Intravenous Versus Combined (Intravenous and Intra-Arterial) Thrombolysis in Acute Ischemic Stroke
A Transcranial Color-Coded Duplex Sonography–Guided Pilot Study

Lucka Sekoranja, MD; Jaouad Loulidi, MD; Hasan Yilmaz, MD; Karl Lovblad, MD; Philippe Temperli, MD; Mario Comelli; Roman F. Sztajzel, MD

Background and Purpose—Determine feasibility and safety of intravenous (IV) versus combined (IV-IA [intra-arterial]) thrombolysis guided by transcranial color-coded duplex sonography (TCCD).

Methods—Thirty-three patients eligible for IV thrombolysis, within 3 hours of onset of symptoms, with occlusion in middle cerebral artery territory (TCCD monitoring, thrombolysis in brain ischemia [TIBI] flow grade [0–3]), underwent IV thrombolysis (tissue plasminogen activator, 0.9 mg/kg). In case of recanalization (modification of TIBI score ≥1) after 30 minutes IV thrombolysis was continued over 1 hour; otherwise, it was discontinued, with subsequent IA thrombolysis. Recanalization was determined by TIBI (TCCD) and angiographically by thrombolysis in myocardial infarction (TIMI) flow grades. Clinical outcome measures were assessed at baseline, 24 hours (NIHSS) and 3 months (modified Rankin Scale).

Results—In the IV group, 10/17 patients (59%) with complete or partial recanalization after 30 minutes had a favorable outcome at 3 months (modified Rankin Scale 0 to 2). TIBI flow grades 3 to 5 after 30 minutes of IV thrombolysis predicted a good prognosis compared with TIBI grades 1 to 2 (P<0.05). In the combined IV/IA therapy group (no recanalization after 30 minutes), 9/16 patients (56%) had a favorable outcome at 3 months. One symptomatic intracerebral hemorrhage occurred in each group.

Conclusions—Combined IV-IA versus IV thrombolysis guided by TCCD was feasible and safe. Recanalization after 30 minutes of IV thrombolysis led to a favorable outcome in 59% of the patients, provided TIBI flow grades were of 3 to 5. In the absence of early recanalization during IV thrombolysis, there was clinical benefit to proceed to IA therapy for a significant proportion of patients (56%).

Key Word: stroke thrombolysis transcranial ultrasonography

Although intravenous (IV) thrombolysis has gained wide acceptance as a treatment of acute stroke, the persistence of proximal arterial occlusion of the middle cerebral artery (MCA) without signs of early recanalization immediately after IV thrombolysis is reported to be a poor prognostic sign. Recent studies observed that a rapid arterial recanalization, occurring within <30 minutes after IV thrombolysis is associated with a better short-term clinical outcome in comparison with a more slow flow improvement predicting a less favorable prognosis.1,2 It has been shown that patients treated with IV tissue plasminogen activator (tPA) within 3 hours of onset of cerebrovascular symptoms are ∼30% more likely to exhibit complete or nearly complete recovery at 3 months than a placebo-treated group.3 However, ∼50% to 60% of the eligible patients still show unfavorable long-term outcome. Furthermore, in angiographic controlled trials of IV thrombolysis, the rate of partial or complete recanalization of occluded proximal MCA is not >25%.4 Intra-arterial (IA) thrombolysis may offer some advantages over IV treatment, in particular, regarding its recanalization rate.4,5 In the Prol- yse in Acute Cerebral Thromboembolism II (PROACT II) trial, 20% of the 121 patients had a total recanalization and 46% had partial recanalization. However, the median time to start IA therapy was 5.3 hours and recanalization, if it occurred, often happened >7 hours after stroke onset.

Combined (IV-IA) thrombolytic therapy may, therefore, be more efficient than either technique alone by offering the benefits of a rapid administration of IV thrombolytic and a higher recanalization rate achieved with IA therapy.6,7,8,9,10 Several studies emphasized the role of transcranial Doppler (TCD) and also transcranial color-coded duplex (TCCD) as useful tools for the diagnosis of MCA occlusion or recanal-
zation in the setting of acute ischemic stroke. We, therefore, sought to evaluate the feasibility and safety of IV versus IV-IA thrombolysis guided by TCCD.

