Comparison of Intraarterial and Intravenous Thrombolysis for Ischemic Stroke With Hyperdense Middle Cerebral Artery Sign

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Background and Purpose—It is unclear whether intraarterial (IAT) or intravenous (IVT) thrombolysis is more effective for ischemic stroke with hyperdense middle cerebral artery sign (HMCAS) on computed tomography (CT). The aim of this study was to compare IAT and IVT in stroke patients with HMCAS.

Methods—Comparison of data from 2 stroke units with similar management of stroke associated with HMCAS, except that 1 unit performed IAT with urokinase and the other IVT with plasminogen activator. Time to treatment was up to 6 hours for IAT and up to 3 hours for IVT. Outcome was measured by mortality and the modified Rankin Scale (mRS), dichotomized at 3 months into favorable (mRS 0 to 2) and unfavorable (mRS 3 to 6).

Results—One hundred twelve patients exhibited a HMCAS, 55 of 268 patients treated with IAT and 57 of 249 patients who underwent IVT. Stroke severity at baseline and patient age were similar in both groups. Mean time to treatment was longer in the IAT group (244 ± 63 minutes) than in the IVT group (156 ± 21 minutes; P = 0.0001). However, favorable outcome was more frequent after IAT (n = 29, 53%) than after IVT (n = 13, 23%; P = 0.001), and mortality was lower after IAT (n = 4, 7%) than after IVT (n = 13, 23%; P = 0.022). After multiple regression analysis IAT was associated with a more favorable outcome than IVT (P = 0.003) but similar mortality (P = 0.192).

Conclusion—In this observational study intraarterial thrombolysis was more beneficial than IVT in the specific group of stroke patients presenting with HMCAS on CT, even though IAT was started later. Our results indicate that a randomized trial comparing both thrombolytic treatments in patients with middle cerebral artery occlusion is warranted. (Stroke. 2008;39:379-383.)

Key Words: acute stroke ∙ therapy ∙ thrombolysis

In the National Institute of Neurological Disorders and Stroke (NINDS) trial a beneficial effect of intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA) administered within 3 hours after the onset of stroke symptoms has been shown.1 This improved clinical outcome was confirmed by a meta-analysis including other controlled randomized trials (CRT).2 The investigators in the Prolyse in Acute Cerebral Thromboembolism (PROACT) II study found that intrarterial thrombolysis (IAT) with prourokinase within 6 hours after onset of symptoms was beneficial in patients with middle cerebral artery (MCA) occlusion.3 However, it has remained unknown whether IAT or IVT is more effective in patients with symptomatic MCA occlusion, because this issue has not been investigated in any CRT. Recanalization of an occluded MCA is associated with a favorable clinical outcome,4,5,6 and has been observed more often after IAT than after IVT.7,6 These findings suggest that patients with symptomatic MCA occlusion have a better clinical outcome after IAT than IVT.

The hyperdense MCA sign (HMCAS) on computed tomography (CT) has been shown to be a marker of acute thrombosis of the main stem of this vessel.8–11 The specificity and positive predictive value of the HMCAS for detecting MCA occlusion have been shown to be very high.8–11

The aim of this 2-center study was to compare the mortality and clinical outcome of consecutive patients with a MCA territory stroke associated with HMCAS treated with IAT or IVT.

Methods

Patients
Consecutive patients with MCA territory stroke exhibiting HMCAS on CT from the 2 academic centers Zürich and Bern were included.
in the study. Patients were recruited from July 1998 through March 2006. Patients admitted to the university hospital Bern were all treated with IAT in the 6-hour window, after digital subtraction angiography (DSA) confirmed an occlusion of the main stem of the MCA. All patients admitted to the university hospital Zürich received IVT in the 3-hour window according to the NINDS criteria. All patients or their family members consented to thrombolytic treatment.

Patients who exhibited a hyperdense terminal (C1) segment of the internal carotid artery (n=10; Zürich, n=5; Bern, n=5) or participated in another stroke treatment study (neuroprotective trial: Zürich, n=9) were excluded. Patients who were evaluated with MRI (MRI) instead of CT were also excluded from this study.

Baseline investigations included a neurologic and physical examination, assessment of stroke severity using the National Institutes of Health Stroke Scale (NIHSS), routine blood analysis, 12-lead ECG (ECG), and brain CT. Candidates for IAT also underwent DSA.

