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Conservative treatments for acute nonarteritic central retinal artery occlusion: Do they work?

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Abstract:

Acute central retinal arterial occlusion has a very poor visual prognosis. Unfortunately, there is a dearth of evidence to support the use of any of the so-called "conservative" treatment options for CRAO, and the use of thrombolytics remains controversial. In this review, we address a variety of these "conservative" pharmacologic treatments (pentoxifylline, isosorbide dinitrate, and acetazolamide) and nonpharmacologic approaches (carbogen, hyperbaric oxygen, ocular massage, anterior chamber paracentesis, laser embolectomy, and hemodilution) that have been proposed as potential treatments of this condition. We conclude that the available evidence for all treatments is insufficient to conclude that any treatment will influence the natural history of this disorder. Management of CRAO patients should instead focus on reducing the risk of subsequent ischemic events, including cerebral stroke. Certain patients may be considered for acute treatment with thrombolytics, although further research must clarify the efficacy, safety, and optimal use of these therapies.

Keywords:

Acute stroke, central retinal artery occlusion, hyperbaric oxygen therapy, thrombolysis

Introduction

Acute central retinal arterial occlusion (CRAO) typically causes permanent, profound visual loss and therefore qualifies as a true ophthalmic emergency.[1] Occurrences of CRAO are most often due to emboli originating from the heart, carotid arteries, or aortic arch (termed "nonarteritic"). Less common, but even more concerning, are CRAOs caused by vasculitis (termed "arteritic" and usually the result of giant cell arteritis), a mechanism that is outside of the scope of this review.

The role of the ophthalmologist in the management of acute CRAO is essential and has been extensively described.[2] This discussion is crucial, as the consequences of a CRAO extend far beyond the visual system. Ophthalmologists must recognize CRAO as the ocular equivalent of a stroke of the cerebral vasculature and manage patients with an appropriate level of urgency; patients with CRAO have a high risk of experiencing concurrent or subsequent ischemia to other end organs, especially the brain.[3-6]

Even for ophthalmologists aware of the systemic and neurologic implications of CRAO, the approach to treatment of this condition remains an issue of great uncertainty. Secondary risk prevention is an essential component of CRAO management but is one that relies primarily on the input of nonophthalmic practitioners (primarily stroke neurologists). There is growing optimism regarding thrombolysis as an evidenced-based treatment for acute CRAO, but there is certainly no consensus regarding the many other treatments that have been described in the literature. Thus, one crucial issue of greatest concern to ophthalmologists remains unanswered:

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Which acute treatments, if any, should be offered to patients to maximize the potential for visual recovery?

In 2009, a Cochrane review concluded that various so-called "conservative" treatment approaches for CRAO (e.g., sublingual isosorbide dinitrate, pentoxifylline, methylprednisolone, acetazolamide, mannitol, anterior chamber paracentesis, inhalation of a carbogen, hyperbaric oxygen [HBO], ocular massage, and globe compression) are no better than placebo.[7] A subsequent meta-analysis of 8 studies, including 419 patients who received ocular massage, anterior chamber paracentesis, and/or hemodilution, demonstrated a significantly lower visual recovery rate among treated patients compared to the natural history control group ($P < 0.001$), with a number needed to harm of 10 (95% confidence interval [CI], 6.8–17.4).[8] Accordingly, no conservative therapy is recommended by the current American Academy of Ophthalmology (AAO) Practice Pattern on this topic.[9]

Our review outlines in detail the most up-to-date evidence regarding the available conservative treatment approaches (treatments not involving intravenous or intra-arterial thrombolysis). This article also does not address the management of iatrogenic CRAO, such as CRAO caused by hyaluronic acid fillers.[10]

What is the Natural History of a Central Retinal Arterial Occlusion?

Patients with CRAO typically present with painless, severe monocular vision loss. The final visual acuity in patients with CRAO ranges from near normal (in a minority of patients with an accessory perfusion of the macula via a cilioretinal artery) to counting fingers or worse; 93.2% of patients with nonarteritic CRAO without cilioretinal artery sparing will have a final visual acuity of counting fingers or poorer.[1] Patients tend to experience only a limited degree of spontaneous visual improvement, typically in the first 7 days following vision loss,[1] although it is likely that some CRAO patients experience spontaneous recovery after a few hours of visual loss and do not seek medical care. Immediate involvement of an ophthalmologist is necessary for a definite diagnosis.

