Intravenous Thrombolysis With Low-dose Recombinant Tissue Plasminogen Activator in Central Retinal Artery Occlusion

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• PURPOSE: **To evaluate the beneficial effect of intravenous thrombolysis aiming at rapid restoration of blood flow during the early hours of a central retinal artery occlusion (CRAO).**

• DESIGN: **Interventional case series.**

• METHODS: **In the present study, we prospectively evaluated the visual outcome after thrombolytic treatment with low-dose (50 mg) rt-PA (recombinant tissue plasminogen activator) and concomitant intravenous heparinization in patients with acute CRAO, best-corrected visual acuity (BCVA) ≤ 20/100, and onset of symptoms within 12 hours prior to treatment.**

• RESULTS: **Twenty-eight patients (28 eyes) were included in this study. Final visual acuity was improved three or more lines in nine eyes (32%), stable in 18 (64%), and worse in one eye. Time to treatment ≤ 6.5 hours was associated with a better gain of lines of vision ($P = .004$). Seven of 17 eyes (41%) that received thrombolytic treatment within the first 6.5 hours achieved a final BCVA ≥ 20/50, compared to none in the subgroup of patients with onset to treatment >6.5 hours ($P = .023$). We observed no serious adverse events.**

• CONCLUSIONS: **Our findings indicate that thrombolytic treatment with intravenous low-dose rt-PA is of value for an improved visual recovery in patients with acute CRAO, if administered within the first 6.5 hours after the onset of symptoms. (Am J Ophthalmol 2008; 146:700–706. © 2008 by Elsevier Inc. All rights reserved.)**

CENTRAL RETINAL ARTERY OCCLUSION (CRAO) IS an uncommon cause of unilateral visual impairment and a rare cause of blindness. Because of its rarity and a lack of consensus among ophthalmologists about therapeutic approaches, there are no consistent recommendations regarding treatment of this vascular emergency. Proposed therapies include administration of antiplatelet agents or anticoagulants; lowering intraocular pressure (IOP) by ocular massage, aqueous tap, or using antiglaucoma drugs; hemodilution to increase the perfusion of the retina; or various surgical procedures.[1–5] To date, none of these therapeutic approaches has ever proven to be effective.

Because early intervention aimed at restoration of blood flow could be critical for a favorable outcome, several researchers advocate the use of thrombolytic agents such as rt-PA (recombinant tissue plasminogen activator).[6] Over the past years, thrombolysis for the treatment of acute CRAO has been the subject of intense investigation. Most authors, however, have attempted to address this issue by the use of intra-arterial thrombolysis.[7–14] In contrast, available data on intravenous thrombolysis are largely limited to isolated case reports or retrospective case series.[2,15–17] As a result, no systematic information with regard to clinical outcomes or clinical practice guidelines such as indication criteria, doses, or the optimal window of treatment is available. In addition, a major concern regarding the use of thrombolytic agents in retinal vessel occlusion is the risk of cerebral hemorrhage or other bleeding complications.[18,19]

In the present study, we prospectively investigated the clinical outcome after intravenous thrombolysis with rt-PA in patients with acute CRAO. Because hemorrhage associated with systemic thrombolysis constitutes a dose-dependent problem, we selected a low-dose regimen of 50 mg of rt-PA.

PATIENTS AND METHODS

ALL PARTICIPANTS GAVE WRITTEN INFORMED CONSENT. Patients were eligible for the study if they presented with CRAO with initial best-corrected visual acuity (BCVA) equal to or less than 20/100 and onset of symptoms within less than 12 hours prior to the initial visit.

Eligible subjects were immediately investigated for possible contraindications such as recent stroke, severe arterial hypertension, bleeding disorders, recent major vascular puncture, head trauma, major surgery or organ biopsy, known intracranial tumor, recent gastrointestinal or genitourinary bleeding, and progressive diabetic or hypertensive retinopathy. Patients were excluded if they had one or more of the criteria outlined in Table 1.

See accompanying Editorial on page 631.