**Patients and Methods**

Thirty-three consecutive patients admitted between September 2003 and February 2005 at our hospital for an acute ischemic stroke in the MCA circulation in a 3-hour window, eligible for IV thrombolysis (0.9 mg/kg, 90 mg maximum, 10% of dose as a bolus over 1 minute, then 90% at a 1-hour perfusion rate), were included in the study, based on initial TCCD monitoring showing thrombolysis in brain ischemia (TIBI) flow grades of 0 to 3 (occlusion of the MCA or distal internal carotid artery [ICA]). National Institute of Neurological Disorders and Stroke (NINDS) inclusion and exclusion criteria were applied, as well as radiological exclusion criteria of the European Cooperative Acute Stroke Study (ECASS) II trial, in particular the CT signs of edema involving >35% of the MCA territory were also used. After 30 minutes IV thrombolysis, in case of partial or complete recanalization observed on TCCD, a decision was made to administer IV thrombolysis over a total period of 60 minutes. In the absence of recanalization, IA thrombolysis was performed with the remaining tPA dose. The local ethics committee approved the study.

**TCCD**

All patients were monitored by TCCD performed before and during thrombolysis by 2 experienced sonographers (L.J., S.R.) with the use of an Accuson Sequoia machine (2 to 3.7 MHz). TIBI criteria were applied to diagnose arterial occlusion. TIBI flow grades were measured on both MCAs at a depth between 40 and 55 mm. Exocranial ultrasonography of the proximal carotid artery was performed in every patient. Distal ICA occlusion (T occlusion) was diagnosed whenever a high-resistance signal pattern was recorded on the proximal ICA and if no or minimal signals from M1 and A1 segments were found.

Recanalization was diagnosed as partial when the signal improved by at least 1 TIBI grade. Complete recanalization was considered if the peak systolic flow velocity improved to normal (as compared with the contralateral side; TIBI 5) or to elevated values (low-resistance stenotic signal; TIBI 4). In case of insufficient temporal bone window, a contrast agent was administered (Sonovue).

**IA Thrombolysis**

Digital subtraction angiography was performed by the femoral approach using the Seldinger method. The prethrombolytic angiogram protocol included bilateral ICA and vertebral artery injection. After identification of the proximal MCA occlusion, superselective angiography was performed using a microcatheter. A bolus injection of 2000 U of heparin was given intravenously followed by an infusion of 1000 U per hour until the end of the procedure. A microcatheter (Excel 14, Target/BSC) and a microguide wire (Transend 14, Target/BSC) were used to reach the occlusion site and to infuse locally the thrombolytic agent with doses ranging from 8 to 34 mg. Several control digital subtraction angiography series were performed to regularly assess the degree of recanalization. The IA injection of tPA was stopped if the time window of 6 hours was reached or if a complete recanalization of the occluded vessel was achieved. In all the cases, the maximum dose injected was not above 34 mg.

Arterial recanalization was evaluated by the thrombolysis in myocardial infarction (TIMI) grade. Arteries showing a TIMI grade of 0 to 1 were regarded as not recanalized, grade 2 as partially recanalized, and grade 3 as completely recanalized. If the patient had a significant stenosis of the ICA then the stenosis was traversed with the microcatheter to approach a distal occlusive thrombus.

**Neuroradiological Evaluation**

After thrombolytic therapy, all patients underwent brain CT within 24 hours. An additional imaging was performed if hemorrhage was clinically suspected. Symptomatic intracranial hemorrhage was defined as neurological worsening of >4 points in National Institutes of Health Stroke Scale (NIHSS) score and attributable to the presence of the hematoma.

