without an upper age limit [12]. Please see Supplementary data, Appendix 1 available in *Age and Ageing* online for detail treating process.

**Definition of haemorrhagic events**

All patients received brain scans (either computed tomography (CT) or magnetic resonance imaging) before and within 36 h after thrombolysis. The radiologic definition of haemorrhagic events was according to the European Cooperative Acute Stroke Study classification [13]. Parenchymal haemorrhage (PH) was classified as follows: PH1—blood clots in ≤30% of the infarcted area, with slight space-occupying effect and PH2—blood clots in >30% of the infarcted area, with a substantial space-occupying effect. Results of the official neuroradiology report were used to determine the presence of ICH on follow-up scans. Radiologists were blinded to the patient clinical characteristics.

**Outcome measures**

This study aimed to investigate safety of IVT in very elderly patients. Among haemorrhagic events, PH2 was shown to be of clinical significance [14]. Therefore, the primary outcome measure was SICH which was defined as in SITS-MOST [12] (a National Institute of Health Stroke Scale (NIHSS) score increase of ≥4 points or leading to death and a local or remote PH2 on the 22-h to 36-h post-treatment CT scan). We also added SICHs defined in National Institute of Neurological Disorders and Stroke [NINDS] criteria [15] (an NIHSS score increase of ≥1 points or death within 36 h and a PH on CT in a location compatible with the clinical symptoms). The classification of SICH was determined by one senior stroke neurologist in each hospital (CCH, MCS; NCKUH, CHC; NTU, JS; CYCH, SFS).

The secondary outcome was 3-month mortality. We also analysed favourable outcome which was defined as the proportion of patients with a modified Rankin Scale (mRS) score of 0–1 or recovery to pre-stroke functional status at 3 months.

**IV thrombolysis for the very elderly in Asians**

**Statistical analysis**

The baseline characteristics, safety and outcome were analysed. Comparisons between octogenarians and nonagenarians were performed with the t-test, the Mann–Whitney test, Fisher’s exact test or the χ² test, whenever applicable. A P-value of <0.05 was considered to be statistically significant.

**Results**

From January 2007 to December 2012, 1,018 patients receiving IVT were registered from 4 hospitals (CCH 302; NCKUH 274; NTUH 281; CYCH 161). A total of 186 (18.3%) patients were aged 80 and older, including 166 octogenarians (CCH/NCKUH/NTUH/CYCH 62/54/38/12) and 20 nonagenarians (CCH/NCKUH/NTUH/CYCH 8/6/3/3). Patient characteristics are presented in Supplementary data, Appendix 2 available in *Age and Ageing* online.

Table 1 shows the percentage of ICH and 3-month status in all patients, octogenarian and nonagenarian groups. Overall, PH was higher in the nonagenarians, but not statistically significant. There was no PH2 in the nonagenarians. Therefore, none of the nonagenarians had SICH per SITS-MOST. The percentage was 5.4% in the octogenarian group and 4.8% in all enrolled patients. SICH per NINDS was 8.6% in all enrolled patients and was similar in both groups. One octogenarian was not followed up at 3 months. Overall, follow-up patients were 185 (99.5%). Three-month mortality was 14.1% (26/185) in all follow-up patients and without difference between the two groups. Favourable outcome was 23.2% in all follow-up patients. Both age groups had similar percentage of favourable outcome. More patients in the octogenarian group than the nonagenarian group had an mRS score 0–1 at 3 months. Percentage of patients recovered to pre-event functional status was higher in the nonagenarians.

To evaluate the independent predictors of SICH and 3-month mortality, logistic regression analysis was applied. The variables entered were age, sex, initial NIHSS score, hypertension, diabetes mellitus, prior stroke, smoking habit, initial systolic blood pressure, platelet count and stroke subtype (cardioembolism versus non-cardioembolism). No independent predictor for SICH was identified. Age group (octogenarian versus nonagenarian) was not a predictor for SICH per SITS-MOST (P = 0.998) or per NINDS (P = 0.856). Initial NIHSS score (OR 1.077, 95% CI 1.005–1.154, P = 0.036), but not other variable, was a predictor for 3-month mortality. In comparison with aged <80, less favourable outcome was found in aged ≥80, but the SICH per SITS-MOST was similar (Supplementary data, figure available in *Age and Ageing* online).

**Discussion**

The results of our study indicated that there is no significant difference in safety and outcome between nonagenarians and octogenarians treated with IVT. We searched the literature on IVT for stroke in octo- and nonagenarians and only two
Table 1. ICH and 3-month status in all patients, octogenarian and nonagenarian groups

<table>
<thead>
<tr>
<th>Total (n = 186)</th>
<th>Octogenarians (n = 166)</th>
<th>Nonagenarians (n = 20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PH (ECASS definition)</td>
<td>27 (14.5)</td>
<td>23 (13.9)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>PH1</td>
<td>14 (7.5)</td>
<td>10 (6.0)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>PH2</td>
<td>13 (7.0)</td>
<td>13 (7.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>sICH per SITS-MOST (%)</td>
<td>9 (4.8)</td>
<td>9 (5.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>sICH per NINDS (%)</td>
<td>16 (8.6)</td>
<td>14 (8.4)</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>3-month status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>26 (14.1)</td>
<td>23 (13.9)</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Favourable outcome</td>
<td>43 (23.2)</td>
<td>38 (23.0)</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>mRS 0-1</td>
<td>20 (15.7)</td>
<td>28 (17.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Pre-stroke status</td>
<td>27 (14.6)</td>
<td>23 (13.9)</td>
<td>4 (20.0)</td>
</tr>
</tbody>
</table>

sICH, symptomatic intracranial haemorrhage.

aOne missing data in the octogenarian group.
bPatients recovered to pre-stroke functional status.