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TABLE 1. Contraindications to Intravenous Thrombolysis With Recombinant Tissue Plasminogen Activator in Central Retinal Artery Occlusion

• Intramuscular injection within last seven days
• Trauma or surgery within last four weeks
• Gastrointestinal ulceration or hemorrhage within last three months
• Cerebrovascular ischemia or hemorrhage within last 12 months
• Hemorrhagic disorders
• Bacterial endocarditis
• Pregnancy (≤14 weeks)
• Arterial hypertension (systolic >160 mm Hg/diastolic >100 mm Hg)
• Hypertensive retinopathy
• Temporal arteritis
• Proliferative diabetic retinopathy

In order to save time, pretreatment evaluation was limited to a minimum of diagnostic evaluation and laboratory studies. Before entry into the study, a physical examination with blood pressure measurements and laboratory tests including a complete blood count, erythrocyte sedimentation rate, and a blood coagulation profile including prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen were assessed in each individual. Patients who were taking anticoagulants or who had an elevated aPTT or PT were excluded, as were those with platelet counts below 100,000 per cubic millimeter. Noncontrast head computed tomography (CT) scanning, which is essential in the evaluation required before thrombolytic therapy in stroke patients for rapidly distinguishing ischemic from hemorrhagic infarction, was not part of the pretreatment evaluation in order to avoid time delays to treatment.

Clinical data were recorded prospectively by the authors with standardized forms. If patients stated they had high blood pressure or were using an antihypertensive medication, they were considered to have systemic arterial hypertension. Furthermore, we documented additional vascular risk factors such as diabetes mellitus or previous thromboembolic events.

The funduscopic inclusion criteria were as follows: narrowed retinal arteries in all four quadrants and ischemic retinal edema with a cherry-red spot at the center of the macula. The diagnosis of CRAO was made if both of these criteria were present. Patients were excluded whenever retinal or vitreous hemorrhage was present at the initial examination. Furthermore, we excluded patients who had received photocoagulation prior to their initial visit or who presented with additional ocular diseases such as diabetic retinopathy or age-related macular degeneration.

The primary clinical outcome measure was improvement in BCVA from baseline. Changes in BCVA were defined as improvement (increase of three or more Snellen