How are Acute Retinal Ischemic Events Currently Managed?

Numerous recent publications[2,6,11] have highlighted the need to manage patients with acute retinal ischemic events in a similar manner to those patients with acute cerebral ischemia. However, treatments vary tremendously depending on whether patients are first evaluated by neurologists or ophthalmologists, as shown in a recent U. S. survey.[12] In 2017, only 20% of US hospitals had a formal policy in place. The approach to treatment varied widely: intravenous fibrinolysis was an available treatment option at 52% of institutions and was a preferred treatment modality at 36% of centers; other treatments, such as anterior chamber paracentesis, ocular massage, and HBO, were offered 42%, 66%, and 7% of the time, respectively. The most recent Practice Pattern guideline from the AAO[13] recommends that patients with acute nonarteritic CRAO be immediately sent to the nearest stroke center for consideration of an acute intervention but also acknowledged that there are no proven therapies or treatments at this time.

What is the Therapeutic Window for Central Retinal Arterial Occlusion Treatment?

One challenge in evaluating potential therapies for CRAO involves the uncertainty regarding retinal tolerance time or the duration of retinal ischemia, after which irreversible infarction occurs. Hayreh's research in nonhuman primates indicated that the ganglion cell layer will survive without infarction if central retinal artery perfusion is restored within 90–240 min following experimental occlusion.[14-16] However, there has been some criticism of the validity of Hayreh's experimental results, with other authors suggesting that retinal infarction occurs much sooner (perhaps within as little as 12 min) following a complete CRAO.[17] A shorter retinal tolerance time undermines the result of some studies which have purported visual benefit of CRAO treatments given up to 24–48 h after occlusion occurs.[18,19] Regardless, it is apparent that any treatment for CRAO should be undertaken as rapidly as possible to maximize the preservation of tissue that is ischemic but not yet infarcted, analogous to the rescue of the ischemic penumbra in cerebral stroke.

What is the Role of Thrombolysis in the Management of Central Retinal Arterial Occlusion?

The use of intravenous or intra-arterial thrombolysis as a treatment for acute retinal arterial occlusions has mostly been evaluated in retrospective studies.[11] Only two small randomized controlled trials have been published.[20,21] Although observations of dramatic visual recovery have been described, most studies have had disappointing results, likely explained by the long treatment windows of beyond 6 h in most studies. Based on the immense success of these therapies in patients with cerebral ischemia, it is not surprising that the enthusiasm for these therapies in the treatment of acute CRAO is high. However, the efficacy and safety of both intravenous and intra-arterial therapies for patients with CRAO are less well known, and further studies

are needed before this treatment can be recommended on a routine basis.[22,23]

What "Conservative" Therapeutic Options Exist to Treat Central Retinal Arterial Occlusion?

Several nonthrombolytic (or "conservative") therapies have been described as potential treatments for acute CRAO, but few have been evaluated in prospective, controlled studies. A variety of pharmacologic treatments (pentoxifylline, isosorbide dinitrate, and acetazolamide) and nonpharmacologic approaches (carbogen, HBO, ocular massage, anterior chamber paracentesis, laser embolectomy, and hemodilution) have been studied. Through a variety of potential mechanisms, the common goal of all treatments is to improve or restore retinal circulation before the onset of retinal necrosis. Ophthalmologists may feel compelled to attempt some form of treatment even in the absence of strong evidence, as CRAO patients often experience devastating visual loss and a very limited degree of spontaneous visual recovery in only about 20% of cases.[24-26] However, performing an intervention that has no proven efficacy may result in unintended harm.