After thrombolytic treatment, all patients underwent follow-up CT or brain MRI within 24 hours of thrombolysis, as well as diagnostic color duplex ultrasonography of the extra- and intracranial cerebral arteries. Additional laboratory studies such as various antibodies, thrombophilia investigations, together with 24-hour ECG monitoring, and transhoracic or transesophageal echocardiography were performed at the discretion of the treating physician. The TOAST classification was used to determine the etiology of the patient's stroke.15

In any case of neurologic deterioration, CT was performed to exclude symptomatic intracranial hemorrhage (SICH). SICH was defined as an intracranial hemorrhage causing a 2-point increase in NIHSS score.3

Clinical outcome measures were mortality and the modified Rankin scale (mRS) score, dichotomized into favorable (0 to 2) and nonfavorable (3 to 6), at 3 months.13 The mRS score was assessed by a neurologist from the clinical examination or from a structured telephone interview with the patient or caregiver. The neurologists at both centers were certified for mRS and NIHSS score assessment.

**Thrombolytic and Antithrombotic Treatment**

IVT was performed with rt-PA (Actilyse in a dose of 0.9 mg per kilogram of body weight (maximum, 90 mg), 10% of which was given as an initial bolus followed by a constant infusion of the remaining 90% over 60 minutes.1 Some patients who received IVT in this study have already been reported in other publications.14–16 IAT was performed using 500'000 to 1'250'000 IU urokinase (Urokinase HS Medac) over 60 to 90 minutes. In addition to intraarterial infusion of urokinase, mechanical catheter disruption of the thrombus was also performed when feasible. At the end of IAT, DSA was repeated with the indwelling catheter to assess the effect of the intervention and the degree of recanalization. Data of some patients and details of the technique used for IAT have also been previously published.6,17

All patients were kept under continuous medical surveillance in the stroke unit during thrombolysis and at least for the next 24 hours. Antiplatlet therapy was given to all patients, immediately after IAT or 24 hours after IVT, irrespective whether their ictus happened while on antiplatelet agents or not. Low dose subcutaneous heparin was initiated in all patients after 24 hours.

**Stroke Risk Factors**

The following stroke risk factors were determined during the hospital stay or from the history: age, sex, hypertension, diabetes mellitus, current cigarette smoking, and hypercholesterolemia.18 Hypertension was defined by predmission history and medical records, and diabetes by venous plasma glucose concentration ≥7.0 mmol/L after overnight fasting on at least 2 separate occasions, abnormal glucose tolerance test (serum glucose ≥11.1 mmol/L 2 hours after the ingestion of 75 g of oral glucose and on one other occasion during the two hour test), or predmission history. Current cigarette smoking was defined as smoking within the last 5 years, and hypercholesterolemia as a total plasma cholesterol >5.0 mmol/L or predmission history.18

### Table 1. Demographics and Vascular Risk Factors of Patients Treated With Intravenous and Intraarterial Thrombolysis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Intravenous</th>
<th>Intraarterial</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>57</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Mean age±SD (range), y</td>
<td>61±14 (27–84)</td>
<td>61±12 (27–78)</td>
<td>0.963</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>38 (67)</td>
<td>28 (51)</td>
<td>0.090</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>30 (53)</td>
<td>27 (49)</td>
<td>0.708</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>10 (18)</td>
<td>7 (13)</td>
<td>0.478</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>39 (75)</td>
<td>26 (61)</td>
<td>0.172</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>17 (30)</td>
<td>10 (18)</td>
<td>0.150</td>
</tr>
<tr>
<td>Atrial fibrillation, n%</td>
<td>21 (37)</td>
<td>20 (36)</td>
<td>0.960</td>
</tr>
</tbody>
</table>

P indicates the difference between subgroups by χ² test or Mann–Whitney test.

**Neuroimaging Studies**

Noncontrast and contrast-enhanced cranial CT scans were obtained on 1 of several different CT scanners at the 2 hospitals. Slice thickness was 3 to 5 mm for the posterior fossa and 5 to 7 mm for the cerebral hemispheres. A HMCAS was diagnosed by an experienced neuroradiologist when the M1 segment of the MCA was (1) denser than the contralateral MCA on noncontrast CT and (2) showed no increase in attenuation after intravenous contrast.11 For the purpose of this study all CT scans were independently reviewed a second time by M.A. and R.W.B. Disagreements between the 2 reviewers were resolved by consensus.

**Statistical Methods**

Statistical analysis was performed using SPSS v.10.0 for Macintosh statistical software (SPSS Inc, 2001). For differences in categorical variables χ²-tests were performed. Continuous variables were compared with the Mann–Whitney Test. The following variables were analyzed: age, sex, side of stroke, hypertension, diabetes, hypercholesterolemia, current smoking, NIHSS on admission, stroke etiology, and time from symptom onset to thrombolysis.