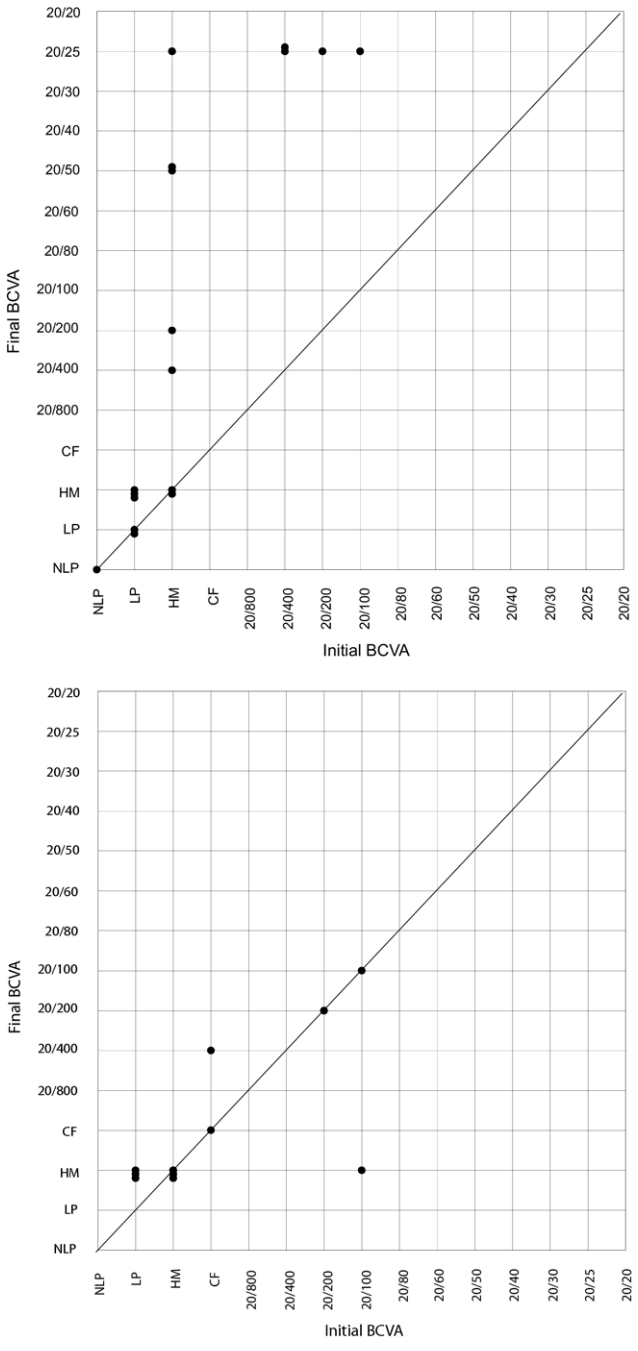

FIGURE. Scatterplots showing initial and final best-corrected visual acuities (BCVAs, Snellen lines) in central retinal artery occlusion (CRAO) patients after intravenous thrombolysis with recombinant tissue plasminogen activator. (Top) BCVAs in CRAO patients treated within 6.5 hours of symptom onset. Among these patients, nine (53%) exhibited an improvement of three or more lines. A final visual acuity equal to or better than 20/50 was noted in 7 eyes (41%). (Bottom) BCVAs in CRAO patients treated after >6.5 hours of symptom onset. None of these patients achieved an improvement of three or more Snellen lines or a final BCVA ≥20/50. CF = counting fingers; HM = hand motions; LP = light perception; NLP = no light perception.

TABLE 2. Clinical Profile of 28 Consecutive Patients With Central Retinal Artery Occlusion Before and After Intravenous Thrombolysis With Recombinant Tissue Plasminogen Activator

Patient No.	Age (y)	Gender	Vessel	Eye	Time to Treatment (hrs)	Visual Acuity Preoperative	Visual Acuity Postoperative
1	50	m	CRAO	OS	3	20/200	20/25
2	73	m	CRAO	OS	1.5	LP	LP
3	56	f	CRAO	OD	11	20/100	20/100
4	68	m	CRAO	OS	12	HM	HM
5	69	m	CRAO	OS	11	LP	HM
6	65	m	CRAO	OS	1.5	20/400	20/25
7	72	m	CRAO	OS	10	HM	HM
8	76	m	CRAO	OD	5	HM	20/200
9	85	m	CRAO	OS	5	LP	LP
10	69	m	CRAO	OD	4	LP	HM
11	69	m	CRAO	OS	6	HM	20/400
12	54	m	CRAO	OS	3	20/400	20/25
13	74	m	CRAO	OS	12	LP	HM
14	66	f	CRAO	OS	9	HM	HM
15	72	f	CRAO	OS	6	HM	20/25
16	75	f	CRAO	OD	7	LP	HM
17	53	m	CRAO	OD	5	HM	20/50
18	56	f	CRAO	OS	8	20/100	HM
19	55	f	CRAO	OS	9	CF	20/400
20	74	m	CRAO	OD	6	HM	HM
21	69	m	CRAO	OD	2	LP	HM
22	61	f	CRAO	OS	7	20/200	20/200
23	78	m	CRAO	OD	3.5	LP	HM
24	48	f	CRAO	OD	5	20/100	20/25
25	30	m	CRAO	OD	12	CF	CF
26	74	m	CRAO	OD	5	HM	HM
27	45	m	CRAO	OD	6.5	HM	20/50
28	35	f	CRAO	OD	5	NLP	NLP

CF = counting fingers; CRAO = central retinal artery occlusion; f = female; HM = hand motions; hrs = hours; LP = light perception; m = male; NLP = no light perception; OD = right eye; OS = left eye; y = years.

visual acuity [VA] lines), stable (within <three lines from baseline VA), and worse (loss of three or more Snellen VA lines). In all patients, complete bilateral ocular examinations including BCVA using the Snellen chart, slit-lamp biomicroscopy, applanation tonometry, and indirect ophthalmoscopy were conducted, at the initial examination, during the course of their hospitalization (days one to five), and at the long-term follow-up examination. Color fundus photography was performed, whenever possible, at the initial examination.

