Early profiles of clinical evolution after intravenous thrombolysis in an unselected stroke population

M G Delgado, P Michel, M Naves, et al.

*J Neurol Neurosurg Psychiatry* 2010 81: 282-285 originally published online
October 22, 2009
doi: 10.1136/jnnp.2009.185363

Updated information and services can be found at:
http://jnnp.bmj.com/content/81/3/282.full.html

These include:

**References**
This article cites 23 articles, 15 of which can be accessed free at:
http://jnnp.bmj.com/content/81/3/282.full.html#ref-list-1

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To order reprints of this article go to:
http://jnnp.bmj.com/cgi/reprintform

To subscribe to *Journal of Neurology, Neurosurgery & Psychiatry* go to:
http://jnnp.bmj.com/subscriptions
Early profiles of clinical evolution after intravenous thrombolysis in an unselected stroke population

M G Delgado,1 P Michel,2 M Naves,1 P Maeder,3 M Reichhart,2 M Wintermark,4 J Bogousslavsky5

ABSTRACT

Background Intravenous recombinant tissular plasminogen activator (rt-PA) is the only approved pharmacological treatment for acute ischaemic stroke. The authors aimed to analyse potential causes of the variable effect on early course and late outcome. Methods and results 136 patients (42% women, 58% men) treated with intravenous rt-PA within 3 h of stroke onset in an acute stroke unit over a 3-year period, were included. Early clinical profiles of evolution at 48 h were divided into clinical improvement (CI) (decrease >4 points in the National Institute of Health Stroke Scale (NIHSS)); clinical worsening (CW) (increase >4 points NIHSS); clinical worsening after initial improvement (CWFI) (variations of >4 points in the NIHSS). Patients with clinical stability (no NIHSS modification or <4 points) were excluded. The patients showed in 66.9% CI, 13.2% CW 8.1% CWFI and 11.8% remained stable. Female sex, no hyperlipaemia and peripheral arterial disease were associated with CW. Male sex and smoking were associated with CI. Absence of arterial occlusion on admission (28.4%) and arterial recanalisation at 24 h were associated with CI. Main causes of clinical deterioration included symptomatic intracranial haemorrhage (sICH), persistent occlusion and cerebral oedema. 23.5% developed ICH, 6.6% of which had sICH. At 3 months, 15.5% had died. Mortality was increased in CW, mainly related to sICH and cerebral oedema. The outcome of CWFI was intermediate between CW and CI. Conclusions Early clinical profiles of evolution in thrombolysed patients vary considerably. Even with CI, it is critical to maintain vessel permeability to avoid subsequent CW.

INTRODUCTION

Intravenous recombinant tissular plasminogen activator (rt-PA) has been approved in 1996 by the Food and Drugs Administration for the USA and in 2002 by the European Medicines Agency for Europe, for acute stroke treatment within 3 h of stroke onset. After intravenous rt-PA treatment, clinical evolution varies, with minimal or no changes in clinical status, improvement or worsening, sometimes after some clinical improvement. The aim of our study was to analyse the causes of these clinical profiles of evolution within 48 h after intravenous rt-PA treatment in a thrombolysed stroke population.

METHODS

We studied consecutive patients treated with intravenous rt-PA at a University Hospital (Centre Hospitalier Universitaire Vaudois—Lausanne). Inclusion criteria were ischaemic stroke in any territory, age 18 years or older (if over 80 years old, treatment depending on prestroke dependency and comorbidity), onset to treatment time ≤3 h, cranial tomography (CT) scan without haemorrhagic lesion and neurological status ≥6 points in the National Institute of Health Stroke Scale (NIHSS). Exclusion criteria were similar to those used in the NINDS study.1 The treatment was initiated in the emergency department after the CT study, using intravenous rt-PA (0.9 mg/kg). Non-contrast CT scan and perfusion CT (P-CT) was performed prior to the rt-PA treatment, whereas intracranial and extracranial angio-CT were performed at 24 h after the procedure and whenever the patient worsened. If creatinine clearance was <50 ml/min using the Cockcroft formula (<50 ml/min if patient on metformin), the patient was not given intravenous contrast. If creatinine clearance was 50–50 ml/min, the patient received 300 ml of isotonic sodium chloride solution in 30 min followed by 1 ml kg−1 h−1 over the following 12 h, and oral N-acetylcysteine for 48 h. None of the patients who received contrast medium developed renal failure.