Mechanism 1: Increasing blood oxygen tension

Hyperbaric oxygen

HBO is thought to increase the partial pressure of oxygen in the choroidal vasculature, promoting oxygen delivery to ischemic retinal tissues until spontaneous or assisted reperfusion can occur,[27] but the exact pathophysiology remains debated. HBO is typically administered as either a single or multiple sessions of 1.0–2.8 atmosphere absolute for 90 min or more as soon as possible after the onset of vision loss.[28] Its clinical use in the United States remains limited[12] despite a favorable side effect profile, as the treatment requires a specialized HBO chamber (either a single unit or a pressurized room). There are only a few studies that report visual improvement, and most are case reports or small series without a control group [Table 1].[29-39]

A meta-analysis by Wu *et al*. in 2018[28] included seven randomized controlled trials of 251 patients treated with some form of "oxygen therapy" for retinal artery occlusions (CRAO or branch retinal artery occlusion [BRAO]). Six studies involved HBO and one involved inhaled carbogen (95% O_2 and 5% CO_2) therapy (discussed later in this review). Most HBO studies showed a "low risk of bias," indicating a high likelihood of statistically valid results. However, five of the six HBO studies included additional treatments (anterior chamber paracentesis, ocular massage, acetazolamide, and/or hemodilution), making it impossible to determine whether HBO in itself has an independently favorable effect on visual outcome. All studies used visual acuity as the primary endpoint. Patients were treated as soon as 30 min, but as late as 5 days, after the onset of symptoms (two studies treated all patients within 12 h, two additional studies treated all patients within 48 h, and the final two studies treated patients as late as 5 days after symptom onset[28]). Oxygen therapy exhibited a significant visual acuity improvement in retinal artery occlusion patients compared with the nonoxygen therapy group (odds ratio, 5.61; 95% CI, 3.60–8.73). This meta-analysis indicates that in a very limited number of studies, oxygen therapy (most often HBO) showed some visual benefit when combined with other therapies.

Risks of HBO treatment primarily involve barotrauma, which refers to stretching and tearing of the tympanic membrane that results from an inability to equalize the pressure gradient between the middle ear and the external environment. In addition, HBO requires specialized equipment and often requires multiple sessions over several days. Given the very limited number of studies indicating the benefit of HBO as a singular therapy for CRAO patients, it cannot be deemed evidence based.

Mechanism 2: Vasodilation

Pentoxifylline

Pentoxifylline is a competitive, nonselective phosphodiesterase inhibitor that is thought to decrease red blood cell rigidity, reduce blood viscosity, and reduce the potential for thrombus formation.[40] It has been used in peripheral vascular disease, cerebrovascular disease, and several other conditions involving abnormal regional microcirculation.[41] Its use as a potential therapy for retinal vascular disorders dates back several decades.[42] One randomized controlled trial of ten patients evaluated treatment with oral pentoxifylline (1800 mg daily) in patients with acute CRAO.[43] The authors reported a greater increase in retinal blood flow using duplex scanning and a greater degree of subjective visual improvement in treated patients but did not report visual acuity outcomes. Thus, it cannot be concluded that treatment with pentoxifylline conferred visual improvement in treated patients. The medication is generally safe and well tolerated[44] and is therefore relatively low risk. However, given the paucity of evidence to support its ability to affect visual outcomes, routine use of the medication for CRAO patients is unsubstantiated.

Carbogen

Carbogen therapy (approximately a 95% oxygen/5% carbogen dioxide mixture) has been proposed as a method to improve retinal oxygenation (with

Table 1: Summary of main studies (published in English) evaluating hyperbaric oxygen as a therapy for nonarteritic central retinal artery occlusion (minimum of 5 cases)

