Selective Intra-Arterial Fibrinolysis of Acute Central Retinal Artery Occlusion

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Background and Purpose—Occlusion of the central retinal artery (CRAO) causes a sudden decrease of monocular vision. Because early restoration of blood flow may improve outcome, we attempted to treat CRAO with selective intra-arterial fibrinolysis.

Methods—Intra-arterial fibrinolysis was performed within 6 hours after symptom onset in 17 patients with thromboembolic CRAO. Symptoms were painless, acute and severe decrease of vision. Urokinase (100 000 to 900 000 IU) was given through a microcatheter into the ophthalmic artery over 10 to 90 minutes. For comparison, the history and visual outcome of 15 control patients who did not receive fibrinolytics were evaluated. In both groups some of the patients underwent paracentesis and/or received carbonic anhydrase inhibitors.

Results—Patients who underwent fibrinolysis fared better than control patients (P=0.01). Three patients (17.6%) recovered completely after fibrinolysis and regained visual acuity of 20/20 (n=2) to 25/20 (n=1). Two additional patients (11.8%) showed a marked improvement to a visual acuity of 20/30. In 6 patients (35.3%) vision improved slightly. They were able to count fingers, detect hand movements, or perceive light. In 6 patients (35.3%), fibrinolytic treatment was without effect. Among control patients, 1 patient (6.7%) showed partial, 4 patients (26.7%) minimal, and 10 (66.7%) no improvement of vision.

Conclusions—A complete or marked improvement of visual acuity was achieved in one third of intra-arterial fibrinolysis patients but in none of the control patients. Intra-arterial fibrinolysis seems to have the potential to “lighten” the spontaneously poor outcome of CRAO. (Stroke. 1998;29:2076-2079.)

Key Words: fibrinolysis ▪ retinal artery occlusion ▪ thrombolysis

In acute central retinal artery occlusion (CRAO), conventional therapies such as anterior chamber paracentesis, ocular massage, pentoxifylline, or carbonic anhydrase inhibitors hardly change the unfavorable spontaneous course.1 Based on the increasing experience and beneficial results of fibrinolytic therapy in cerebral, coronary, and peripheral artery occlusions, attempts have been made to use selective fibrinolysis in treatment of CRAO also.2,3 In an animal model,4 this technique proved its efficacy. With the advent of advanced microcatheter technology and the growing experience of investigators, the use of this technique in humans has become feasible and safe.5

The retina is part of the brain; therefore, many principles of fibrinolysis in brain vessels can be applied to CRAO as well. The time window for successful treatment in stroke is short, usually within 3 to 6 hours.6,9 In the monkey, the retina tolerates complete ischemia for about 100 minutes.10 In human CRAO there may be some residual blood flow.11,12 Therefore, the human retina might sustain ischemia for longer periods and recanalization with fibrinolytics within hours might result in a better clinical outcome. For these reasons, we tried to restore the retinal circulation by local intra-arterial fibrinolysis in a series of patients with acute CRAO.

Subjects and Methods

Study Design

This is a retrospective nonrandomized study comparing 2 groups of patients with CRAO. Inclusion criterion was acute decrease of vision because of noninflammatory thromboembolic occlusion of the central retinal artery (CRA). Patients with CRA branch occlusions, systemic or local vasculitis, arteriovenous malformations, or blood dyscrasias were excluded. All patients (patient group and control group) were seen at the department of ophthalmology for diagnosis. Visual function was assessed using a standardized chart and lighting. One group of patients (n=17) was treated with intra-arterial fibrinolysis, the other group (n=15) served as controls. In addition, in both groups some patients underwent anterior chamber paracentesis (35.3% and 6.7%, fibrinolysis versus control), received carbonic anhydrase inhibitors (5.9% and 13.3%, fibrinolysis versus control), or none (11.8% and 53.3%, fibrinolysis versus control) of those conventional therapies. Initial symptoms of CRAO were acute, painless monocular decrease of vision in all the patients. Fibrinolysis was performed after conventional treatment whenever possible. Patients who under-
Baseline Characteristics of Patient and Control Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controls (n = 15)</th>
<th>Fibrinolysis (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>64.4±14.3</td>
<td>60.8±15.2</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8 (53.3)</td>
<td>7 (41.8)</td>
</tr>
<tr>
<td>Male</td>
<td>7 (46.7)</td>
<td>10 (58.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (53.3)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0 (0)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Cardiac pathologies</td>
<td>3 (20)</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>Atherosclerosis of ICA</td>
<td>4 (26.7)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>2 (13.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior chamber paracentesis</td>
<td>1 (6.7)</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>2 (13.3)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Paracentesis and acetazolamide</td>
<td>4 (26.7)</td>
<td>8 (47.1)</td>
</tr>
<tr>
<td>No conventional therapy</td>
<td>8 (53.3)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td><strong>Visual acuity before treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No light perception</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Light perception</td>
<td>6 (40)</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>Hand movement</td>
<td>6 (40)</td>
<td>9 (52.9)</td>
</tr>
<tr>
<td>Finger counting</td>
<td>2 (13.3)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>&gt;20/1000</td>
<td>1 (6.7)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

ICA indicates internal carotid artery. Values are number of patients, with percentages in parentheses.