All study patients received thrombolytic treatment with 50 mg of rt-PA (Actilyse; Boehringer Ingelheim, Ingelheim am Rhein, Germany) given intravenously in the emergency room over a period of 60 minutes. Concomitant intravenous heparinization was started at 1200 units per hour and continued over five days as monitored by activated partial thromboplastin time (aPTT; target range, 60 to 80 sec). In addition, all patients received daily doses of aspirin (100 mg/d).

• **STATISTICAL ANALYSIS:** Group comparisons were performed by using the Fisher exact test. Acceptable significance was recorded when P values were $<.05$.

RESULTS

FROM NOVEMBER 1996 TO JULY 2004, WE ENROLLED A TOTAL of 28 patients (28 eyes) who presented with CRAO of acute onset (<12 hours). Nineteen subjects were men and nine were women, with a mean age of 63.3 years (range, 30 to 85 years). Two patients were age <40 years by the time of initiation of therapy. Mean time to treatment was 6.46 hours (range, 1.5 to 12 hours). Baseline VA ranged from no light perception (NLP) to 20/100. There was no significant relation between initial VA and final visual outcome. During the course of the follow-up (mean, 2.2 months; range, one to four months), none of the patients in our study developed contralateral CRAO. None of the

patients had a history of previous retinal vessel occlusion in the fellow eye. There were no serious adverse events or withdrawals because of adverse events.

Overall, final VA was improved three or more lines in nine eyes (32%), stable in 18 eyes (64%), and worse in one eye (4%). Visual outcome was strongly associated with time to treatment. A final VA equal to or better than 20/50 was noted in seven of 17 eyes (41%) that received thrombolytic treatment within the first 6.5 hours after the onset of symptoms. In contrast, none of the 11 patients with time to treatment >6.5 hours achieved a final BCVA ≥20/50. This difference was statistically significant ($P = .023$). Moreover, time to treatment ≤6.5 hours was significantly associated with a better gain of lines of vision. Of those patients who received thrombolytic treatment within 6.5 hours after the onset of symptoms, nine (53%) exhibited an improvement of three or more Snellen VA lines, whereas none of the individuals treated after >6.5 hours exhibited a comparable visual outcome ($P = .004$). One patient, a 56-year-old woman who received thrombolytic treatment eight hours after the onset of symptoms, lost five lines of VA from baseline. Scatterplots of initial vs final VA are provided in the Figure. An overview of baseline characteristics and changes in VA is given in Table 2.

DISCUSSION

SEVERAL STUDIES HAVE INDICATED THAT THROMBOLYSIS during the early hours of a central retinal artery occlusion has the potential to improve clinical outcomes. However, controversy exists regarding the window of treatment. Although experimental studies have demonstrated that irreversible cell injury with necrosis of the inner retina occurs as early as four hours after the onset of retinal ischemia,[20] the conservative approach involves treatment up to 24 hours.

In the present study, we observed a clear association between time to treatment and visual outcome. Seven of 17 individuals (41%) who received thrombolytic treatment within the first 6.5 hours achieved a final BCVA ≥20/50, compared to none in the subgroup of patients with onset to treatment >6.5 hours. Moreover, rapid intervention was associated with a significantly better gain of lines of vision. Of those patients treated within 6.5 hours, 53% exhibited an improvement of three or more Snellen VA lines. In contrast, none of the patients treated after more than 6.5 hours showed a comparable visual outcome.