Author, year (reference number)	Patient population Type of study	Treatment window range	Hyperbaric oxygen protocol	Combined treatments	Reported visual outcome
Beiran *et al.*, 2001[29]	72 patients 35 treated 37 untreated (controls; from a separate hospital) Retrospective case series	<8 h (individual treatment windows not specified)	2.8 ATA for 90 min BID for 3 days then QD until no further visual improvement for 3 consecutive treatments	Ocular massage, retrobulbar block, timolol, acetazolamide, paracentesis	At discharge: In treated patients, logMAR VA improvement in 29/35 (82.9%) of cases with mean VA improvement of 0.1957±0.3000; for control patients, VA improvement in 11/37 (29.7%) of cases with mean VA improvement of 0.0457±0.1498. Comparing mean discharge VA between treated and untreated patients, *P*<0.03
Cope *et al.*, 2011[30]	11 RAO Retrospective case series	5-144 h	2.4 ATA	None	"Eight of eleven patients experienced improved visual acuity"
Menzel-Severing *et al.*, 2012[31]	80 CRAO 51 treated 29 untreated (control) Retrospective case series	<12 h Mean: 5.3 h in treated patients and 5.7 h in control patients	2.4 ATA 90 min TID for 24 h with 5 total treatments in the first 48 h	Treatment group received HBO and hemodilution; control group received hemodilution only	After treatment: In treated patients, mean Snellen VA change of 3.0±5.0 lines (*n*=51); in controls, mean VA change of 1.0±4.2 lines (*n*=28); *P*=0.07. At 3 months: In treated patients, mean change of VA 3.2±5.7 lines (*n*=28); in untreated patients, mean change of VA 1.3±3.2 (*n*=13); *P*=0.26
Elder *et al.*, 2017[32]	31 RAO Retrospective case series	Range: 3-25.5 h 20 ≤8 h 27 ≤12 h 31 ≤25.5 h	2.0 or 2.4 for 90 min or 2.8 ATA for 60 min; "treatment plans determined on a case-by-case basis"	Oral acetazolamide, ocular massage, AC paracentesis, ASA, low-dose heparin, warfarin, clopidogrel	Immediately following treatment: 23/31 (74.2%) reported initial subjective improvement of vision. At variable follow-up (between 1 and 79 months): 7/31 (22.5%) had final Snellen VA of 20/60 or better; 2/31 (6.5%) had final Snellen VA between 20/60 and 20/200; 14/31 (45.1%) did not sustain visual improvement; 8/31 (25.8%) did not show visual improvement
Hadanny *et al.*, 2017[33]	128 CRAO Retrospective case series	Mean (SD): 7.8±3.8 h	2.0-2.4 ATA for 90 min TID for 24 h; QD until no further visual improvement	Ocular massage, AC paracentesis, oral aspirin, oral acetazolamide, or topical beta-blockers	Mean improvement in VA (logMAR) of 0.526±0.688 (from 2.14±0.50 to 1.61±0.78). VA gain >0.3 logMAR in 86 (67%) of patients
Bagli *et al.*, 2018[34]	10 CRAO Prospective case series	Mean (SD) 21.8±15.1 h 2 patients ≤8 h 4 patients ≤12 h 10 patients ≤24 h	2.4 ATA BID for 3 days; QD for 14 days	Oral acetazolamide Topical beta-blockers	Mean initial VA=LogMAR 3.0; mean final VA=LogMAR 1.8; VA improvement in 7 (70.0%) of patients
Coelho *et al.*, 2018[35]	14 CRAO Retrospective case series	11 ≤8 h 13 ≤12 h 14 ≤24 h	2.4 ATA for 90 min BID for 3 days; QD until VA stabilized	None	Pretreatment mean (SD) logMAR VA: 2.34±1.16; posttreatment mean (SD) VA: 1.39±0.94; P=0.007. VA gain ≥0.3 in 10 (71.4%) of patients
Masters *et al.*, 2019[36]	39 CRAO Retrospective case series	10/39 ≤6 h 27/39 ≤12 h 12/39 >12 h	2.8 ATA for 90 min then 2.4 ATA for 90 min BID for 10 total treatments over 5 days	TPA, AC paracentesis, ocular massage, IOP-lowering drops	28/39 (71.8%) patients had improvement in Snellen VA (mean 5.05 lines)
Lopes *et al.*, 2019[37]	13 RAO (9 CRAO, 4 BRAO) Retrospective case series	Range: 2-20 h Median: 9 h 77% of cases ≤12 h	2.5 ATA for 90 min QD×3 days then QD until VA stabilized (median sessions=7)	Topical and oral hypotensive medication, ocular massage, aspirin	Pretreatment mean logMAR VA: 0.005; posttreatment mean VA: 0.05; *P*=0.03. Clinically significant improvement (≥0.3 logMAR) in 5/9 CRAO patients (55.5%)
Gupta, 2019[38]	52 CRAO Prospective case series	Mean: 7.3±4.1 h	2.0 ATA for 90 min BID for 3 days then QD for 4 days	None	Clinically significant improvement (≥ 0.3 logMAR) comparing initial and discharge acuity in 42/62 patients (67.7%)

Contd...