The frequency of a favorable outcome (mRS score of 0 to 2) and patient mortality were compared between IAT and IVT.

Multiple regression analysis, including all variables with a probability value <0.20 after univariate analysis, was performed to determine if there was an independent association between the mode of thrombolytic treatment and clinical outcome.

**Results**

**Baseline Data**

Fifty-five (21%) of 268 patients treated with IAT in Bern showed a HMCAS and 57 (23%) of 249 patients who underwent IVT in Zürich were included in this study. All patients with a HMCAS selected for IAT showed an occlusion of the M1 segment of the MCA on DSA. Stroke severity and etiology, sex, patient age, and vascular risk factors did not differ between the 2 groups (Tables 1 and 2). Mean time from symptom onset to treatment was longer in the IAT (244±63 minutes) than in the IVT group (156±21 minutes; P=0.0001) (Table 1).

SICH occurred in 4 patients (7%) treated with IAT and in 1 patient (2%) who underwent IVT (P=0.16).

**Recanalization**

At the end of IAT recanalization of the MCA was as follows: Absent (TIMI grade 0) in 7 (13%) of 55 patients, minimal (TIMI 1) in 9 (16%), partial (TIMI 2) in 30 (55%), and
Table 2. Stroke Severity, Etiology, and Time From Stroke Onset to Treatment in Patients Treated With Intravenous and Intraarterial Thrombolysis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Intravenous (n=57)</th>
<th>Intraarterial (n=55)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean NIHSS score on admission</td>
<td>17.5±4.5</td>
<td>16.7±5.1</td>
<td>0.608</td>
</tr>
<tr>
<td>Stroke etiology</td>
<td></td>
<td></td>
<td>0.144</td>
</tr>
<tr>
<td>Cardioembolic, n (%)</td>
<td>27 (47)</td>
<td>37 (67)</td>
<td></td>
</tr>
<tr>
<td>Large artery disease, n (%)</td>
<td>11 (19)</td>
<td>5 (9)</td>
<td></td>
</tr>
<tr>
<td>Other determined, n (%)</td>
<td>5 (9)</td>
<td>5 (9)</td>
<td></td>
</tr>
<tr>
<td>Undetermined, n (%)</td>
<td>14 (23)</td>
<td>8 (15)</td>
<td></td>
</tr>
<tr>
<td>Mean time from symptom onset to treatment, minutes</td>
<td>156±21</td>
<td>244±63</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale; P, difference between subgroups by χ² test or Mann–Whitney test.

Complete (TIMI 3) in 9 patients (16%). In patients who underwent IVT recanalization was not systematically assessed at a defined time point. Therefore, no reliable data on MCA recanalization is available in the IVT patients.

Clinical Outcome
Seventeen (15%) of the 112 patients in this study were dead at 3-month follow-up. Fifteen of 17 patients died of their initial stroke (IAT, n=4; IVT, n=11), 1 of a recurrent stroke after 20 days (IVT, n=1), and another of a ruptured abdominal aortic aneurysm after 41 days (IVT, n=1). The cause of the 15 stroke-related deaths was brain edema leading to transtentorial herniation in 12 patients (IAT, n=3; IVT, n=9), pneumonia in 2 patients (IVT, n=2), and intracerebral hemorrhage in 1 patient who underwent IAT.

Follow-up was assessed in all 95 survivors by clinical examination (Bern, n=43; Zürich, n=42) or a structured telephone interview (Bern, n=8; Zürich, n=2). Favorable outcome was more frequent in patients treated with IAT (n=29, 53%) than IVT (n=13, 23%; P=0.022), and mortality was lower in patients treated with IAT (n=4, 7%) than IVT (n=13, 23%; P=0.022; Figure).

After multiple regression analysis IAT remained independently associated with a favorable outcome (P=0.003), but there was no difference of mortality with IAT and IVT (P=0.192).

Discussion
In this study, patients with ischemic stroke and HMCAS who underwent IAT had a more favorable outcome than patients who received IVT. The outcome after IAT was more favorable even though time from symptom onset to IAT was on average 88 minutes longer than in the IVT group. Mortality was also lower in the IAT group according to univariate analysis, but not after multivariate analysis.