Table 2. Comparisons of different studies with octogenarian and nonagenarian groups

<table>
<thead>
<tr>
<th>Country</th>
<th>Taiwan (current) N = 186</th>
<th>Switzerland [17] N = 284</th>
<th>Canada [16] N = 270</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age groups</td>
<td>80–89</td>
<td>90–99</td>
<td>80–89</td>
<td>90–99</td>
</tr>
<tr>
<td>N</td>
<td>166</td>
<td>20</td>
<td>238</td>
<td>46</td>
</tr>
<tr>
<td>NIHSS*</td>
<td>17.0</td>
<td>17.8</td>
<td>12.9</td>
<td>14.4</td>
</tr>
<tr>
<td>SICH per SITS-MOST (%)</td>
<td>4.8</td>
<td>6.0</td>
<td>4.7</td>
<td>13.3</td>
</tr>
<tr>
<td>SICH per NINDS (%)</td>
<td>8.6</td>
<td>7.1</td>
<td>8.4</td>
<td>10.0</td>
</tr>
<tr>
<td>3-month status (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>14.1</td>
<td>25.6</td>
<td>35.3</td>
<td>45.2</td>
</tr>
<tr>
<td>Favourable outcome</td>
<td>23.2</td>
<td>27.8</td>
<td>25.7</td>
<td>51.9</td>
</tr>
</tbody>
</table>

*Mean in Taiwan and Switzerland studies, median in Canada study.

bPatients who had mRS 0-1 in Canada and Switzerland studies, patients who had mRS 0-1 or recovered to pre-stroke functional status in Taiwan study.

studies were identified (Table 2). The Canadian study suggested there is no significant difference in 90-day mortality, 30-day functional outcome or rate of SICH between nonagenarians and octogenarians [16]. On the contrary, the Swiss study suggested that nonagenarians less often had a favourable outcome and had a higher incidence of mortality and SICH than octogenarians [17]. Because the definition of SICH in the Canadian study was different from SITS-MOST and NINDS, the results was not used for direct comparison. The overall rate of SICH in octo- and nonagenarians was not significantly different between ours and the Swiss study, either with the definition of SITS-MOST or NINDS. Interestingly, we did not find that nonagenarians had a higher risk of SICH than octogenarians as in the Swiss study. Less diabetes in our nonagenarian group might be the reason. Diabetes was demonstrated to be a predictor of SICH after thrombolysis for stroke [18]. Similarly, nonagenarians had less diabetes than octogenarians in the Canadian study (4 versus 13%, *P* = 0.219), but not in the Swiss study (13.9 versus 11.1%, *P* = 0.619). Small sample size could be the reason that we did not find diabetes as a predictor for SICH. Data of mortality at 3 months were available in the two studies. Mortality rates of the follow-up patients, octogenarians and nonagenarians at 3 months were the lowest in our study and the highest in the Canadian study. The results suggest that safety of IVT in our patients was comparable with that in Western patients.

Reports regarding IVT in Asian octo- and nonagenarians are limited in the literature (Supplementary data, Appendix 3 available in Age and Ageing online). A total of 217 Asian patients aged ≥80 were identified. The 3-month mortality rate was 15.7%, which is not >32.2% in the Western reports (Supplementary data, Appendix 3 available in Age and Ageing online). 26.7% of Asian and 31.5% of non-Asian patients had an mRS score 0–2 at 3 months. In terms of 3-month mortality after thrombolysis, Asian patients aged ≥80 were not at higher risk than Western patients. A limitation of our study is that optimal dose of t-PA in Asia remains controversial, ranges from 0.6 to 0.9 mg/kg body weight [19, 20]. The mean t-PA dose used in our patients was 0.77 mg/kg body weight that was lower than standard dose (0.9 mg/kg body weight) used in the Western. Although there is no randomised controlled trial on optimal t-PA dose for Asians, we have demonstrated that low dose may have similar safety and efficacy as standard dose [19]. To our knowledge, this is the first Asian report on IVT for
ischaemic stroke in octogenarians and nonagenarians. The other two Western reports for comparison were also multicentre studies [16, 17]. All three studies represented a real world experience of thrombolysis for octogenarians and nonagenarians. Another limitation is the small number of nonagenarians. The other limitation is that half of our nonagenarians had a pre-event mRS ≥2. This might interfere with the evaluation of functional outcome after treatment. Pre-event functional status was not presented in the other two reports [16, 17].

In conclusion, the results of our study indicate that octogenarian and nonagenarian patients have a similar safety outcome of IVT for ischaemic stroke. It is not likely that Asian patients aged 80 and older are at higher risk of SICH and mortality than Western patients.

Key points

- Very elderly Asians are particularly at risk of ICH receiving intravenous t-PA.
- Previous studies reporting thrombolytic therapy for the very elderly were mainly from Caucasians.
- Very elderly Asians are not at higher risk of ICH and mortality than Western stroke patients.

Supplementary data

Supplementary data mentioned in the text are available to subscribers in Age and Ageing online.

Conflicts of interest

None declared.

References


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