Central retinal artery occlusion (CRAO) is an ophthalmological emergency that can result in complete blindness in the affected eye if untreated. It is a result of sudden cessation of circulation to the inner retinal layer, which is considered to be a part of the CNS. This condition was first described in 1859 by Albrecht von Graefe, a famous German ophthalmologist known for his contributions in glaucoma and cataract treatment. Since then, there has been an abundant accumulation of literature regarding the disease.

Although the pathophysiological features of CRAO are well described in the literature, the natural history of this disease is poorly understood. Prolonged retinal ischemia is usually irreversible, suggesting a grim prognosis if the occlusion is not corrected in a timely manner. In a matter of hours cellular hypoxia will ensue, with subsequent necrosis if circulation is not restored. The central retinal artery is usually occluded by a thrombotic embolus (of internal carotid artery or cardiac origin, 15.5% of cases); a calcified embolus (commonly of diseased cardiac valve origin, 10.5% of cases); or cholesterol embolus (74.5% of cases) (Table 1). Other causes include sudden narrowing of the arterial wall (hemorrhage into an atheromatous plaque) and inflammatory processes (arteritic CRAO) secondary to temporal arteritis. There is a high association of CRAO with atherosclerosis, diabetes, and systemic hypertension.

### Epidemiology, Etiology, and Presentation

The true incidence of CRAO in the population is unknown. One report estimated CRAO to occur in 1 per 10,000 outpatient visits. The department of ophthalmology at the Western Galilee–Nahariya Medical Center in Nahariya, Israel, estimated an incidence of acute CRAO (with a less than 48-hour onset) at that institution to be approximately 0.85 per 100,000 per year or 1.13 per 10,000 outpatient visits. Of these patients, 1%–2% present with bilateral involvement. Men are more frequently affected than are women, and the average age at presentation is in the early 60s, with rare cases as early as in the 30s. Patients suffering from central retinal artery embolism have a 56% mortality rate over 9 years, compared with 27% for age-matched individuals without emboli. Life expectancy is 5.5 years postdiagnosis for patients with CRAO compared with 15.4 years for age-matched individuals without CRAO.

Diagnosis is usually made based on clinical history and physical examination. Ninety percent of patients present with a complaint of acute, persistent, painless loss of vision. Some patients may report a history of amaurosis fugax lasting anywhere from seconds to several hours. Ophthalmoscopic examination may reveal diminished blood vasculature in the retina, retinal edema, pale optic disc, and a cherry red spot. Approximately 18.7% of the
population has some macular circulation from a cilioretinal artery, which is spared in CRAO. These patients will show finger-like areas of normal retina with patent arterioles that are not connected to the occluded stalk. In 20% of cases, the embolus can be directly visualized. Fluorescein angiography may show delayed filling or occlusion during the arterial phase (11–12 seconds) (Fig. 1).

Due to the high probability of permanent visual loss, immediate correction of the occlusion is a priority. In less than 10% of cases, spontaneous recanalization of the occlusion may occur. In eyes with presenting visual acuity of finger counting or worse, visual acuity deteriorated in 12% of cases. Nevertheless, medical treatment should be sought on an emergency basis. Several therapeutic options exist, ranging from noninvasive medical options to the controversial thrombolysis treatment. This review of the literature discusses all the endovascular therapeutic options available following the onset of CRAO, with a focus on intraarterial fibrinolysis (IAF), with concurrent recommendations.

**Natural History**

Central retinal artery occlusion is an ophthalmological emergency that can lead to permanent visual loss if left untreated. Restoration of circulation distal to the occlusion can result in complete recovery if recanalization occurs rapidly. The monkey retina can tolerate complete ischemia for up to 105 minutes before irreversible damage occurs, and up to 4 hours in the presence of residual blood circulation. In humans CRAO is usually not complete; there remains some residual blood flow distal to the occlusion. This allows a window for treatment before significant morbidity occurs. It has been postulated that treatment is only beneficial if commenced within 8 hours of occlusion. However, beneficial effects were seen with treatment given up to 24 hours after the onset of symptoms. Furthermore, significant visual improvement was reported with treatment given after 48 hours of ischemia. Nevertheless, shorter latency to treatment results in better outcomes. It is therefore important to review all treatment options that aim to restore circulation to the ischemic retina.

Reports of spontaneous recovery are inconsistent. Certain authors report no spontaneous recovery, whereas other case studies report some spontaneous recovery. A recent study of the natural history of CRAO concludes that classification of disease is important and spontaneous recovery can be determined by several factors, such as presenting symptoms and etiology of occlusion.