Our finding that visual prognosis after intravenous thrombolysis is significantly related to time to treatment perfectly compares to the results of intra-arterial thrombolysis in the management of CRAO. Just recently, Arnold and associates described a retrospective analysis of intra-arterial thrombolysis in central retinal artery occlusion within 6 hours of symptom onset in 37 patients.[13] Based on their results, the authors defined a subclass of patients with CRAO who would have a greater chance of benefiting from intra-arterial thrombolysis. In light of recommendations for thrombolysis in cerebral ischemic stroke, they suggested that treatment within three hours might be the goal. Schumacher and associates reported on intra-arterial thrombolysis with urokinase or rt-PA in a series of patients with CRAO.[8] In this study, 26% of cases showed a marked improvement in VA, whereas no benefit was observed in a subgroup of patients with a mean time to treatment of more than 20 hours. According to their results, the authors concluded that thrombolytic treatment should be initiated within the first six to eight hours after the onset of symptoms. Interestingly, the finding that recovery of vision correlates with duration of visual impairment also supports an earlier study regarding the visual prognosis following conservative treatment of acute CRAO.[21]

However, unknown factors other than the time to thrombolysis may contribute to the outcome in acute CRAO. In a retrospective case series, Richard and associates observed a visual improvement of more than two lines in 47.2% of all cases after treatment with intra-arterial thrombolysis. In contrast to other investigators, they found no relationship between visual outcome and time to treatment.[9] In our study, 47% of those patients who received thrombolytic treatment within 6.5 hours after the onset of symptoms showed no visual improvement. Of the three eyes with a time to therapy equal to or less than two hours, two failed to achieve a final VA better than hand movements. CRAO has many causes, including atherosclerosis and retinal embolism. Emboli of the central retinal artery most often originate from fragmentation of atheromatous plaques of the larger arteries, with formation of calcific or platelet-fibrin emboli.[22,23] It seems plausible that these emboli vary substantially in composition, and may consist of much older and harder clots that might be less likely to respond to thrombolytic agents alone. Moreover, CRAO may be precipitated by hemorrhage beneath an atheromatous plaque or the lumen of the central retinal artery may become totally or partially occluded by an arteriosclerotic plaque.

In contrast to intra-arterial thrombolysis, the literature describing the use of intravenous thrombolysis in the management of CRAO consists mainly of anecdotal case reports or small case series.[2,15–17] Of these, only few investigations used rt-PA as the thrombolytic agent of choice. A recent meta-analysis of available studies evaluating thrombolytic therapy in CRAO demonstrated that 48.5% of all patients treated with intravenous thrombolysis, compared with 34.9% of patients who received intra-arterial thrombolysis, exhibited a visual improvement of at least four Snellen lines. However, in light of the numerous publication biases, it was concluded that existing reports probably overestimate the efficacy of thrombolysis in CRAO.[24]

The theoretical advantages of intra-arterial thrombolysis include direct infusion of the medication into the ophthalmic artery with higher local drug concentrations, lower systemic concentration of thrombolytic agent, and less risk of extracra-

nial hemorrhagic complications.[25,26] The disadvantages of this approach are the increased risk of direct vascular injury, the need for an interventionalist, and the additional time necessary to perform the endovascular procedure. Arnold and associates reported that as many as one-third of CRAO patients seen within six hours could not be treated because no neuroradiologist was available. Moreover, adverse events occurred in two patients who experienced transient ischemic attacks and in one patient who suffered brain infarction.[13] Catheter placement within the internal carotid artery during anterograde selective intra-arterial thrombolysis has been shown to cause neurologic symptoms in 0.54% to 5.66% of cases.[12,13]

However, the risk of hemorrhagic complications such as stroke or gastrointestinal hemorrhage is the major problem with thrombolysis.[18,19] The perceived risk of bleeding, along with the brief window of time and the considerable logistic problems associated with setting up a protocol for intra-arterial thrombolysis, have limited its application to a small proportion of patients with CRAO. In a recent in-patient survey on intra-arterial thrombolysis for CRAO in the United States, Suri and associates reported that intra-arterial thrombolysis was used in 27 of 1379 cases (1.9%).[27] Interestingly, there was no in-patient mortality or intracranial hemorrhage reported among any of these patients. Available data suggest that the occurrence of intracerebral hemorrhage might be further reduced by identifying patients at high risk. There appears to be a higher risk in elderly, significantly hypertensive patients, and possibly those with prior cerebrovascular disease.[18,19,28] In our study, no hemorrhagic complications were seen. All subjects had been carefully investigated for potential hemorrhagic risks prior to the initiation of therapy.