**Outcome Measures**

The patient’s NIHSS score was obtained on arrival at the emergency room and at 24 hours; modified Rankin Scale (mRS) was assessed at 3 months after onset of symptoms. Improvement at 24 hours was defined by a change of at least 4 points on the NIHSS. Favorable outcome at 3 months after onset was defined as favorable with a mRS score of 0 to 2 and unfavorable with a mRS score of 3 to 6.

**Statistical Analysis**

Given the small number of patients, only $\chi^2$ tests and odds ratio were used to analyze differences. $P<0.05$ was considered significant.

**Results**

Of 1020 patients admitted for acute stroke at our emergency department, 36 (3.5%) were eligible for IV thrombolysis and monitored by TCCD. Because of insufficient temporal bone window, 10 patients received ultrasonographic contrast agent (Sonovue), which allowed a satisfactory monitoring in 7 cases; the 3 other patients were excluded. After 30 minutes of IV thrombolysis, 17 patients (17/33, 51.5%) showed signs of partial (10 patients) or complete (7 patients) recanalization. IV thrombolysis was then achieved over a total period of 60 minutes without any further change in recanalization. TCCD signs of recanalization were observed between the 12th and 31st minute of thrombolysis. Sixteen patients (16/33, 48.5%) did not show any signs of recanalization after 30 minutes and underwent further IA thrombolysis. There were 11 patients with TIBI 0 to 1 and 5 with TIBI 2 to 3 at the end of 30 minutes of IV thrombolysis. Before beginning of IA thrombolysis, there were TIMI 0 to 1 in 9 and TIMI 2 in 7 patients. Thus, TIBI and TIMI flow grades matched in 88% of the cases; in 2 patients TIMI flow showed signs of complete occlusion (TIBI 0 to 1), whereas TIMI flow demonstrated signs of partial recanalization (TIMI 2).

In this IV-IA group, partial recanalization was achieved among 6 patients (37.5%), complete recanalization among 6 (37.5%) and no recanalization among 4 patients (25%). The baseline characteristics of the 2 groups (IV and IV-IA) are summarized in Table 1. In the IV group, 65% (11/17) of the patients improved at 24 hours by at least 4 points on their NIHSS. Among them, 10 had a favorable outcome at 3 months. Six out of 7 (86%) patients with complete recanalization after 30 minutes of IV thrombolysis improved their NIHSS at 24 hours as compared with only 5/10 (50%) with partial recanalization ($P<0.02$). At 3 months, patients with complete recanalization at 30 minutes after IV thrombolysis showed a favorable outcome more frequently (6/7, 86%) in comparison with patients with partial recanalization (4/10, 40%; $P=0.05$; Table 2). Among the 16 patients who underwent combined IV-IA thrombolysis, 9 (56%) presented a favorable outcome at 3 months, of whom 8 presented an improvement of at least 4 points on their NIHSS at 24 hours: 5/6 (83%) were patients with complete recanalization, 2/6 (33%) with partial and 1/4 (25%) with no recanalization ($P<0.05$; Table 2). This proportion of patients is significantly greater than expected because a recent study showed a good
TABLE 1. Baseline Characteristics of the Patients With IV and Combined (IV-IA) Thrombolysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IV-IA Thrombolysis, n=16</th>
<th>IV Thrombolysis, n=17</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range)</td>
<td>68 (38–90)</td>
<td>67.5 (38–90)</td>
<td>0.4</td>
</tr>
<tr>
<td>Male/female</td>
<td>8/8</td>
<td>12/5</td>
<td>0.29</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (81%)</td>
<td>13 (76%)</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (11%)</td>
<td>3 (20%)</td>
<td>1</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>8 (50%)</td>
<td>7 (41%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Smoking</td>
<td>4 (22%)</td>
<td>4 (24%)</td>
<td>1</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5 (31%)</td>
<td>4 (24%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Anti-platelet treatment</td>
<td>4 (24%)</td>
<td>4 (24%)</td>
<td>1</td>
</tr>
<tr>
<td>Antiocoagulant treatment</td>
<td>3 (19%)</td>
<td>1 (6%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Mean NIHSS at admission</td>
<td>14.3</td>
<td>14.6</td>
<td>0.13</td>
</tr>
<tr>
<td>Mean time to IV thrombolysis</td>
<td>2 h 29</td>
<td>2 h 20</td>
<td>...</td>
</tr>
<tr>
<td>Mean time to IA thrombolysis</td>
<td>4 h 32</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Occlusive site on TCCD and angiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>12 (75%)</td>
<td>16 (94%)</td>
<td>&lt;0.17</td>
</tr>
<tr>
<td>T occlusion</td>
<td>4 (25%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
</tbody>
</table>