Table 1: Contd...

Author, year (reference number)	Patient population Type of study	Treatment window range	Hyperbaric oxygen protocol	Combined treatments	Reported visual outcome
Kim *et al*., 2020[39]	34 total patients; included 10 CRAO treated and 9 CRAO untreated (control) Retrospective case series	3 patients ≤8 h 5 patients ≤12 h 8 patients ≤24 h 10 patients ≤25 h Excluded patients ≥25 h	(2.8 ATA for 45 min then 2.0 ATA for 55 min) BID during the first 24 h; then daily until no further visual improvement	Digital ocular massage Oral diuretics AC paracentesis	At 6 months: Change of logMAR VA 0.0 (−3.0-1.2) in control group and 0.6 (−2.0-3.0) in treated group; *P*=0.043

AC=Anterior chamber, ASA=Aspirin, SD=Standard deviation, ATA=Atmosphere absolute, BID=Twice daily, CRAO=Central retinal artery occlusion, HBO=Hyperbaric oxygen, logMAR=Logarithm of the Minimum Angle of Resolution, QD=Once daily, RAO=Retinal artery occlusion (branch retinal artery occlusion or central retinal artery occlusion), TID=Three times per day, VA=Visual acuity

inhaled oxygen) while preventing oxygen-induced vasoconstriction and maintaining the dilatation of retinal arterioles (with inhaled carbogen dioxide).[45-47] Carbogen is delivered by mask, typically for 10 min every hour[26] during all waking hours and every 4 h during the night for 48–72 h.[19] Treatment is generally well tolerated, with only a few patients experiencing discomfort due to increased resistance to breathing. However, given the frequent dosing, patients often require hospital admission, which significantly increases the cost of treatment.

In an uncontrolled study in 1980, Augsburger and Magargal reported visual recovery to better than 6/30 in 12 of 34 consecutive patients treated with carbogen, but all patients were also treated with anterior chamber paracentesis, lowering of the intraocular pressure, and ocular massage.[19] In 1995, Atebara *et al*. compared 89 consecutive patients with acute CRAO who were treated with both anterior chamber paracentesis and carbogen (49 patients) or with neither treatment (40 patients)[26] and found no treatment benefit. Results from prior studies have been inconsistent, and there is little evidence to support the use of carbogen therapy at this time.

Sublingual isosorbide dinitrate

Isosorbide dinitrate is a nitrate with long-acting vasodilator properties, most often used in the treatment of angina via sublingual administration.[48] Through the generation of nitric oxide, nitrates have been implicated as contributors to the basal vascular tone of the retina,[49] choroid,[50] and optic nerve.[51] Side effects of the treatment include headache, dizziness, lightheadedness, and nausea. Isosorbide dinitrate (at a dose of 10 mg) has only been evaluated as part of combination treatment approaches[24] for CRAO. To our knowledge, isosorbide dinitrate has never been studied as a singular treatment, and there is little evidence beyond basic scientific rationale to support its use as a treatment for CRAO.