*Significantly different (P<0.02).

went fibrinolysis were informed about the potential risks and benefits of fibrinolysis, and they agreed to treatment.

**Fibrinolysis Group**

The 17 patients who received fibrinolytics were on average 60.8 years old (range, 29 to 83 years; median, 64 years). Vascular risk factors are given in the Table[1b]. The diagnosis of CRAO was made by an ophthalmologist. Diagnosis was based on an acute decrease of vision and funduscopic findings such as ischemic macular edema, a cherry red spot, or reduced or absent retinal blood flow. To save time, fluorescein angiography was not used. Visual acuity was assessed before, 1 to 14 days after, and again 8 weeks after fibrinolysis by an ophthalmologist.

The delay from decrease of vision to fibrinolytic therapy was on average 4.2 hours (range, 1 to 6 hours). Fibrinolytic therapy was performed by the neuroradiologist. Before treatment, complete angiography of both carots and the vertebrobasilar system was performed in every patient to exclude vessel occlusions and stenoses and to assess collateral blood supply. The ophthalmic artery, its branches, and the chorioretal blush were assessed before and after fibrinolysis as seen on angiography and by funduscopic. Urokinase served as the fibrinolytic agent. We applied 100 000 to 900 000 IU (mean, 594 000 IU) over 10 to 90 minutes. We injected the drug manually and stepwise (approximately 100 000 IU per 10 minutes) through a microcatheter (Tracker 18). Its tip was placed in the proximal segment of the ophthalmic artery. Immediately after fibrinolysis, full-dose heparinization with unfractionated heparin was started, and the patient admitted to the neurological ward.

**Control Group**

The control group was made up of 15 patients seen at the Department of Ophthalmology (Table). The patients had a mean age of 64.4 years (range, 39 to 93 years; median, 64 years) and were all seen within 6 hours after decrease of vision. Five were seen before fibrinolysis treatment was available at our institution, and 7 arrived at the hospital when there was no neuroradiologist on call who was capable of performing the procedure. In 3 control patients angiography showed a tight carotid stenosis. Because we felt it would be risky to pass the stenosis with the microcatheter, fibrinolysis was not performed. The presenting symptoms and signs were the same as in the fibrinolysis group. Visual acuity was assessed before and ≥4 weeks after treatment by an ophthalmologist.

**Statistical Analysis**

Numerical values of vision were assigned for finger counting (20/1000), perception of hand movement (20/2000), and perception of light (20/20000). The Wilcoxon rank sum test served to assess differences between fibrinolysis and control patients. For correlations, the Spearman rank correlation test was used.

**Results**

Visual acuity before treatment ranged from light perception to 20/250. It did not differ between the fibrinolysis and the control groups (P=0.44). No patient in either group was completely blind, 37.5% (35.3% in the fibrinolysis group and 40% in the control group) perceived light, 46.9% (52.9% and 40%, fibrinolysis versus control) detected hand movements, 12.5% (11.8% and 13.3%, fibrinolysis versus control) were able to count fingers, and 1 patient in the control group (6.7%) had a visual acuity of 20/250.

Visual outcome in fibrinolysis patients was significantly better than in control patients (P=0.01). With fibrinolysis, 3 patients (17.6%) recovered completely and regained a visual acuity of ≒20/20. Two patients (11.8%) showed a marked improvement, with a posttreatment visual acuity of 20/30. Six patients (35.3%) had an outcome with slight improvement. They were able to perceive light, detect hand movements, or count fingers. In 6 patients fibrinolytic treatment did not improve vision (35.3%) (see the Figure). In 2 patients a transient ischemic attack was observed during angiography.
and fibrinolysis. Complications causing permanent neurological deficits did not occur. There were no intracranial or retinal hemorrhages.

Among control patients the initial visual deficit remained the same or got worse in the majority of patients (66.7%). Four control patients showed slight improvement of their vision (26.7%), and 1 had a visual acuity of 20/60 at follow-up (Figure).

Conventional therapy was better than no treatment among control patients (P = 0.005), but anterior chamber paracentesis, carboanhydrase inhibitors, or a combination of the 2 did not have any additional effect on visual outcome in the fibrinolysis group (P = 0.428). There was no evidence for other statistically relevant influences on visual improvement. In neither group was there a significant correlation between age and visual outcome (fibrinolysis, P = 0.172; control, P = 0.095). The delay between symptom onset and treatment within the limits of 6 hours did not affect the resulting vision (P = 0.692 versus P = 0.396, fibrinolysis versus controls). Initial visual acuity had no predictive value for the visual outcome either (P = 0.564 versus P = 0.618, fibrinolysis versus controls). In the fibrinolysis group there was no correlation between the severity of the chorioretinal blush before (P = 0.58) or after (P = 0.347) fibrinolysis, between severity of blush and dose (P = 0.807), or between severity of blush and application time of urokinase (P = 0.293) and visual improvement.

