Intravenous Tirofiban With Intra-Arterial Urokinase and Mechanical Thrombolysis in Stroke
Preliminary Experience in 11 Cases
Salvatore Mangiafico, MD; Martino Cellerini, MD; Patrizia Nencini, MD; Gianfranco Gensini, MD; Domenico Inzitari, MD

Background and Purpose—To evaluate preliminarily efficacy and safety of intravenous tirofiban combined with mechanical clot disruption and urokinase in patients with stroke attributable to major cerebral artery occlusion.

Methods—Eleven consecutive patients with stroke attributable to acute occlusion of a major cerebral artery were treated with an intravenous bolus injection of the platelet glycoprotein IIb/IIIa antagonist tirofiban combined with heparin and by endovascular procedures including mechanical thrombolysis and locally delivered urokinase. Of the 11 cases, 9 involved angioplasty and 2 only microcathether and microguidewire manipulation.

Results—There were 7 patients with internal carotid or middle cerebral artery occlusion treated within 6 hours and 4 patients with basilar artery occlusion treated within 12 hours of symptom onset. Median National Institutes of Health Stroke Scale (NIHSS) score on admission was 20. After the interventional procedure, vessel recanalization was partial (thrombolysis in myocardial infarction grade flow 2 [TIMI 2]) in 7 patients and absent or insufficient in 4 patients. Twenty-four hours after the procedure, all the patients but 1 improved substantially, and on control angiography, the occluded vessel was totally patent (TIMI 3) in 10 of the 11 patients. One patient with partial recanalization did not improve and died 3 months later from pulmonary embolism. Neither a symptomatic intracerebral hemorrhage nor systemic bleedings requiring blood transfusion occurred in any patient. At discharge, median NIHSS score was 2. The 3-month outcome was excellent in 8 patients (modified Rankin Scale [mRS] 0 to 1), good in 2 patients (mRS 2), and poor in 1 patient (mRS 6).

Conclusions—The combination of intravenous tirofiban with intra-arterial mechanical clot disruption and urokinase may be successful in reopening an occluded major cerebral vessel without increasing the hemorrhagic risk and with good functional outcome. This strategy cannot be recommended as the systematic treatment of stroke attributable to major cerebral artery occlusion until tested in a controlled study design. (Stroke. 2005;36:2154-2158.)

Key Words: endovascular therapy — platelet glycoprotein GPIIb-IIIa complex — stroke

Many strokes are attributable to thromboembolic occlusion of a major cerebral artery, and prompt restoration of perfusion to the ischemic area is the key task. The intravenous administration of standard recombinant tissue plasminogen activator (rtPA) doses within 3 hours from stroke onset was proven to be effective in improving the clinical outcome.1 Symptomatic cerebral hemorrhage in up to 6%1 and vessel recoclusion are the major limitations to this treatment.3 Furthermore, intravenous rtPA may be less effective in reopening major cerebral arteries (eg, internal carotid, middle cerebral–main stem, and basilar artery [BA]).3 In the Prolyse in Acute Cerebral Thromboembolism (PROACT) studies I and II,4,5 intra-arterial (IA) thrombolysis with recombinant pro-urokinase in patients with middle cerebral artery (MCA) occlusion was at least as equally effective as intravenous thrombolysis in improving the outcome and more effective in reopening the occluded artery (in approximately two thirds of cases), even if performed in a larger time window. Mechanical techniques are being increasingly used, including microcathether- and microguidewire-aided thrombus disruption, angioplasty of the thrombus, suction thrombectomy, and clot retrieval.

The platelet glycoprotein IIb/IIIa (GPIIb/IIIa) receptors play a key role in the process of platelet aggregation and accumulation. Inhibitors of the GPIIb/IIIa receptor are being used alone or in combination with fibrinolytics to treat patients with acute myocardial or cerebral ischemia.6–10 The combination of GPIIb/IIIa inhibitors with thrombolitics is justified by their enhancing effect on clot lysis.11,12 They seemingly prevent recoclusion of partially recanalized ves-
sels\textsuperscript{14} and, preserving the microcirculation patency, are able to alter the no-reflow phenomenon.\textsuperscript{14}

Herein, we describe a consecutive series of 11 patients presenting with acute ischemic stroke attributable to the occlusion of a major cerebral vessel, treated with a procedure starting with an intravenous bolus of the GPIIb/IIa inhibitor tirofiban (Aggrastat; Merck), followed by mechanical clot disruption combined with locally delivered urokinase, and continuing with the infusion of tirofiban throughout and after (for 48 hours) the interventional maneuvers.

Materials and Methods

Between April and December 2003, we treated 11 patients (6 males and 5 females; 42 to 80 years of age; mean age 66.6 years) selected on the following criteria: <6-hour time window for anterior circulation and 12 hours for posterior circulation stroke, occlusion of a major cerebral artery, and absence or subtle early ischemic signs on admission computed tomography (CT) of the head (Alberta Stroke Programme Early CT Score [ASPECTS] \textsuperscript{-}7).\textsuperscript{15} Neurological assessments were performed by an independent neurologist using the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS). The cause of the ictus was cardioembolic in 5 patients (chronic atrial fibrillation in 3, aortic valve endocarditis and paroxysmatic atrial fibrillation combined in 1, and patent foramen ovalis in 1). In the remaining patients, despite the presence of $\geq$1 important risk factors for thromboembolism (smoking, use of oestrogentrinics, diabetes, ischemic heart disease), the source of embolism remained unidentified. On admission, 7 patients presented with an anterior circulation and 4 with a posterior circulation stroke, the severity of which ranged from 18 to 25 (median 20) points on the NIHSS. Two patients with chronic atrial fibrillation were on coumadin with INR values of 2.0 and 2.5, respectively. A CT angiography (CTA) was obtained in 6 patients. Intravenous tirofiban (0.4 $\mu$g/kg per minute bolus for 3 minutes, followed by infusion of 0.1 $\mu$g/kg per minute) was started combined with heparin (bolus of 2500 to 3000 IU IV) immediately after the admission CT study. Digital subtraction angiography (DSA) was performed after the CT–CTA examinations. In patients with anterior circulation stroke, the endovascular approach was homolateral to the occluded vessel in 5 patients and contralateral in 2 patients whose occlusion site was reached by a contralateral approach through the anterior communicating artery because of anatomic vessel constrains (kinking and looping of ipsilateral cervical internal carotid artery [ICA]). All patients had an immediate postprocedural CT study, they were monitored with transcranial Doppler (TCD) for $\geq$72 hours, and had a follow-up CT and a DSA 24 hours later. The infusion of tirofiban (0.1 $\mu$g/kg per minute) and heparin (500 to 1000 IU per hour) was maintained for 24 hours in 4 patients and for 48 hours in 1 patient. In 6 patients, tirofiban was suspended earlier based on the presumption of an impending risk of cerebral bleeding (parenchymal contrast enhancement) or for noncerebral bleeding (groat hematoma, hematruia).

Endovascular Techniques

All procedures were performed in a neuroangiography suite equipped with DSA and road-mapping capabilities. General anaesthesia was required in 3 patients who were agitated and uncooperative. A baseline activated clotting time (ACT) was obtained and then repeated every hour. ACT was maintained during the procedure between 200 and 300 seconds. A 6-F sheath was placed in the femoral artery and a 6- or 5-F guiding catheter was advanced in the ICA or in the vertebral artery. Thromboaspiration was performed through the guiding catheter with a 60-mL syringe in 3 cases of ICA occlusion and in 1 case of BA occlusion. Under road-mapping, an over-the-wire, soft, compliant 4$\times$15 mm microballoon (Hyperligeride; MTI Micro Therapeutics, Inc) in 9 cases or a microcatheter in 2 cases was advanced into the occluding thrombus. The microballoon was slowly and gently inflated once or twice for a few seconds under road-mapping visual control using a hand-held device (Cadence; MTI Micro Therapeutics, Inc). Attempts of mechanical disruption with the microguide the microballoon were always performed before the local delivery of urokinase (Ukidan). The latter was given up to a total dose of 300 000 to 600 000 IU in 8 cases (6 carotid and 2 basilar stroke) and 1 000 000 to 1 500 000 IU in 3 cases (2 basilar and 1 carotid T lesion). In all cases but 2, angioplasty of the occluding clot was also performed. Tirofiban and heparin were continued throughout the interventional procedure and after this, for 24 to 48 hours, whenever there was no bleeding; in 1 case, they were suspended because of hematruia and initial groin hematoma, and in 1 because of CT subtle signs of focal subarachnoid hemorrhage. Femoral artery hemostasis was obtained with a vascular closure device (Angio Seal; St. Jude Medical) 24 hours later. After the interventional procedure, all the patients were moved either to the intensive care unit for 24 to 48 hours and then to the stroke unit, or directly to the stroke unit.

All the procedures reported were approved by the local ethical committee.

Results

The timing as well as the most important neurological and imaging features are summarized in Tables 1 and 2. The time lag between tirofiban and urokinase administration ranged

<table>
<thead>
<tr>
<th>TABLE 1. Timings, Interventional Procedures, and Results of Imaging Studies in the 11 Patients</th>
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<tbody>
<tr>
<td><strong>Sex/Age, y</strong></td>
</tr>
<tr>
<td>F/65</td>
</tr>
<tr>
<td>F/69</td>
</tr>
<tr>
<td>M/73</td>
</tr>
<tr>
<td>M/73</td>
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<tr>
<td>M/42</td>
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<tr>
<td>M/49</td>
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<td>M/66</td>
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<td>M/66</td>
</tr>
<tr>
<td>M/80</td>
</tr>
<tr>
<td>F/72</td>
</tr>
<tr>
<td>M/78</td>
</tr>
</tbody>
</table>

UK indicates urokinase; F, females; M, males; R, right; L, left; BG, basal ganglia; “T,” carotid T lesion.
from 30 to 80 minutes (mean 53 minutes), corresponding to the time necessary to prepare the angiographic suite and reach the occlusion site with the microcatheter. On admission, the median NIHSS score was 20.

CTA showed occlusion of the intracranial vessel consistent with the clinical picture in 5 patients. DSA revealed a scant cortical collateral circulation (leptomeningeal anastomoses) between anterior cerebral artery and MCA and posterior cerebral artery and MCA in all the patients but 1 with an anterior circulation stroke and was absent in all the patients with a posterior circulation stroke. The recanalization at the end of the procedure was absent or insufficient (thrombolysis in myocardial infarction grade 0 to 1 [TIMI 0 to 1]) in 4 patients: 2 with a carotid T lesion, 1 with MCA (M1 tract of MCA [M1]), and 1 with BA occlusion. Partial recanalization (TIMI 2) was observed in 7 patients: 2 with a carotid T lesion, 3 with MCA (M1), and 2 with BA occlusion. Intraprocedural neurological improvement was noted in 7 patients (3 left carotid T lesion, 2 left M1, and 2 basilar), despite an insufficient (TIMI 1 in 2 patients) or partial (TIMI 2 in 5 patients) recanalization after the procedure. The clinical picture remained unchanged in 2 patients with TIMI 2 recanalization and worsened in 2 patients with TIMI 2 and TIMI 0, respectively. In 4 patients, the postprocedural CT showed foci of abnormal enhancement within the ischemic territories (basal ganglia in 3 patients and brain stem in 1 patient) that prompted the suspension of tirofiban and heparin infusion after the assumption of an increased risk of bleeding. In all 4 patients, the abnormal enhancement disappeared 24 hours later, consistent with a contrast medium extravasation through an altered blood–brain barrier. During the next 24 hours, the clinical picture progressively improved in 8 of 11 patients. Twenty-four hours later, all foci of enhancement disappeared and were replaced by an area of low attenuation without mass effect. No hemorrhagic transformation occurred. Apart from 1 patient who had a partial recanalization (TIMI 2), in all the other patients, the control DSA at 24 hours showed a complete recanalization (TIMI 3) of the occluded vessel and its peripheral territories. This situation persisted afterward in all the patients followed up by serial TCD studies.

At discharge, the NIHSS score was markedly improved in all the patients (median NIHSS score 2) as shown in Table 2. At the 3-month follow-up, the functional outcome was excellent (mRS score 0 to 1) in 8 of the 11 patients, good (mRS score 2) in 2 patients, and poor (mRS 6) in 1 patient who eventually died from pulmonary embolism.

**Discussion**

Our experience suggests that the combination of intravenous tirofiban with endovascular mechanical clot disruption and locally delivered urokinase may be successful in reopening an occluded major cerebral vessel and in preventing rethrombosis without increasing the hemorrhagic risk. Compared with the poor prognosis of patients with this type of stroke, the clinical and the functional outcomes may be excellent. However, because of the small series of patients, the heterogeneous treatment and the noncontrolled study design, caution is mandatory in generalizing these conclusions. Our patients were carefully selected, excluding those with extensive early CT changes (ASPECTS ≤7). Time to treatment was in the 6-hour window in patients with hemispheric stroke, and in the 12-hour window in patients with BA stroke.

A few topics characterize the present experience: (1) the complete reopening of the occluded vessel in the majority of patients; (2) the vessel recanalization occurring progressively throughout the 24 hours after the interventional procedure; and (3) the neurological improvement continuing in the 24 hours after the procedure. Overall, despite the small number of patients in our study limiting comparison, our recanalization rate at the completion of the procedure was high (7 of 11; 64%), similar to the 66% in PROACT II and despite our higher NIHSS score of 20 versus 16 in PROACT II. At 24 hours, recanalization rate was even better (10 of 11; 90%).

### Table 2: Preprocedural and Postprocedural Clinical, Imaging, and Treatment Features With NIHSS and mRS Evaluation at Discharge and at 3-Month Follow-Up

<table>
<thead>
<tr>
<th>Sex/Age, y</th>
<th>NIHSS on Admission</th>
<th>CT on Admission</th>
<th>Angiography</th>
<th>Postprocedural Clinical Course</th>
<th>Postprocedural CT</th>
<th>Postprocedural Tirofiban/Heparin</th>
<th>NIHSS Score at Discharge</th>
<th>mRS at 3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/65</td>
<td>25</td>
<td>Early signs + MCA Hyper</td>
<td>Left “T” ICA</td>
<td>Improved Enhancement</td>
<td>Stopped</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>F/69</td>
<td>18</td>
<td>Negative</td>
<td>BA</td>
<td>Improved Enhancement</td>
<td>Stopped</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>M/73</td>
<td>20</td>
<td>Negative</td>
<td>Left M1</td>
<td>Stable</td>
<td>Subarachnoid hemorrhage</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>M/73</td>
<td>18</td>
<td>MCA hyper</td>
<td>Left “T” ICA</td>
<td>Improved Negative</td>
<td>Continued 48 hours</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>F/42</td>
<td>25</td>
<td>Early signs + BA Hyper</td>
<td>BA</td>
<td>Worsened Enhancement</td>
<td>Stopped</td>
<td>8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>M/49</td>
<td>20</td>
<td>Early signs</td>
<td>Left “T” ICA</td>
<td>Worsened</td>
<td>Unchanged</td>
<td>Continued 24 hours</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>M/66</td>
<td>25</td>
<td>BA hyper</td>
<td>BA</td>
<td>Stable</td>
<td>Unchanged</td>
<td>Stopped</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>M/66</td>
<td>25</td>
<td>Negative</td>
<td>BA</td>
<td>Improved Enhancement</td>
<td>Stopped</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>F/80</td>
<td>18</td>
<td>MCA hyper</td>
<td>Left M1</td>
<td>Improved Negative</td>
<td>Continued 24 hours</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>F/72</td>
<td>18</td>
<td>MCA hyper</td>
<td>Left M1</td>
<td>Improved Negative</td>
<td>Continued 24 hours</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>M/78</td>
<td>20</td>
<td>MCA hyper</td>
<td>Left “T” ICA</td>
<td>Improved Negative</td>
<td>Continued 24 hours</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

F indicates females; M, males; “T,” carotid T lesion; early signs, subtle early ischemic signs; hyper, relative hyperdensity.
suggesting that tirofiban may play a role in continuing the thrombolytic process and preventing reocclusion. We used tirofiban in combination with endovascular mechanical clot disruption supported by the idea that it could sustain the microcirculation before, during, and after the interventional procedures. In the small vessels, GPIIb/IIIa inhibitors may prevent fibrin and platelet aggregate deposition triggered by the endothelial procoagulant response to flow reduction and leading to the collapse of microcirculation (the so called “no-reflow phenomenon”).\(^{14-16}\) In contrast, the marked procoagulant activity observed in stroke patients treated with intravenous alteplase\(^{17}\) suggests that fibrinolytics may activate the coagulation cascade, resulting in thrombin formation. Thrombin increases fibrin deposition favoring incorporation of platelets into the thrombus in the downstream vascular territories\(^\) and may obscure heparin-binding sites impeding heparin to prevent reocclusion.\(^{19}\) According to these observations, GPIIb/IIIa inhibitors might enhance the fibrinolytic response. The interaction between hypoperfusion and thromboembolism may explain the reduced chance of late recanalization after intravenous or IA treatment using fibrinolytics only or the reocclusion of partially disobliterated vessels (accompanied by clinical deterioration) in a fairly high proportion of patients in the TIMI I or 2 classes at the end of interventional procedures. We performed direct percutaneous transarterial angioplasty of the thrombus using a very low-invasive technique (low pressure, soft compliant microballoon, hand-held inflation device, slow and short inflation, no more than twice) to crush the clot.\(^{20}\)

The bleeding risk related to the association of intravenous GPIIb/IIIa inhibitors with IA urokinase in acute stroke patients was yet unknown. Tirofiban and low-dose rtPA given intravenously in a small group of ischemic stroke patients did not produce any symptomatic hemorrhage.\(^{7}\) No difference was observed comparing the bleeding risk after the IA use of urokinase with or without intravenous abciximab.\(^{8}\) Using intravenous tirofiban with IA urokinase, we had only minor bleedings and no symptomatic hemorrhage, even in the 2 patients on coumadin. In patients with progressive stroke, tirofiban was not associated with an increased bleeding risk, even if administered within a broad time window.\(^{19}\) The combined use of tirofiban and heparin was derived from the cardiologists’ experience of a superiority of this combination in terms of safety and efficacy in the treatment of patients with coronary symptoms over the use of tirofiban alone.\(^{10}\) The choice of using a rapid bolus of tirofiban over 3 minutes instead of 30 minutes was also based on the experience of a trial in acute coronary syndromes since 1997\(^{11}\) and was supported by the intention to speed the preparatory effect of tirofiban in a scenario in which technical organization of the endovascular procedure was expected to take time.\(^{22}\) In contrast to abciximab and similar to eptifibatide (Integrilin), the nonpeptide antagonist tirofiban had fewer side effects given its short half-life (t\(_1/2\) = 2 hours) and no allergic properties, allowing several consecutive treatments without the risk of incurring allergic reactions.\(^{23}\)

Conclusions

Early intravenous administration of tirofiban combined with mechanical clot disruption and locally delivered urokinase seems a promising approach in treating patients with severe strokes attributable to occlusion of a major cerebral artery. Given the very limited sample size, this strategy cannot be recommended as the systematic approach to such patients unless tested in a controlled experimental design.

Acknowledgments

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