Enhanced external counterpulsation

Enhanced external counterpulsation is a noninvasive procedure intended to increase the perfusion of internal organs.[52] It has been used as a method to reduce myocardial ischemia in patients with coronary artery disease.[53] The treatment involves applying pressure to the peripheral vascular bed using pneumatic cuffs, which are inflated at the onset of diastole. The result is augmented arterial pressure and increased coronary, cerebral, and ocular perfusion.[52]

In 2004, Werner *et al*.[52] conducted a prospective, randomized, nonmasked trial assessing the use of enhanced external counterpulsation in twenty patients with retinal artery occlusions. The mean age of occlusion of treated patients was 2.7 + 1.3 days; the mean age of occlusion in the control group was 2.4 + 1.6 days. Ten patients were treated with hemodilution and 2 h of enhanced external counterpulsation; another ten were treated with hemodilution alone. Hemodilution was achieved with 500 mL of IV hydroxyethyl starch or with electrolyte solution. The treatment was well tolerated, with no adverse events. The authors used outcome measures involving the quantification of retinal perfusion (using scanning laser Doppler flowmetry) and found greater perfusion in treated patients. However, this effect was lost 48 h after treatment and was not accompanied by an improvement in visual acuity. Thus, there is insufficient evidence to support the use of this therapy.

Mechanism 3: Dislodging the embolus

Ocular massage

Ocular massage, performed either with digital pressure[54] or using a contact lens,[24] is a method intended to create fluctuations in intraocular pressure (IOP) and promote the dislodgment of the causative embolus. The embolus then either disintegrates or migrates into a peripheral portion of the retinal vasculature, allowing for retinal reperfusion.[27] The technique of ocular massage involves applying repeated increased pressure to the globe for

10–15 s, followed by "a sudden release with an in-and-out movement using a 3-mirror contact lens for 3–5 min."[20] Some authors have proposed continuing the massage for up to 15–20 min.[27] Anecdotal case reports have reported visual restoration with this treatment. To our knowledge, no recent studies have evaluated the efficacy of ocular massage as a singular therapy; all studies have used the treatment in conjunction with other therapies, and these studies have not yielded strong evidence to suggest benefit.[55]

Neodymium: Yttrium-aluminum-garnet laser embolysis

In CRAO cases with a large causative embolus visible on fundus examination, physical breakdown (embolysis) or complete dislodgment (embolectomy) using photodisruption has been attempted as methods to restore retinal perfusion. Emboli are visible in approximately 20% of cases of CRAO.[56] Neodymium: yttrium-aluminum-garnet lasers have been primarily used, with the standard technique involving the use of a fundus contact lens, with the laser focused slightly posterior to the visible arterial wall at the site of the embolus. Laser energy can be up-titrated to achieve the desired effect.[57]

The use of this method is primarily based on the favorable results of five individual case reports[57-61] and one case series involving 10 CRAO patients.[56] However, an animal model demonstrated that laser did not reliably disrupt visible emboli,[62] and a 2017 meta-analysis of 61 cases of CRAO and BRAO reported that although noncontrolled studies did suggest a visual improvement (average initial acuity of 20/252 and average postprocedure acuity of 20/30), complications including vitreous and preretinal hemorrhage occurred in 57% of cases.[63] Given the lack of a control group, the heterogeneity among these studies, and the inclusion of both CRAO and BRAO cases, there is insufficient evidence to support the routine use of this therapy. Furthermore, the not insignificant complication rate associated with the procedure indicates that it should be attempted with caution, if at all.

Mechanism 4: Increasing retinal artery perfusion pressure

Anterior chamber paracentesis

The premise to support anterior chamber paracentesis suggests that rapidly lowering the IOP dilates the retinal vessels, increases the retinal perfusion pressure, and thus promotes reperfusion of the retinal arterial system.[19,26,64] Such changes have been visualized using ocular coherence tomography angiography of the retinal circulation.[65]

Paracentesis is typically performed after instillation of topical anesthesia (i.e., tetracaine) and a prophylactic antimicrobial agent, such as topical antibiotics or povidone-iodine. A 27G needle on a tuberculin syringe or a paracentesis blade can then be used to puncture the cornea to drain a small volume of aqueous fluid. The procedure may be performed at the slit lamp or under an operating microscope. A successful paracentesis should remove only the aqueous volume necessary to lower IOP to the desired level.[64] The normal anterior chamber volume is only 250 μL, so the practitioner may opt to remove small volumes (e.g., 50 μL) at a time to achieve sufficient IOP lowering while still maintaining some volume of the anterior chamber. Flattening the anterior chamber would predispose the patient to many of the primary risks of the procedure, which include inadvertent ocular trauma (to the cornea, lens, or iris), corneal decompensation due to iridocorneal touch, intraocular hypotony (with risk of choroidal folds and choroidal effusion or hemorrhage), and infection.