Discussion

In general, CRAO is said to have a gloomy outcome although, to the best of our knowledge, the exact natural history of patients with CRAO without any therapeutic intervention has not been reported. In a series of 34 patients treated with anterior chamber paracentesis and carboanhydrase inhibitors or both, only 2 recovered completely. The majority of patients (66.7%) did not improve at all. In another series of 33 treated patients, visual outcome was even worse. Recent attempts to treat CRAO with local intra-arterial fibrinolysis have been promising. Schumacher and coworkers noted an improved visual outcome after fibrinolysis compared with historic controls.

In this retrospective study we performed fibrinolysis in 17 patients with CRAO within 6 hours after decrease of vision. Treatment was performed locally in the ophthalmic artery with the help of a microcatheter. The outcome was compared with that in 15 control patients who did not receive fibrinolysis. Patients with fibrinolysis had a better outcome than patients treated conservatively (P = 0.01). Three patients regained a complete vision and 2 a vision of 20/30 after fibrinolysis. There were more patients who regained complete or partial vision after fibrinolysis than without, and there were fewer patients in the fibrinolysis group who did not show any improvement at all. Without fibrinolysis, the best results achieved were a visual acuity of 20/200 and 20/60 in 1 patient each, but none regained a normal vision.

Thus, our data corroborate previous retrospective observations that fibrinolysis improves visual outcome when performed early after symptom onset. However, as demonstrated by the 2 patients with transient ischemic attacks during the procedure, fibrinolysis for CRAO is not without danger. To avoid complications, patients with CRAO should be selected carefully for fibrinolysis. Patients with vasculitis or hematological disorders such as leukemia carry a higher risk of bleeding and should probably be excluded from fibrinolysis. In addition, stenoses of the carotid arteries can be both an obstacle and a risk for local intra-arterial fibrinolysis. For this reason, we first performed an ordinary angiography to assess the aortic arch and the extracranial and intracranial cerebral arteries bilaterally. If there was a high-grade carotid stenosis, lysis was not attempted. The angiographer did not pass the stenosis with the catheter because of the potential risk of arterio-arterial embolism and stroke. In patients without stenosis, if technically feasible, the tip of the microcatheter was placed in the proximal segment of the ophthalmic artery to perform a selective angiography. On average, 594,000 IU urokinase was applied.

The time window for fibrinolysis within 6 hours after visual decrease is somewhat arbitrary. This time window was chosen by analogy with stroke. In stroke, systemic fibrinolysis within 3 hours turned out to be beneficial (NINDS rt-PA study). It can be beneficial up to 6 hours when patients are selected according to strict criteria (ECASS). The main risk is cerebral hemorrhage. In the study of Schumacher and coworkers, fibrinolysis of CRAO was performed within 36 hours. Patients treated before 6 hours showed better results than patients treated later. In our study, patients with complete recovery underwent fibrinolysis no later than 4 hours after visual decrease. This may be chance, because statistical analysis did not show any significant correlation between outcome and delay of treatment up to 6 hours. Intracranial or retinal bleeding did not occur in this series.

Frequently, in ophthalmic artery angiography, a contrast enhancement of the posterior eye bulb is seen, a so-called chorioretinal blush. If present, it did not correlate with a better visual outcome in our patients. The chorioretinal blush results from contrast filling of the choroidal arterioles, which are supplied by the posterior ciliary arteries and branches of the circle of Haller-Zinn. Anastomoses to the CRA or branches do not exist. This may explain why the presence or absence of a chorioretinal blush does not influence the outcome of fibrinolysis.

Patients with a tight internal carotid artery stenosis or occlusion pose a problem for ophthalmic artery catheterization and local fibrinolysis. Systemic application of fibrinolytic agents might be more beneficial for these patients, because the fibrinolytics could reach the CRA over numerous collaterals from the external carotid artery to the ophthalmic artery. In addition, the risk of cerebral hemorrhage may be lower than in stroke and closer to the risk of patients with myocardial infarction. However, no study has yet demonstrated whether a systemic intravenous fibrinolysis in CRAO is effective and safe. Alternatively, the fibrinolytics could be applied locally into the external carotid artery because most tight internal carotid artery stenoses cause a flow reversal in the ophthalmic artery and the eye becomes mostly supplied by the external carotid artery. For these reasons and because of the easier practicability of intravenous fibrinolysis, future therapeutic trials in CRAO should study both local and
systemic fibrinolysis in patients with and without carotid stenosis.

In conclusion, this retrospective study demonstrates improved visual outcome of local intra-arterial fibrinolysis in CRAO compared with conventional treatment if performed within 6 hours after symptom onset. Fibrinolysis may have the potential to “lighten” the otherwise gloomy outcome of CRAO. Our results, based on this retrospective study, need confirmation by a larger prospective, randomized trial.

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References
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