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Combined IV–intra-arterial thrombolysis: A color-coded duplex pilot study

Abstract—The authors compared the transcranial color-coded duplex pattern of the middle cerebral arteries (MCAs) before and after IV and combined IV–intra-arterial (IV–IA) thrombolysis in consecutive first-ever stroke patients. Patients receiving combined IV–IA thrombolysis showed greater improvement in flow signal and higher incidence of complete MCA recanalization vs those receiving IV thrombolysis, especially when the MCA was occluded or had only minimal flow.

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Because stroke patients with no residual flow signal on transcranial Doppler have less than 20% chance for early complete recanalization with IV thrombolysis, intra-arterial (IA) treatment has been suggested.1 The duration of impaired cerebral perfusion is associated with the degree of infarction,2,3 and the time from impaired perfusion onset to treatment initiation is an important outcome predictor in thrombolysis. Because the preparation of the IA procedure takes approximately 30 minutes, this preparation can be done during initial IV thrombolysis so that an immediate shift to IA thrombolysis can be made after 30 minutes if the IV procedure has produced no improvement in flow. In this pilot study, we compared the transcranial color-coded duplex (TCCD) signal pattern of 44 patients with acute first-ever stroke of the middle cerebral artery (MCA) territory classified according to the thrombolysis in brain ischemia (TIBI)4 scale before and after IV and combined IV–IA thrombolysis. Fourteen of these patients were not thrombolysed but were also examined and compared with the others. In this study, we determined whether the combined IV–IA procedure was superior to IV thrombolysis alone, and we compared results with those from patients for whom no thrombolysis could be performed.

Methods. This was a prospective, nonrandomized study with 44 consecutive first-ever stroke patients (27 men, mean age 67 ± 29 years) admitted with a suspicion of infarction of the MCA territory (median NIH Stroke Scale [NIHSS] score 11). Fourteen patients (mean age 66.5 ± 12.5 years; 6 men; median NIHSS score 7) were not eligible for thrombolysis (>6 hours after stroke onset or NIHSS score <6) and served as “controls.” Thirty patients were eligible for thrombolysis (<3 hours after stroke onset), of whom 21 patients (mean age 66 ± 28 years; 15 men; median NIHSS score 13) underwent IV thrombolysis and 9 patients (mean age 66.5 ± 22.5 years; 6 men; median NIHSS score 12) underwent combined IV–IA thrombolysis.

Doppler ultrasound examination. We measured residual flow signal patterns in the MCA by TCCD before, during (after 25 to 30 minutes), and after (within 12 hours) thrombolysis. The 14 patients who did not undergo thrombolysis were examined at admission and after 12 hours. Three experienced examiners performed TCCD using a 2- to 3.5-MHz sectorial transducer (Acuson, Sequoia, Mountain View, CA) and interpreted their results online. MCAs were examined from the ipsilateral and contralateral temporal bone windows. Patients with insufficient temporal bone windows received 5 mL microbubble echo contrast agent (Sonovue, Bracco SA, Switzerland) infusion.

Thrombolysis procedure. In 30 patients, the IV recombinant tissue plasminogen activator (rTPA) standard protocol5 (0.9-mg/kg dose, 10% bolus, 90% continuous infusion over 1 hour) was initiated. After 30 minutes (half of the dose infused), TCCD was repeated. If the initial TCCD finding was identical or worsened (9 patients), IA rTPA in situ infusion of the remaining half of the dose via a microcatheter (Excell 14, Target/BSC) at the clot site was initiated, and IV treatment was discontinued. If there was an improvement of the initial TCCD finding (by 1 TIBI grade or more) (19 patients), and in the 2 patients in whom flow was normal (TIBI V), IV treatment was continued.

Flow measurements. The TIBI4 flow model grading system was used to define six flow grades (0 through V) on spectral TCCD display (figure 1). All pretreatment TCCD flow grade patterns of the affected MCAs were compared with those obtained after either IV or combined IV–IA thrombolysis (table). TCCD flow grade patterns of the MCAs of patients who were not thrombolysed were analyzed and compared with the same procedure within 12 hours. Rate of recanalization according to TIBI grades was compared with Rx, magnetic resonance, or CT angiography.