The HMCAS is usually associated with a severe acute neurologic deficit at presentation, an extensive area of brain infarction, and a poor neurologic outcome, irrespective of IVT or absence of thrombolytic treatment.8–10,19–22 When treated with IVT, Agarwal and coworkers reported good outcome (nRS 0 or 1) in 2 of 15 (13%) MCA strokes with HMCAS on CT, whereas in the absence of HMCAS outcome was good in 24 of 51 (47%).10 Even in the European Cooperative Acute Stroke Study (ECASS I), where patients with infarctions involving more than one third of the territory of the MCA were excluded at the outset, the HMCAS was a predictor of poor outcome after univariate analysis.23 In contrast, the HMCAS did not influence clinical outcome in patients treated with IAT.10,24

The mortality of our patients who underwent IVT (Figure) is similar to the results reported in the active group of ECASS I. Fourteen (30%) of 46 patients with HMCAS died in ECASS I, and 13 (23%) of 57 patients in the present study.23 A comparison with a secondary analysis of NINDS is not feasible, because patients with hyperdense artery signs were not specified according to the vascular territory involved.25

A pooled analysis of the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS), ECASS, and NINDS rt-PA stroke trials reported time from symptom to treatment onset as an independent predictor of a favorable outcome after IVT.2 According to PROACT II and nonrandomized studies of IAT in acute stroke, NIHSS score at baseline, patient age, diabetes, location of the vessel occlusion, time to treatment, complicating hemorrhages, and degree of recanalization all independently predicted outcome.3,4,5,6 In the present study, baseline NIHSS score, patient age, the frequency of diabetes, and the frequency of intracranial hemorrhage were similar in both treatment groups. Patients underwent IAT on average 88 minutes earlier than IAT, which should have favored the IVT group. Nevertheless, outcome after IAT was more favorable than after IVT. Therefore, in our study it is likely that a higher recanalization rate after IAT than IVT resulted in better functional outcome after IAT. However, we cannot confirm this hypothesis, because we do not have the information on early recanalization in the IVT group. Recanalization after IAT was assessed systematically by DSA at the end of thrombolysis, but DSA was not performed in the IVT group. Neumann-Haefelin and coworkers, using MR angiography, assessed recanalization on day 1 in 52 stroke patients pres-
enting with MCA main stem occlusion. They found TIMI-2 or -3 recanalization grades in 20 of 52 patients (38%) after IVT and a positive correlation between recanalization and functional outcome. In this study, TIMI-2 or -3 recanalization grades were observed in 39 of 55 patients (71%) who had been treated with IAT.

The present study confirms that the HMCAS on CT, though not very sensitive, has a high specificity and positive predictive value for diagnosing acute occlusion of the M1 segment of the MCA, as DSA showed in all patients of the IAT group an occluded M1 MCA.

The main limitation of our study is its observational nature, though all data were prospectively collected. Another drawback is the well-known low sensitivity of the HMCAS for detecting MCA occlusion. A further study limitation is that patients in each treatment group were recruited in different centers, suggesting that differences in patient management might also partly explain the different outcomes observed in the 2 patient groups. However, both centers have a long experience with thrombolysis for stroke and have similar management regimens except in their mode of thrombolytic treatment with MCA occlusion. Furthermore, both centers have had an intensive scientific collaboration for many years, and 3 of the present authors (H.P.M., G.S., R.W.B.) have worked at both hospitals. All these facts suggest that dissimilarities in the stroke management between the 2 centers are unlikely to explain the better outcome after IAT. Furthermore, our results should not be generalized, because the success of endovascular procedures depends on the skills of the interventionists. Our high rate of favorable outcome after IAT was achieved by a team with long experience in interventional neuroradiology.

To date, no large trial has been completed comparing IVT and IAT in acute stroke. The Interventional Management of Stroke (IMS) III Trial started to recruit patients in August 2006 to compare iv-rtPA within 3 hours after symptom onset and iv-rtPA followed by IAT, and there is also an ongoing Italian study, SYNTHESIS, comparing IAT and IVT within the 3-hour time window in MCA stroke patients. In addition, a European consortium has applied for funding at the European Commission to improve endovascular recanalization techniques and to compare IVT and endovascular recanalization in acute stroke. However, we cannot expect the answer before a few years whether IAT improves outcome after stroke compared with IVT and which stroke victims should be selected for IVT or preferably IAT.

In conclusion, the results of this observational study suggest that IAT might be more effective than IVT in the treatment of the specific group of patients with acute ischemic stroke and HMCAS on CT. The findings also suggest that controlled randomized trials are timely and warranted to compare IAT and IVT in selected groups of stroke patients.

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Disclosures
None.

References


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