Evaluation of Minimally Invasive Therapies and Rationale for a Prospective Randomized Trial to Evaluate Selective Intra-arterial Lysis for Clinically Complete Central Retinal Artery Occlusion

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Objectives: To determine the effect of commonly used minimally invasive treatments for clinically complete non-arteritic central retinal artery occlusion (CRAO) and design a prospective randomized trial to evaluate selective intra-arterial lysis for this condition.

Methods: In this retrospective noncomparative case series, all medical records of patients with a diagnosis of CRAO treated at the Department of Ophthalmology, Ludwig-Maximilians-Universität, Munich, Germany, from 1994 through 1999 were reviewed for treatments administered and course of visual acuity.

Main Outcome Measures: Best-corrected visual acuity (BCVA) at initial and last visit.

Results: We identified 102 patient medical records; 71 were suitable for further analysis. Forty-four (62%) of the 71 patients included were treated with oral acetylsalicylate; 44 (62%), with oral acetazolamide; 32 (45%), with ocular massage; 22 (31%), with isovolemic hemodilution; 19 (27%), with oral pentoxifylline; 8 (11%), with topical β-blocker; 6 (8%), with paracentesis of the anterior chamber; 4 (6%), with subcutaneous heparin. A mean ± SD number of treatments of 2.5 ± 1.4 was administered per patient, and BCVA increased by a mean ± SD number of Snellen lines of 0.7 ± 2.8. The BCVA in 11 patients (15%) increased by 3 or more lines. Multivariate stepwise regression did not reveal any single or combination treatment as a significant factor for improvement in BCVA. Patient age and duration of visual impairment before initial examination were not significant predictors of final BCVA.

Conclusions: Commonly used minimally invasive treatments of CRAO do not improve the natural course of the disease. A prospective trial by the European Assessment Group for Lysis in the Eye is under way to evaluate selective intra-arterial lysis, and in this trial some of these minimally invasive treatments are used in the control group.

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SUDDEN AND SEVERE loss of vision because of central retinal artery occlusion (CRAO) is one of the most dramatic ophthalmic events for both the patient and the physician. Since Albrecht von Graefe described the presumed cause and the characteristic features of CRAO, the disease has remained a therapeutic dilemma.1 Ever since then, a variety of treatment attempts have been proposed. None of these treatment attempts has shown a clear therapeutic benefit or is uniformly accepted. Because it remains unclear whether these treatments improve the natural course of the disease, most physicians tend to use a cocktail of treatments with relatively few potential adverse effects such as ocular massage, oral acetazolamide, and/or topical antiglaucomatous.

Selective intra-arterial lysis has been used successfully in a variety of occlusions of the vertebrobasilar vascular system during the past 2 decades in the emerging field of interventional neuroradiology. It has also been proposed for the treatment of CRAO, and after the initial enthusiastic articles by Schumacher et al.,2-4 others have confirmed their positive experience.5 However, in contrast to most other treatment attempts proposed for CRAO, selective intra-arterial lysis has potential serious adverse effects, such as embolization of atherosclerotic material to other parts of the vascular system, which might lead to stroke and even death. Thus, there is a clear need to demonstrate in a prospective randomized trial that this potentially harmful treatment has a clear therapeutic benefit in patients with CRAO vs those in a control group.

Several models of such a control group were discussed in preparation for this trial. First, it is conceivable that such a control group would receive no treatment at all.
However, there are several arguments against this model. Probably few patients seeking treatment for an ophthalmic emergency would be willing to participate in a trial in which they would randomly receive either a relatively invasive high-tech treatment such as selective intra-arterial lysis or no treatment at all. Additionally, most publications and guidelines still list several minimally invasive therapies as state of the art, which means the physician would have to justify to the patient and other treating physicians why no action at all was being taken in an acute emergency causing severe visual loss. Patients initially willing to participate might also later decide they want treatment if they are randomly placed in a control group receiving no treatment. This change of mind would result in a large number of patients dropping out, especially in the control group.