The P-CT examination consisted of two 40-series at an interval of 5 min, each series consisting of one image per second in cine mode during intravenous administration of iodinated contrast material. The acquisition parameters for both series were 80 kV and 100 mA. For each series, CT scanning was initiated 7 s after the injection of 50 ml iohexol at a rate of 5 ml s−1 into an antecubital vein with a power injector. The time delay before contrast material reached the brain parenchyma allowed the acquisition of baseline images without contrast enhancement. Multidetector-array technology allowed data acquisition from two adjacent 10 mm sections for each series. The two P-CT series thus allowed data acquisition in four adjacent 10 mm cerebral CT sections.2 The mean transit time map results from a deconvolution of the parenchymal concentration curves by a reference arterial curve. The deconvolution operation requires a reference arterial input function, the selection of which is automatically performed by the P-CT software. The cerebral blood volume (CBV) map is inferred from a quantitative measurement of the partial size-averaging effect, which is absent at the centre of the large superior sagittal venous sinus. A simple equation combining CBV and mean transit time (MTT) values leads to the cerebral blood flow (CBF) value.3 Penumbra and infarct maps can thus be inferred from relative CBV and relative CBF maps. The
cerebral and cervical CT angiography was performed from the origin of the aortic arch branch vessels to the circle of Willis.

Carotid and transcranial duplex were carried out within 48 h after admission. NIHSS, Barthel Index and modified Rankin Scale (mRS) were used to assess clinical status and functional status. Patients who died were given the worst possible score in clinical scales such as the NIHSS. We used the TOAST criteria for stroke aetiological classification. Information on demographics, risk factors and previous strokes was obtained from the patient, next of kin and family physician. Pretreatment glycaemia, temperature, cholesterol, fibrinogen, INR, platelet count, blood pressure and haematocrit were recorded.

Clinical profiles of evolution within the first 48 h were divided into clinical improvement (CI), with a decrease of ≥4 points NIHSS; clinical worsening (CW), with an increase of ≥4 points NIHSS; and clinical worsening after initial improvement (CWFI), with a decrease of ≥4 points NIHSS followed by an increase of ≥4 points NIHSS. Patients with clinical stability (no NIHSS modification or <4 points in the NIHSS) were excluded. Patients were observed clinically in a neurological intermediate care unit on an hourly basis during the day and every 3 h at night. We defined intracranial symptomatic haemorrhage (sICH) as clinical worsening of ≥4 points in the NIHSS best attributed to intracranial haemorrhage. Any other ICH was considered as asymptomatic (aICH).

We classified causes of clinical deterioration as symptomatic intracranial haemorrhage (sICH), cerebral oedema, early stroke recurrence defined as an acute onset clinical worsening that was best explained by a new ischaemic event after repeat radiological evaluation, persistent arterial occlusion (or reclosure) and others (including systemic and unknown causes). Occlusion that was still present at the neuroimaging control study at approximately 24 h was labelled ‘persistent arterial occlusion,’ although we cannot exclude early recanalisation followed by reocclusion in some patients.

Table 1 Demographic and clinical variables and their relationship with clinical evolution

<table>
<thead>
<tr>
<th>Sex gender (female/male) (percentage of patients)</th>
<th>NINDS</th>
<th>ECASS</th>
<th>ECASS II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking (percentage of patients)</td>
<td>36</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>High blood pressure (percentage of patients)</td>
<td>48</td>
<td>66</td>
<td>39.6</td>
</tr>
<tr>
<td>Diabetes mellitus (percentage of patients)</td>
<td>16</td>
<td>24</td>
<td>11.8</td>
</tr>
<tr>
<td>Cardiac disease (percentage of patients)</td>
<td>23</td>
<td>43</td>
<td>19.5</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>8</td>
<td>11</td>
<td>3.2</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>27</td>
<td>18</td>
<td>17.5</td>
</tr>
<tr>
<td>Previous TIAT/stroke (percentage of patients)</td>
<td>29</td>
<td>39</td>
<td>27.3</td>
</tr>
<tr>
<td>Antithrombotic treatment (percentage of patients)</td>
<td>26</td>
<td>41</td>
<td>12.5</td>
</tr>
<tr>
<td>NIHSS at admission (median)</td>
<td>16</td>
<td>14</td>
<td>12</td>
</tr>
</tbody>
</table>
(90.9%) had initial worsening within 24 h, and 1/11 patients (9.1%) one at 48 h. The exact time points of worsening before improvement were: five patients during the first 12 h (one at 2 h, one at 3 h, one at 10 h, one at 12 h and one at 12 h); three patients during 12–24 h; two patients at 24 h; and one patient 48 h.