### Treatment Options

The patient may begin treatment prior to arrival in the emergency room by massaging the affected eye. Mechanical force on the central retinal artery may dislodge the embolus and restore circulation. This technique will only work if the occlusion is due to an embolus. The patient may also breathe expired air using a paper bag. The subsequent hypercapnia will cause vasodilation of the retinal arteries, with an increase in circulation. Carbogen, a fixed mixture of 95% oxygen and 5% carbon dioxide, may be used if available. Retinal arteries may also dilate after sublingual isosorbide dinitrate is administered.

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**TABLE 1: Known causes of CRAO**

| 1. systemic hypertension |
| 2. embolism |
| 3. thrombotic |
| 4. atherosclerotic changes |
| 5. temporal arteritis |
| 6. hypercoagulable state |
| 7. collagen vascular disease |
| 8. cardiac valvular disease |
| 9. cardiac anomalies |
| 10. oral contraceptives |
| 11. diabetes mellitus |
| 12. polycythemia |
| 13. polyarteritis nodosa |
| 14. Behçet disease |
| 15. syphilis |
| 16. sickle cell disease |
| 17. migraine |
| 18. glaucoma |
| 19. prolonged orbital pressure |

* According to Fraser and Siriwardena.

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**Fig. 1.** Fluorescein angiographic photograph of CRAO. Note the delayed and segmented arteriolar filling (a) in each of the major arteriolar trunks distal to the central occlusion, and a small segment of an inferior temporal arteriole (b) that is strongly enhancing and may represent a fragment of distal embolization from the central blockage. Venous transit is severely prolonged, and the typical laminar flow is nearly absent (http://www.rvscny.com/retinalarteryocclusion.html). Copyright Retina Vitreous Surgeons of Central New York. Published with permission.
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temic vasodilation may occur, causing decreased blood pressure.

Immediate reduction of intraocular pressure (IOP) may cause an increase in ocular perfusion pressure and therefore circulation as well. This may be attempted with intravenous or oral acetazolamide, a carbonic anhydrase inhibitor.\textsuperscript{36} Mannitol may act as an osmotic diuretic and may also be used to reduce IOP. Anterior chamber paracentesis of aqueous humor\textsuperscript{3} and trabeculectomy\textsuperscript{19} are alternative methods for reducing IOP. Systemic steroids may be used to reduce vascular endothelial edema.\textsuperscript{20} In Table 2, various methods for reducing IOP are listed.\textsuperscript{6} However, the evidence was not enough to recommend these methods in the treatment of CRAO.\textsuperscript{6} The thrombolytic agent of choice is rt-PA, due to the shorter half-life and lower risks for complications. A meta-analysis of all previous literature regarding the use of rt-PA in cases of CRAO from 2000 suggests marginal visual benefit compared with conventional therapy (Table 2).\textsuperscript{6} However, the evidence was not enough to recommend rt-PA in the treatment of CRAO. The thrombolytic agent of choice is rt-PA, due to the shorter half-life and lower risks for complications. A meta-analysis of all previous literature regarding the use of rt-PA in cases of CRAO from 2000 suggests marginal visual benefit compared with conventional therapy (Table 2).\textsuperscript{6} However, the evidence was not enough to recommend rt-PA in the treatment of CRAO. The thrombolytic agent of choice is rt-PA, due to the shorter half-life and lower risks for complications. A meta-analysis of all previous literature regarding the use of rt-PA in cases of CRAO from 2000 suggests marginal visual benefit compared with conventional therapy (Table 2).\textsuperscript{6} However, the evidence was not enough to recommend rt-PA in the treatment of CRAO.

Despite the various options, a retrospective study of 178 patients showed no significant benefit in conventional conservative methods.\textsuperscript{41} Several other series suggest a low success rate with conservative treatment.\textsuperscript{5,14,31} The current thrombolytic approach, known as IAF, consists of local infusion of urokinase or recombinant tissue plasminogen activator (rt-PA) at the site of occlusion via catheterization of the ophthalmic artery. The thrombolytic agent of choice is rt-PA, due to the shorter half-life and lower risks for complications. A meta-analysis of all previous literature regarding the use of IAF in cases of CRAO from 2000 suggests marginal visual benefit compared with conventional therapy (Table 2).\textsuperscript{6} However, the evidence was not enough to recommend IAF in the treatment of CRAO. In the aforementioned retrospective study of 178 patients, 62 patients with CRAO were treated with IAF in which urokinase or rt-PA was used, and were compared with 116 controls treated using conservative methods.\textsuperscript{41} Those treated with IAF had a greater chance of better outcome than those treated conservatively. Another series of 56 patients concluded that IAF enhanced the chances of improvement compared with conservative treatment.\textsuperscript{1} In that study, 8 of 37 patients treated with IAF regained visual acuity of greater than 0.6 compared with none in the control group.