Second, the control group might receive a sham treatment (ie, selective intra-arterial lysis, as described later, with infusion of balanced salt solution rather than lysis substances). Again, several strong arguments went against this model. Such a treatment would expose the patient to nearly all the risks of catheterization, especially embolization of atherosclerotic material and exposure to radiation, without the potential benefit of the lysis itself. On the other hand, this sham treatment would have to include heparin administration, as described later, and therefore already induce a potential beneficial effect on the natural course of CRAO.

With these considerations, the preparing members of the European Assessment Group for Lysis in the Eye (EAGLE) trial agreed that the control group should receive a cocktail of different minimally invasive treatments that allow patients to feel their serious condition is being treated but that these treatments should have little or no therapeutic benefit during the natural course of CRAO. For this reason, we performed a retrospective analysis of the effectiveness of commonly used minimally invasive therapeutic regimens in our patients with CRAO and compared these results with those in the literature.

### METHODS

In a retrospective analysis, we reviewed all medical records of patients treated for CRAO from 1994 through 1999 in the outpatient clinic of the Department of Ophthalmology, Ludwig-Maximilians-Universität, Munich, Germany. Informed consent was not required by the institutional review committee for this medical record review. The CRAO was diagnosed according to the clinical symptoms of sudden, painless, and severe loss of vision and according to the ophthalmoscopic appearance of the fundus, including an ischemic retina and a cherry-red spot. Other diagnostic tests such as fluorescein angiography of the visual field were performed only when other ischemic diseases had to be differentiated. In all cases, risk factors for temporal arteritis were obtained from the patient's medical record. If temporal arteritis was suspected, erythrocyte sedimentation rate and C-reactive protein level were determined; if considered necessary, an additional examination by the internal medicine service was also performed.

Only patients with nonarteritic clinically complete CRAO were included in this study. Those with arteritic or incomplete CRAO were excluded; incomplete CRAO was determined by means of funduscopy nonperfusion and visual acuity better than 20/60 at initial examination. Patients with a funduscopically visible fovea-sparing cilioretinal artery and patients with missing follow-up data or last follow-up visits within 2 days after the initial visit were excluded. For all patients, we analyzed risk factors for CRAO, time from CRAO onset until first clinic visit, best-corrected visual acuity (BCVA), and treatments administered. At initial and follow-up visits, BCVA as the main outcome variable was measured with a Snellen chart in logarithmic steps. If the patient had several follow-up visits, the one closest to 4 to 6 weeks after presumed CRAO was used.

The spectrum of treatment regimens was chosen by the attending physician after consideration of the patient's personal risk factors from the following minimally invasive treatment options: oral acetylsalicylate, oral pentoxifylline, isovolemic hemodilution (hematocrit level > 42% [0.42]), systemic heparin administration, ocular massage, oral acetazolamide, topical β-blocker, and paracentesis of the anterior chamber. The variety of treatment regimens used allowed analysis of several treatments in a multiple stepwise regression model. Data were collected and analyzed with SPSS 8.0 (SPSS Inc, Chicago, Ill) for Windows (Microsoft Corp, Redmond, Wash), and the regression model was calculated with JMP 3.1.4 (SAS Institute Inc, Cary, NC).

Of 102 patient medical records with the diagnosis of CRAO, 71 were included in the study. Nine patients were excluded because of a perfused fovea-sparing cilioretinal artery observed funduscopically. Nineteen patients were not included because of incomplete documentation. Three patients treated with selective intra-arterial fibrinolysis also were excluded.

### RESULTS

The mean ± SD age of the 71 patients included was 67 ± 13.7 years (median age, 67 years; age range, 17-93 years). Forty-seven patients were male (66%) and 24 female (34%) (significant difference in exact chi-squared test, P < .01). The right eye was affected in 39 patients (55%) and the left eye in 32 patients (45%). Median follow-up ± SD was 8 ± 217 days (range, 2 days to 3 years); 25% of the patients were seen for the last follow-up 2 to 4 days after CRAO.