Within 24 h, 32/136 patients (23.5%) had ICH, and 9/136 patients (6.6%) showed sICH.

Outcome at 3 months
At 3 months, 21/135 available for follow-up patients had died (15.5%), 13 females and eight males. In these patients, stroke aetiology was predominantly cardioembolic (52%).

Of the patients who died, two patients were in the CI group, 11 patients in the CW group and three patients in the CWFI group (figure 1). Compared with the CI group, the multivariate analysis showed a higher mortality risk in the CW group (RR=45.6, 95% CI 9.6 to 197.5) and in the CWFI group (RR=14.7, 95% CI 2.4 to 88.1).

The Kaplan–Meier curve showed that mortality was higher in sICH and oedema (figure 2). After adjustment for potential confounders (age, sex, onset to lysis, admission NIHSS, hyperlipaemia, diabetes mellitus, high blood pressure and smoking), the presence of sICH increased the risk of mortality (RR=50.0, 95% CI 9.0 to 100.1). sICH was not associated with mortality. In addition, the presence of oedema and persistent occlusion also increased the mortality risk (RR=29.1, 95% CI 8.6 to 97.7 and RR=4.3, 95% CI 1.0 to 17.4, respectively).

DISCUSSION
In this series of thrombolysed patients, we found that CW was related to female sex, no hyperlipaemia and peripheral arterial disease, whereas CI was related to male sex and smoking. Moreover, CI was related to absence of arterial occlusion and arterial recanalisation, whereas CW and CWFI were associated with persistent arterial occlusion.

Cerebrovascular risk factors
Female gender was associated with early clinical worsening in our study, which in turn was associated with increased mortality. This is in line with a generally increased stroke mortality in women.4 This contrasts with reports of higher response to thrombolysis in women in some studies5 6 but not in others.7

Table 3 Angio-CT variables on admission and its relationship with clinical evolution

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Clinically stable</th>
<th>Clinical improvement</th>
<th>Clinical worsening</th>
<th>Clinical worsening after initial improvement</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No arterial occlusion</td>
<td>2 (5.6)</td>
<td>31 (68.1)</td>
<td>2 (5.6)</td>
<td>1 (2.8)</td>
<td>36 (100)</td>
</tr>
<tr>
<td>Arterial occlusion</td>
<td>12 (13.1)</td>
<td>55 (60.4)</td>
<td>15 (16.4)</td>
<td>9 (9.8)</td>
<td>91 (100)</td>
</tr>
</tbody>
</table>

Our study supports previous observations of a beneficial effect of smoking on better functional outcome,8 although we have not observed a protective role against ICH.9

Absence of hyperlipaemia was correlated with CW, and there were more patients without hyperlipaemia in the sICH group (7/2). A neuroprotective effect of cholesterol has also been postulated.10

Peripheral arterial disease is closely associated with coronary and carotid atherosclerosis.11 The relationship with CW in our study may be due to this association.

We did not find any differences either in previous ischaemic cerebrovascular events or in previous antithrombotic treatment for early clinical evolution after intravenous thrombolysis.

Given the small number of patients examined in our study, some correlations between clinical and radiological variable and clinical evolution may be over- or underestimated.

Neuroimaging studies
In our patients, a normal perfusion study or a larger penumbra than infarct volume was correlated with CI. Still, nearly a quarter of these patients had CW (sometimes after initial improvement). Whereas patients with a large penumbra may benefit more from recanalisation, non-recanalisation in these patients may lead to death of at-risk tissue,12–14 explaining CW or CWFI in some of them. Cases have been described using P-CT as exclusion criteria for intravenous thrombolysis treatment,15 intravenous thrombolysis within 3 and 6 h15 16 and in unknown stroke onset.17

We confirmed previous observations that arterial recanalisation in angio-CT was associated with CI.18 Similarly, mortality...
CONCLUSIONS

We conclude that early clinical profiles of evolution after intravenous rt-PA treatment in an unselected stroke population vary considerably. It can be predicted by vascular risk factors, perfusion patterns and arterial pathology. Patients with no hypoperfusion or with large penumbras, and patients with early and persistent recanalisation seem to have a more favourable early and late outcome.

Contributors MGD: conception, design of study and collecting data. MR: collecting data, MN: analysis and interpretation of data. P Michel: collecting data, drafting the article and reviewing. P Maeder, MW and JB: revising article critically for important intellectual content.

Competing interests None.

Ethics approval Ethics approval was provided by the Commission D’Ethique de la Recherche Clinique, Université de Lausanne.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES