Acute Basilar Artery Occlusion Treated With Combined Intravenous Abciximab and Intra-arterial Tissue Plasminogen Activator Report of 3 Cases

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Background—Acute vertebrobasilar occlusion remains a disease with a high mortality even after treatment by local intra-arterial fibrinolysis. Adjunctive treatment with platelet glycoprotein IIb/IIIa receptor inhibitors such as abciximab may facilitate recanalization and improve the neurological outcome. Results after treatment of 3 patients by combined intravenous abciximab and local intra-arterial tissue plasminogen activator (tPA) are reported.

Case Descriptions—Treatment was performed within 6 hours of stroke onset. Angiography revealed embolic occlusion of the basilar artery in 2 patients and atherothrombotic occlusion at the vertebrobasilar junction in 1 patient. Therapy consisted of intravenous abciximab bolus administration (0.25 mg/kg) followed by 12-hour infusion therapy (0.125 µg/kg per minute) and local intra-arterial thrombolysis with tPA (10 mg/h). Heparin was only applied for catheter flushing (500 IU/h). The patient with the atherothrombotic occlusion was treated with additional percutaneous transluminal angioplasty and stenting. Complete recanalization of the basilar artery occurred in 2 patients, whose conditions improved clinically to functional independence. In the third patient only partial recanalization was seen, with only slight clinical improvement. This patient died of cardiac failure 2 months later. Besides a subtle subarachnoid hemorrhage (n=1), no intracranial or extracranial bleeding complication was observed.

Conclusions—The combination of glycoprotein IIb/IIIa receptor inhibitor with local intra-arterial tPA might be a promising therapy for patients with acute vertebrobasilar occlusion. Further studies are necessary to define the clinical benefit and the bleeding rate of this new pharmacological approach. (Stroke. 2002;33:1424-1427.)

Key Words: antibodies, monoclonal ▪ basilar artery ▪ fibrinolysis ▪ stroke, ischemic ▪ thrombolytic therapy ▪ vertebral artery
Technical Procedures

CT scan and CT angiography (CTA) were performed before treatment to exclude intracranial hemorrhage or a brain stem infarct and to confirm the clinical diagnosis of a vertebrobasilar occlusion. Clinical examination was performed by a neurologist before intubation and included scoring according to the modified Rankin Scale (mRS)\textsuperscript{13} and National Institutes of Health Stroke Scale (NIHSS).\textsuperscript{14} Informed consent was obtained in patient 3. Patients 1 and 2 were not able to give informed consent and were treated in accordance with a compassionate treatment protocol as approved by the local ethics committee.

Four-vessel angiography was performed in all patients. After angiographic documentation of the BA occlusion, the intravenous abciximab therapy was initiated (bolus of 0.25 mg/kg body wt) followed by an infusion of 0.125 μg/kg body wt per minute. The infusion therapy was maintained for 12 hours. Further abciximab therapy was initiated. Angiography 20 minutes later disclosed partial recanalization with filling of both PCA and right SCA (Figure 1B), and local fibrinolysis was begun. Nineteen minutes after local tPA infusion, the BA was completely recanalized; however, the right PCA remained occluded even after 2 hours of local tPA therapy. Control CT scan revealed a complete infarction of the right PCA and a thalamic infarction but no brain stem infarction. Intracranial bleeding was not detected. The patient was extubated 2 days later, and the clinical condition improved continuously. After 3 months the patient improved to functional independence (NIHSS score from 31 to 4; mRS score from 5 to 2).

Case 2

Patient 2 (male, aged 80 years) presented with sudden loss of consciousness, ophthalmoplegia with fixed pupils, and spontaneous waves of extensor rigidity (NIHSS score 32; mRS score 5), with subsequent oropharyngeal intubation. On CT scan 5.5 hours after stroke onset, no brain stem lesions were visible. CTA and catheter angiography revealed a mid basilar vessel occlusion, suggesting embolic BO occlusion. Intravenous abciximab and local fibrinolysis were started 6 hours after stroke onset. After 2 hours of local recombinant tPA therapy, incomplete recanalization was achieved. CT follow-up revealed mesencephalic and thalamic infarction and an infarction of the right PCA without hemorrhage. Transcranial Doppler sonography 24 hours after stroke onset disclosed recanalization of the BA. The clinical condition remained stable, with slight improvement of the hemiparesis and increased responsiveness. After 2 months the NIHSS score was 27 and the mRS score was still 5. Two weeks later the patient died of heart failure.

Case 3

Patient 3 (male, aged 56 years) presented with acute onset of ataxia, facial paresis, horizontal gaze palsy, progressive dysarthria, and dysphagia (NIHSS score 9; mRS score 3). CT scan excluded hemorrhage. CTA revealed occlusion of the verteobasilar junction with retrograde perfusion of the distal BA. Neurological deficits progressed over the next 30 minutes, and oropharyngeal intubation was required. Angiography confirmed proximal occlusion of the right VA and intracranial occlusion of the left VA (Figure 2A), suggesting atherothrombotic occlusion at the site of a preexisting stenosis. Abciximab infusion and local fibrinolysis were started 5 hours after symptom onset. After 2 hours of local tPA therapy, no recanalization occurred. The patient was referred to the intensive care unit with a remnant sheath. A control angiogram after termination of abciximab infusion therapy (17 hours after symptom onset) revealed recanalization along with a residual high-grade stenosis (Figure 2B). It was decided to perform an angioplasty. To prevent periprocedural thromboembolic complications, 4000 IU heparin was intravenously applied to elevate the activated clotting time from 162 to 310 seconds. First the stenosis was passed by a guidewire (14-inch Choice PT, Boston Scientific), then a 2.5-mm balloon catheter (10 mm in length) was placed inside the stenosis (Omni Pass, Cordis Europa NV) and inflated with a pressure of 6 atm.

Follow-up neurological examination was performed by an independent neurologist in all 3 patients.

Case 1

Patient 1 (female, aged 62 years) presented with rapid onset of brain stem symptoms (dysarthria, tetraparesis, and double vision) and coma leading to oropharyngeal intubation. NIHSS score was 31 and mRS score was 5 before intubation. CTA 3 hours after symptom onset revealed an embolic distal BA occlusion including both PCA and right superior cerebellar artery (SCA) (Figure 1A). Intravenous abciximab therapy was initiated. Angiography 20 minutes later disclosed a partial recanalization with filling of both the PCA and the right SCA (Figure 1B), and local fibrinolysis was begun. Nineteen minutes after local tPA infusion, the BA was completely recanalized; however, the right PCA remained occluded (Figure 1C) even after 2 hours of local tPA therapy. Control CT scan revealed a complete infarction of the right PCA and a thalamic infarction but no brain stem infarction. Intracranial bleeding was not detected. The patient was extubated 2 days later, and the clinical condition improved continuously. After 3 months the patient improved to functional independence (NIHSS score from 31 to 4; mRS score from 5 to 2).

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Figure 1. Patient 1. A, CTA before treatment, revealing a distal BA occlusion without opacification of either PCA or right SCA. B, After 20 minutes of abciximab application, angiographic depiction via microcatheter in BA (anteroposterior view) discloses a partial recanalization with filling of both PCA and right SCA. C, After 19 minutes of local recombinant tPA infusion, angiographic depiction via left VA (anteroposterior view) shows complete recanalization of BA but persistent occlusion of right PCA.
Discussion

Even with local intra-arterial fibrinolysis, recanalization rates in acute vertebrobasilar occlusion do not exceed 70%, and mortality rates remain 60%.4,5 Increasing the dosage of plasminogen activators has not improved clinical and angiographic results.5 Only the adjunctive therapy with human-

derived lys-plasminogen has improved the recanalization rate and neurological outcome.5,15 Lys-plasminogen, however, is not generally available at present. The production of human-derived lys-plasminogen has been discontinued, and to our knowledge recombinant lys-plasminogen is not available. To accelerate recanalization, new treatment strategies are necessary.

Lysing fibrin from the fibrin thrombus clot through plasminogen activators exposes free thrombin and paradoxically stimulates platelet aggregation and can facilitate rethrombosis. At the site of the vascular injury, for example, an atherosclerotic stenosis, platelet aggregation can cause the formation of a platelet thrombus (“white clot”). A platelet thrombus may also embolize toward the microcirculation and release vasoactive amines. Platelet glycoprotein IIb/IIIa receptor inhibitors such as abciximab induce a rapid and effective inhibition of platelet aggregation. Through thrombolysis of the platelet thrombus and by preventing the process of rethrombosis, adjunctive abciximab application might improve the rate and extent of intra-arterial fibrinolysis in acute stroke. An additional effect may be the improvement of microvascularization, as has been found in patients with coronary artery occlusive disease16 and in animal studies after abciximab application.17,18 In the cerebral circulation, successful adjunctive abciximab therapy after failed intra-arterial fibrinolysis has been described as rescue treatment in rare cases of basilar artery rethrombosis19 and acute middle cerebral artery stroke.20

Pathoanatomic1,21,22 and clinical studies5,23–25 suggest that 2 different occlusion mechanisms exist in acute vertebrobasilar occlusion: atherothrombotic occlusions at the site of an underlying stenosis in the vertebrobasilar junction up to the mid basilar portion of the BA and occlusions in the distal portion of the BA, suggesting embolic occlusion. In most studies on intra-arterial fibrinolysis, recanalization rates and clinical results were found to be better in embolic than in atherothrombotic occlusion.4,5,23 In both types of occlusion, abciximab might facilitate recanalization by thrombolysis of the platelet part of the clot; this is probably more important in the case of atherothrombotic BA occlusion at the site of an atherosclerotic plaque resembling the cardiovascular obstruction type. In the case of residual stenosis after intra-arterial thrombolysis in atherothrombotic BA occlusion, additional PTA/stenting has been reported to improve the clinical outcome.5,26 Abciximab has been shown to be effective in preventing thrombosis and embolic complications during PTA in coronary6–8 and carotid arteries.9 Abciximab ensures sufficient periprocedural inhibition of platelet aggregation if additional endovascular treatment is required. In case of a good collateral situation such as in patient 3 (Figure 2), it might be reasonable to await the effect of the 12-hour abciximab infusion therapy and perform the PTA/stenting later.27

In patient 1, who had an embolic occlusion, a recanalizing effect was already visible after abciximab application before recombinant tPA administration (Figure 1). In embolic occlusion, mechanical approaches to retrieve the clot, such as basket devices or snare systems,28 might be promising options in the immediate future.
The major concern about this combined approach is the risk of intracranial bleeding complications.29 In the GUSTO V Trial,12 extracranial bleeding complications were significantly higher on combined therapy (severe bleeding rate 1.1% versus 0.5%; moderate bleeding rate 3.5% versus 1.8%). The intracranial bleeding rate, however, was low (0.4% in combined therapy versus 0.5%) except in patients older than 75 years (2.1% in combined therapy versus 1.1%). Except for a subtle subarachnoid hemorrhage in patient 3, no intracranial or extracranial bleeding complication was seen in our patients. Cardiological studies have expounded on the significance of heparin in severe bleeding complications. To reduce the bleeding risk we applied a reduced dosage of recombinant tPA (10 mg/h) and applied heparin only for catheter flushing.

Although the number of reported patients is very limited and this novel combined therapy is still a premature experimental treatment, we believe that abciximab in combination with fibrinolysis and, if necessary, with additional PTA/stenting might be a promising therapeutic approach to improve recanalization and clinical outcome in acute basilar occlusion. Many concerns regarding its potential hemorrhagic complications remain, however. Until additional safety data have been collected through further studies, this combined treatment should be restricted to patients with acute basilar occlusion.

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References
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