The initial patient visit to the clinic was a median ± SD of 7 ± 288 hours after symptom onset (range, 1 hour to 12 days). Forty-six patients (65%) sought treatment earlier than 24 hours after onset of symptoms; 42 of these (59%) sought treatment within 12 hours.

### DEMOGRAPHICS

The BCVA at initial and final examination is shown in Figure 1. Visual acuity better than 20/60 was not encountered because of the necessarily severely decreased visual acuity in clinically complete CRAO. As demonstrated in Figure 1, little improvement in visual acuity was observed. The BCVA increased by at least 3 Snellen lines in only 11 patients (15%). Before treatment, 11 patients (15%) had BCVA of at least 20/400, while after treatment 20 patients (28%) achieved this visual acuity.

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ocular massage in 32 patients (45%), isovolemic hemodilution in 22 patients (31%), topical β-blocker in 19 patients (27%), paracentesis in 6 patients (8%), and subcutaneous heparin in 4 patients (6%). A mean ± SD number of treatments of 2.5 ± 1.4 and a median ± SD number of treatments of 3 ± 1.4 (range, 0-6) was chosen. In 52 cases (73%), no more than 3 treatments were chosen; in 68 (96%), no more than 4 treatments were chosen.

**FRESH VS OLD CRAO**

For patients with CRAO of less than 24-hour duration (fresh CRAO), a mean of 3.0 different treatments was chosen (95% confidence interval [CI], 2.6-3.3), whereas CRAO of more than 24-hour duration (old CRAO) tended to be treated less aggressively (mean, 1.6 different treatments; 95% CI, 1.1-2.2). This difference for treating fresh CRAO with more different therapeutic attempts is significant (Mann-Whitney test, P < .001). However, despite the more intensive treatment of and theoretically better prognosis for fresh CRAO, the outcomes in visual acuity are similar: Old CRAO improved by a mean of 0.3 Snellen line (95% CI, −1.1-1.7), and fresh CRAO improved by a mean of 1.0 Snellen line (95% CI, 0.25-1.7). The difference was not statistically significant (Mann-Whitney test, P > .33). These results are summarized in Figure 2, in which the linear regression line of time from CRAO onset to start of treatment independent of improvement in number of Snellen lines is plotted against 95% CIs.

**MULTIPLE STEPWISE REGRESSION**

Multiple stepwise regression with improvement in the number of Snellen lines as the outcome variable for change in BCVA showed no significant single predictor or combination of predictors among the different treatments administered (P > .05). Figure 3 summarizes these results. Use of oral acetazolamide, oral pentoxifylline, oral acetylsalicylate, topical β-blocker, and paracentesis was even slightly negatively correlated with visual prognosis. Isovolemic hemodilution did not show any effect at all, while ocular massage and systemic heparin administration showed slight improvement in patient visual acuity but still did not have a significant effect (P > .1). In only those cases with a duration of symptoms of less than 24 hours, no statistically significant change occurred in the stepwise regression model.

**COMMENT**

We were not able to identify any statistically significant beneficial effect of the treatment regimens used in this retrospective analysis in 71 patients. We were not able to demonstrate any statistically significant beneficial effect of these treatment regimens when considering only CRAO with a duration of symptoms less than 24 hours, and no correlation could be shown between starting treatment early after CRAO onset and final visual outcome. These findings are in accordance with ophthalmologists’ clinical observation that these treatments are rarely effective and also with the results of a meta-analysis of the literature.6

Limitations of this study are the retrospective design, a relatively small number of cases, and, in part, the short follow-up. The retrospective design was necessary to enroll as many patients as possible with this infrequently seen disease. However, the number of patients in this study is larger than that in most other studies of CRAO.7-11 To our knowledge, only 1 retrospective study, with 89 patients, had a similarly large number.12

We consider a 1-week follow-up sufficient, because in our experience and that of others, no substantial change in BCVA is expected after 1 week.12 To our knowledge, the authors of only 1 article describe 4 of 12 patients with
significant improvement in visual acuity within 48 hours; the other 8 patients took longer to recover.7