Although IAF seemed very promising with such abundant support in the literature, randomized controlled clinical trials were needed before recommendations regarding the use of IAF in treatment of acute CRAO could be made. The European Assessment Group for Lysis in the Eye (EAGLE) started a prospective and randomized multicenter study in 2002 to evaluate the efficacy of IAF.\textsuperscript{15} Patients between the ages of 18 and 75 years who had acute CRAO of less than 20 hours’ onset and presenting visual acuity of less than 0.32 were included in the study. Exclusion criteria included presence of branched retinal artery occlusion, cilioretinal artery, elevated IOP greater than 30 mm Hg, or severe general medical disease. Patients were randomly assigned into IAF treatment or control groups. Patients in the treatment group received a total of 50 mg rt-PA injected locally into the ophthalmic artery. Control patients received conservative therapy including massage of the eye, topical beta-blocker, acetazolamide, aspirin, heparin, and isovolemic hemodilution. All patients were treated with heparin postprocedure for 5 days. The primary end point was the best corrected visual acuity assessed 1 month after the procedure. A recent European article states that the study was halted after the first interim analysis because similar outcomes were seen in both groups, with an increased risk of complication in the IAF group.\textsuperscript{46} The investigators concluded that IAF cannot be recommended in treatment of acute CRAO. Of 37 patients treated with IAF, 3 (2 with transient ischemic attacks and 1 with stroke) developed peri-procedural cerebrovascular ischemic events.\textsuperscript{1} Another study reports 2 patients enduring complications (transient aphasia and hemiparesis) with IAF treatment.\textsuperscript{41} For IAF to prove its role in the treatment of acute CRAO, the risk of complications must be reduced. This may be done through more optimal thrombolytic infusion methods, use of a thrombolytic agent with shorter half-life, or with a more experienced neurointerventionalist. Although discouraging, the hope for better results with the EAGLE study lies in the improvement of the IAF protocol.

### Table 2: Studies regarding efficacy of IAF in CRAO

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Thrombolytic Therapy</th>
<th>Outcome</th>
<th>Study Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beatty &amp; Au Eong, 2000</td>
<td>100</td>
<td>urokinase, streptokinase, rt-PA</td>
<td>final acuity 20/20 in 14%; 10/20 in 27%; 1/20 or worse in 60.6%</td>
<td>meta-analysis of 16 studies</td>
</tr>
<tr>
<td>Schmidt et al., 2002</td>
<td>178</td>
<td>urokinase, rt-PA</td>
<td>partial or greater improvement seen in 58% treated w/ IAF compared to 29% treated conservatively</td>
<td>case series</td>
</tr>
<tr>
<td>Arnold et al., 2005</td>
<td>56</td>
<td>urokinase</td>
<td>final acuity 12/20 or greater in 22% treated w/ IAF compared to 0% treated conservatively</td>
<td>case series</td>
</tr>
</tbody>
</table>

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clinical trial evaluating the effect of thrombolysis in CRAO continues to be considered. However, as echoed by Biousse, the first step toward a multicenter trial may be forming a consensus on treatment protocols. Evaluations of patients with acute CRAO before and after intervention must be conducted, with organization of pilot data into an international registry. Meanwhile, alternative therapeutic strategies for CRAO should also be considered. To this end, given the efficacy of intravenous rt-PA for fibrin-platelet clot lysis in ischemic stroke and myocardial infarction, the role of systemic rt-PA has also been explored for CRAO. In a systematic review of 103 cases of acute CRAO, Biousse et al. reported a 48.5% improvement of at least 3 lines of visual acuity. Ultimately, given that the treatment window probably does not exceed 6–12 hours, developing quick transportation modalities for patients to emergency departments is essential. For now, heightened patient awareness and physician collaboration with emergency rooms, stroke units, and interventionists is encouraged.

Conclusions

There is an abundance of literature regarding treatment options for CRAO. Conservative therapy has been used for decades with variable success, but it has not been shown to improve outcomes significantly compared with no treatment. A recent endovascular approach involved IAF with urokinase or rt-PA. Several series report successful outcomes in patients treated with IAF; however, a recent prospective randomized controlled multicenter clinical study has not yet shown significantly better outcomes. Attention must be given to reduction and/or better management of complications associated with IAF as well as more optimal infusion methods. Given the current evidence, IAF cannot yet be recommended for the treatment of acute CRAO.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Prestigiacomo, Agarwal, Gala. Acquisition of data: Agarwal, Gala. Analysis and interpretation of data: Agarwal, Gala. Drafting the article: Agarwal, Gala. Critically revising the article: Agarwal, Gala, Karimi, Turbin, Gandhi. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Prestigiacomo. Statistical analysis: Agarwal. Administrative/technical/material support: Prestigiacomo, Gandhi. Study supervision: Prestigiacomo.

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