In addition, we selected a low-dose regimen of rt-PA. It has been demonstrated that a reduction of the dose of rt-PA significantly reduces the likelihood of hemorrhages.[29,30] Based on the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) study, a randomized controlled clinical mega-trial that compared the effect of commonly used thrombolytic agents for acute myocardial infarction,[31] 50 mg of rt-PA (i.e., exactly half the maximum dose given in the GUSTO trial) was chosen as a suitable dose. Since the GUSTO investigators found that the simultaneous administration of rt-PA and intravenous heparin resulted in a more rapid and complete restoration of coronary flow, which produced the most favorable outcome in their trial,[32] we administered rt-PA in a similar manner.[33]

In light of recent evidence that CRAO may be considered as an infarction in the anterior circulation territory, it is possible to suggest that thrombolysis in retinal artery occlusion should follow the guidelines for the treatment of cerebral ischemia.[34] Studies on intravenous rt-PA therapy for patients with acute ischemic stroke found a sustained benefit when treatment was initiated within three hours of the onset of symptoms.[29,30,35,36] These studies also demonstrated that doses of less than 0.95 mg of rt-PA per kilogram of body weight were relatively safe, although thrombolytic therapy was associated with an increased incidence of symptomatic intracerebral hemorrhage. In view of these observations, it may be speculated whether higher, weight-corrected doses of rt-PA for patients with CRAO would yield better results than those achieved in the current study. The concept of "weight-adjusted" dosing is also in accordance with recent recommendations for thrombolysis in myocardial infarction.[28] Furthermore, available data on the use of intravenous thrombolysis in ischemic stroke raise doubt whether CRAO patients should receive intravenous heparin in addition to rt-PA. In all major clinical trials, heparin therapy was not part of the treatment protocol. The TOAST trial, a large placebo-controlled study of intravenous anticoagulation in acute ischemic stroke, found no evidence of net benefit overall or in cardioembolic stroke. Moreover, there is much evidence that the potential beneficial effects of intravenous anticoagulation may be counterbalanced by a substantial increased risk of intracerebral hemorrhage.[37]

Although limited because of its nonrandomized nature, our study suggests that thrombolytic therapy with low-dose rt-PA aimed at rapid restoration of blood flow in the early acute phase of CRAO may improve the visual prognosis. Based on our data, we would recommend administration of intravenous rt-PA in CRAO patients with severe visual loss ($\leq$20/100), if treatment is initiated within 6.5 hours of clearly defined symptom onset. The ease of administration of the intravenous rt-PA dosage regimen presented in this study and the broad availability of internal medicine intensive care units is conducive to a rapid in-hospital initiation of thrombolytic treatment in patients with CRAO, which reduces the time to treatment. However, physicians should be aware that thrombolysis fails to provide a clinical benefit in a large proportion of CRAO patients, even if it can be deployed quickly after the event. In light of the numerous contraindications to thrombolysis related to bleeding risk, there is a pressing need for a more widely applicable treatment strategy.

THE AUTHORS INDICATE NO FINANCIAL SUPPORT OR FINANCIAL CONFLICT OF INTEREST. INVOLVED IN DESIGN OF STUDY (L.-O.H., I.S.); conduct of study (L.-O.H., C.K.-H., I.S., H.B.); collection of data (L.-O.H., C.K.-H., H.B.); management, analysis, and interpretation of data (L.-O.H.); preparation of the manuscript (L.-O.H.); and review and approval of the manuscript (L.-O.H., C.K.-H., I.S., H.B.).This study was approved by the Institutional Review Board of the Johann Wolfgang Goethe-University Hospital, Frankfurt am Main, Germany and was in adherence to the tenets of the Declaration of Helsinki.

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Biosketch

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