Results. There was no difference for age (Kruskal–Wallis H = 2.284, p > 0.05) or sex (H = 2.105, p > 0.05) among the three groups. NIHSS was different among the three groups (Kruskal–Wallis H = 11.9, p < 0.005). Follow-up pairwise comparisons showed that there was no difference in NIHSS between the IV-alone and IV–IA groups (Mann–Whitney U = 64, p > 0.05, two tailed); however, the NIHSS in the group of nonthrombolysed patients was lower (part of the reason why not thrombolysed) than for both the IV (Mann–Whitney U = 53.5, p < 0.005, 2-tail) and IV–IA (U = 25.5, p < 0.02) thrombolysis groups.

TCCD flow pattern analysis before and after IV–IA vs IV thrombolysis and nonthrombolysed “controls” using the TIBI classification is shown in figure 2.

For a group-differences statistical analysis, the results shown in figure 2 were coded according to the TIBI grading system, e.g., +5 for an improvement from complete occlusion (TIBI 0) to normal flow (TIBI V), 0 for no change in

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TIBI grade, or \(-2\) for a worsening from TIBI II to TIBI 0. The 7 patients (2 with IV treatment alone, 5 nonthrombolyzed) who had initially a normal flow (TIBI V) were not entered into the statistical analysis because we were interested in outcome for restricted flow cases.

A Kruskal–Wallis nonparametric analysis of variance by ranks showed that the three groups differed overall in flow improvement \((H = 13.554, p < 0.001)\). Follow-up pairwise comparisons showed that the IV thrombolysis group, as expected, showed more improvement than the non-thrombolyzed group \((U = 49, p = 0.03, \text{one tailed})\), and that the combined IV–IA therapy showed more flow improvement than did the IV-alone group \((U = 26, p < 0.002, \text{two tailed})\).

The results can also be looked at from the point of view of the individual patient by asking “What is the probability of improvement from initially restricted flow (TIBI 0 to IV) to complete recanalization (TIBI V)?” Figure 2 shows that from this small sample, the answer is 89% (95% CI 55% to

### Table: Rate of recanalization according to TIBI grades and modality of treatment

<table>
<thead>
<tr>
<th>TIBI grade</th>
<th>No. of patients</th>
<th>Thrombolysis</th>
<th>Complete recanalization, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4</td>
<td>IV–IA</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>IV</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>I</td>
<td>3</td>
<td>IV–IA</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>IV</td>
<td>33</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>IV–IA</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>IV</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>IV–IA</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>IV</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>None</td>
<td>0</td>
</tr>
</tbody>
</table>

TIBI = thrombolysis in brain ischemia; IA = intra-arterial.
97%) for the combined IV–IA treatment (8 of 9 patients), 32% (15% to 54%) for IV alone (6 of 19 patients), and 0% (0% to 31%) for the nonthrombolyzed patients (0 of 9 patients). The combined IV–IA therapy recanalization incidence exceeds the IV-alone incidence (Fisher exact test, p < 0.02, two tailed).

Agreement between TCCD rate of recanalization and angiograms was 100%.

Discussion. In this pilot study, we compared the dynamics of the TCCD signal of two thrombolysis procedures: the standard IV thrombolysis and a combined IV–IA thrombolysis in consecutively admitted first-ever stroke patients with suspected ischemia in the territory of the MCA. We also compared both procedures with patients who were not thrombolized. The combined IV–IA thrombolysis showed both a larger overall improvement of the flow signal and a higher incidence of complete recanalization than did IV-alone thrombolysis. This is especially the case for patients with completely occluded MCA (TIBI 0) and those with minimal flow (TIBI 1). Figure 2 suggests that, irrespective of improvement of the flow signal, patients with occluded MCA or MCA with minimal flow would benefit from a passage from IV to IA thrombolysis, whereas for TIBI grades II and higher, IV thrombolysis would suffice. As expected, the IV-alone group showed more improvement of the flow signal than did the nonthrombolyzed group. These results using TCCD confirm previous findings using TCD1,4 and underline the usefulness of the TIBI classification. Although the results of our pilot study suggest that, with patients for whom the flow signal is not improved after 30 minutes of IV thrombolysis and especially when the MCA is still occluded or has only minimal flow, one should shift to IA thrombolysis, the number of patients in this pilot study is too small to reach definite conclusions, and larger studies are needed for confirmation.

References

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The American Academy of Neurology and the European Neurological Society have joined together to offer a 25% discount on dues to neurology professionals outside of the US and Canada who belong to both the AAN and the ENS. The two-year pilot project is designed to improve communication with and among international members and to support a more global neurological community. Visit www.aan.com/joinmembership to learn how to apply and join today.
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