long-term outcome in 25% of the patients in the absence of early recanalization. The use of combined therapy in case of absence of early recanalization would confer an odds ratio of a favorable outcome at 3 months of 3.6 (95% CI, 1.3 to 11.4; P<0.05). All patients (6/6, 100%) with complete recanalization had a favorable outcome at 3 months, but only 3 of 6 (50%) with partial and none of 4 with no recanalization. The proportion of patients with TIBI 3 at baseline was more important in the group who recanalized at 30 minutes in comparison with the group who did not recanalize and underwent further IV-IA thrombolysis; the difference, however, did not reach significance (TIBI 3: 5/17, 29% versus 1/16, 6.3% P<0.02, respectively). On the other hand, the proportion of patients with TIBI 0 to 2 at baseline was not different between the 2 groups of patients (TIBI 0 to 2: 12/17, 71% versus 15/16, 94%; P<0.1). Considering TIBI flow grades at the end of 30 minutes of IV thrombolysis, we found that TIBI flow grades between 3 to 5 predicted a good prognosis as compared with TIBI flow grades of 1 to 2 (P<0.05; Figure).

No local complications in particular at the femoral puncture site were observed. On brain CT-scan performed 24 hours after thrombolysis, 6 patients (3%) presented signs of hemorrhagic transformation in the IV group, and 10 patients (63%) in the IV-IA group (P<0.05). Only 1 symptomatic intracerebral hemorrhage occurred in each group (1/17, 5.8% in the IV group and 1/16, 6.2% in the IV-IA group), with 1 death in IV group.

Discussion

This study demonstrated the feasibility and usefulness of TCCD-monitored thrombolysis as a screening tool in acute stroke in order to assess early recanalization and to guide therapy. TCD has often been used in these recent years for the assessment of recanalization during thrombolysis. In a study involving 54 patients, Labiche and coworkers emphasized the prognostic value of early recanalization determined by TCD and demonstrated that 50% of the patients with complete recanalization had a good outcome at 3 months, 44% with partial recanalization and only 22% with no recanalization at all. Furthermore, Saqur et al demonstrated the high predictive value of TCD for identifying proximal occlusion in the MCA circulation and concluded that TCD may have a potential as a screening tool for IV/IA thrombolysis protocols. However, no study has been performed so far using TCD or TCCD as triage tools.

In our study, we found that IV versus IV-IA thrombolysis guided by TCCD was feasible and safe. In fact, patients presenting a complete or partial recanalization with TIBI flow grade 3 to 5 after 30 minutes of IV thrombolysis were more likely to have a favorable outcome after 24 hours and after 3 months as compared with those patients yielding a residual TIBI flow grade between 1 to 2 (P=0.05 and P<0.05, respectively; Figure). Moreover, for those patients who did not recanalize after 30 minutes of IV therapy, there was a substantial benefit to proceed to further IA thrombolysis. In fact, more than half (9/16, 56%) of these patients reached a favorable outcome at 3 months (mRS 0 to 2), a proportion significantly greater than expected, since a recent study showed that in the absence of early recanalization, a good long-term outcome was observed in only ≈25% of the

TABLE 2. Clinical Outcome of Patients Treated With IV Thrombolysis or Combined (IV-IA) Thrombolysis at 24 Hours (NIHSS) and at 3 Months (mRS)