A heterogeneous picture arises from comparison of CRAO studies. Authors of several studies, some of which are control studies, report single treatments to be effective, yet authors of other studies were unable to prove these same treatments effective. For example, authors of 1 article8 demonstrated paracentesis as effective, while authors of another article12 were not able to show any benefit from paracentesis and administration of carbogen. Heterogeneous results have also been reported for the effectiveness of oral pentoxifylline.4,9,10 We speculate that the major causes of these inconsistent results in different studies are the often small numbers of patients, which causes large CIs. Similarly, differing inclusion criteria, such as inclusion of arterial occlusions other than nonarteritic complete CRAO and criteria for improved visual acuity other than 3 or more Snellen lines gained in logarithmic steps that correspond to doubling of the visual angle, may contribute to this heterogeneity. The prevalence of patients with a fovea-sparing cilioretinal artery in these studies—in some studies in as many as 28% of the cases—also plays an important role in visual outcome.

The prevalence of fovea-sparing cilioretinal arteries in the literature varies between 12% and 32%.13,14 These differences are likely caused by different detection methods, such as fundus photographs, stereo fundus photographs, and fluorescein angiograms. Interestingly, in 1 study, all significant improvements in visual acuity were correlated to the existence of a fovea-sparing cilioretinal artery.7 This finding underlines the importance of identifying cases of fovea-sparing cilioretinal arteries when assessing treatment outcomes. Other authors stress the importance of the cilioretinal artery for outcome in all cases of CRAO.13 Consequently, those cases were excluded in our study.

Our study results did not show a statistical difference for CRAO treated early, as compared with that treated relatively late (≥24 hours), even though CRAO treated early was treated more aggressively. This finding supports our main result that the minimally invasive treatments we tested are not effective. Again, the results in the literature are controversial. Even for pathophysiologically time-dependent selective intra-arterial fibrinolysis, some study results show dependence on how soon fibrinolysis is performed15 and others show no time correlation.16

Experimentally, retinal ischemia tolerance time after complete obstruction is 15 to 270 minutes.17,18 In contrast to results in animal experiments, a partly remaining circulation visible clinically and at fluorescein

Figure 3. Treatment subgroup analysis; no single treatment or combination of treatments improved best-corrected visual acuity (BCVA) prognosis significantly. Short horizontal lines in the boxes represent the group median value. The boxes represent the 25th to the 75th percentile. Short horizontal lines outside the boxes represent the 10th and 90th percentiles. “No” indicates that the treatment was not received and “yes” that the treatment was received.
angiography is often seen in human CRAO.19 This remaining or recanalized blood flow may account for recovery of retinal function even after extended ischemia times.

Local or systemic fibrinolysis may be more effective than minimally invasive treatment regimens. Several groups reported increased improvement rates after lysis treatment.4,11,15,16,20 However, it seems too early to assess lysis treatment in the absence of prospective randomized studies.

In summary, commonly used minimally invasive treatment regimens do not improve the natural course of CRAO; thus, some of these treatments might be applicable in a control group. We also see the potential benefit of selective intra-arterial lysis as reported; consequently, we designed a prospective randomized control study, the EAGLE study. The acronym also defines the study’s goal, which is to achieve the vision of an eagle in patients treated with lysis.

In the EAGLE study, patients with clinically complete CRAO are randomly placed in a group receiving selective intra-arterial lysis or a control group receiving minimally invasive treatments. In the lysis group, a guiding catheter is inserted through the femoral artery and placed in the internal carotid artery. Heparin is administered, and a microcatheter is then advanced into the ophthalmic artery. Subsequently, recombinant tissue plasminogen activator is infused until reperfusion of the central retinal artery occurs or a maximum of 50 mg of recombinant tissue plasminogen activator is administered within 2 hours. Patients in the control group receive some of the minimally invasive treatments listed in this article. The inclusion and exclusion criteria and the complete protocol are available from the corresponding author. Eighteen centers in Germany, Austria, and Switzerland are participating; patient enrollment has begun, and the first results are expected in approximately 2 years.

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REFERENCES