<table>
<thead>
<tr>
<th>Improvement NIHSS ≥4 pts at 24 h</th>
<th>P Values</th>
<th>mRS at 3 mo 0–2</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV thrombolysis, n=17</td>
<td>11/17 (64%)</td>
<td>10/17 (59%)</td>
<td></td>
</tr>
<tr>
<td>Complete recanalization (TIBI 4–5), n=7</td>
<td>6/7 (86%)</td>
<td>6/7 (86%)</td>
<td>P&lt;0.2</td>
</tr>
<tr>
<td>Partial recanalization (change of TIBI score ≥1), n=10</td>
<td>5/10 (50%)</td>
<td>4/10 (40%)</td>
<td>4/10 (40%)</td>
</tr>
<tr>
<td>IV-IA thrombolysis, n=16</td>
<td>8/16 (50%)</td>
<td>9/16 (56%)</td>
<td></td>
</tr>
<tr>
<td>Complete recanalization (TIBI 3), n=6</td>
<td>5/6 (83%)</td>
<td>6/6 (100%)</td>
<td>6/6 (100%)</td>
</tr>
<tr>
<td>Partial recanalization (TIBI 1–2), n=6</td>
<td>2/6 (33%)</td>
<td>2/6 (33%)</td>
<td>P=0.05</td>
</tr>
<tr>
<td>No recanalization (TIBI 0), n=4</td>
<td>1/4 (25%)</td>
<td>0/4</td>
<td></td>
</tr>
</tbody>
</table>

For statistical analysis, partial and no recanalization were considered together.
The use of combined therapy in case of absence of early recanalization would therefore confer an odds ratio of a favorable outcome at 3 months of 3.6 (95% CI, 1.3 to 11.4; P = 0.02).

As in the study reported by Saqqur et al, we also found that TIBI flow grades determined by TCCD predicted with a good accuracy the TIMI grades assessed on angiography. These results suggest that TIBI flow grades may be used as a tool to decide whether to continue IV thrombolysis after 30 minutes or to switch to IA therapy. According to our findings, patients presenting a residual TIBI flow grade between 3 to 5 at 30 minutes of IV thrombolysis should receive only IV thrombolysis, whereas IA treatment should be performed among patients with no recanalization or with TIBI flow grades of 1 to 2.

In our study, the delay between IV thrombolysis and in situ IA thrombolysis was 93 minutes on average, similar to that reported in other trials using combined therapy. Furthermore, in our study, symptomatic hemorrhagic complications were observed in 5.8% in the IV and in 6.2% in the IV-IA group, a result also analogous to those found in other studies with combined thrombolysis.

A therapeutic effect produced by ultrasound in enhancing thrombolysis has been suggested in recent studies. Therefore, the continuous monitoring we have performed by TCCD may have contributed to recanalization. Furthermore, administration of contrast agent may also have improved the recanalization rate, because microbubbles accelerate thrombolysis and possibly lead to a more complete recanalization. Our study, however, was not designed to evaluate specifically the effect of these 2 parameters and more definite conclusions cannot be drawn.

Only very few studies have used a protocol that permits screening either for IV or for combined IV-IA therapy. Suarez and coworkers administered intravenously a reduced dose of tPA to patient candidates for thrombolysis and performed MRI with diffusion-weighted imaging and perfusion-weighted imaging sequences in order to determine which patients would benefit from subsequent IA therapy. MRI would certainly give more information on the extent of the infarct than TCD or TCCD, but is difficult to obtain as an emergency procedure in most centers and also tends to increase the delay between IV and IA thrombolysis. In another recent study, Kim et al performed a rescue localized IA thrombolysis based on the failure of early clinical response after IV tPA therapy.

Conclusions
Combined IV-IA versus IV thrombolysis guided by TCCD was feasible and safe. Recanalization after 30 minutes of IV thrombolysis led to a favorable outcome in 59% of the patients, provided TIBI flow grades were of 3 to 5. In the absence of early recanalization during IV thrombolysis, there was a clinical benefit from proceeding to IA therapy for a significant proportion of patients (56%).

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Disclosures
None.

References


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