The use of anterior chamber paracentesis in patients with CRAO was first described in 1888, when Mules reported a patient who had an embolus migrate distally in the retinal arterial system after undergoing the treatment, mitigating the degree of vision loss. As noted above, Atebara *et al*. in 1995 reported that anterior chamber paracentesis and carbogen together offered little benefit.[26] In 2014, a 13-year retrospective cohort study compared 15 CRAO patients receiving "conservative therapies" with 59 CRAO patients receiving the same treatments and an anterior chamber paracentesis within 6 h of visual loss[64] and found no improvement of mean visual acuity in patients undergoing the procedure.

Intravenous, oral, and topical intraocular pressure lowering medications

In 1993, Rassam *et al*. demonstrated an increased retinal blood flow using laser Doppler velocimetry in ten healthy volunteers treated with 500 mg of intravenous acetazolamide[66] and proposed that the reduction in IOP was responsible. Lowering of the IOP is an attractive potential treatment option given its ease of use and its relatively limited side effect profile. Topical IOP-lowering medications, intravenous acetazolamide (500 mg), 20% intravenous mannitol (1 mg/kg), and 50% oral glycerol (1 mg/kg) have all been used in the treatment of acute CRAO patients.[24]

Topical medications for IOP lowering are generally well tolerated, with variable side effect profiles that can be tailored to the individual patient. However, topical medications are unlikely to achieve the desired degree of IOP lowering within an acceptable time frame. For more rapid IOP lowering, oral and intravenous agents, including mannitol and acetazolamid (most often 500 mg IV), are often used. These medications are associated with a number of bothersome side effects (including fatigue, paresthesia, and a bitter or metallic taste) and may also rarely result in life-threatening complications, including metabolic acidosis, Stevens–Johnson syndrome, anaphylaxis, and

blood dyscrasias. Despite their extensive side effect profiles, carbonic anhydrase inhibitors are routinely used in other ophthalmic conditions, such as acute angle-closure glaucoma, and are therefore familiar to and comfortably used by most ophthalmologists.

Unfortunately, there is a paucity of data to support the use of pharmacologic IOP-lowering medications in acute CRAO. Most supportive studies are case reports or series that evaluated pharmacologic IOP lowering in conjunction with other treatments,[20,24,55,67] and none have established the benefit of IOP lowering as a singular therapy.

Combination therapies (three or more modalities)

In 1999, Rumelt *et al*.[24] treated 11 patients with CRAO of < 48-h duration with a multitherapy regimen that included ocular massage, sublingual isosorbide dinitrate, intravenous acetazolamide, intravenous mannitol or oral glycerol, anterior chamber paracentesis, and intravenous methylprednisolone followed by intravenous streptokinase and retrobulbar tolazoline. The retinal flow was evaluated via contact lens fundoscopy after each treatment. Visual acuity and retinal artery supply (via gross examination) improved in 8 of 11 patients, all of whom had symptoms for < 12 h. There was no control group in the study, and it could not be shown that any individual treatment (or combination of treatments) had influenced the natural course of the disease.

Mueller *et al*.[68] reviewed 102 patients who had received a variety of conservative treatments (oral acetylsalicylate, oral acetazolamide, ocular message, hemodilution, oral pentoxifylline, topical beta-blocker medication, anterior chamber paracentesis, and subcutaneous heparin). The mean number of treatments received was 2.5 + 1.4. A multivariate stepwise regression model did not reveal any single or combination treatment as a significant factor in the improvement of visual acuity.

The 2010 multicenter EAGLE randomized controlled trial evaluated the efficacy of local intra-arterial thrombolysis as a treatment for CRAO. Control patients in the study were treated with isovolemic hemodilution, ocular massage, topical timolol 0.5%, intravenous acetazolamide (500 mg), low-dose heparin, and acetylsalicylic acid;[20] 60% of patients did experience a clinically significant visual improvement (>0.3 logMAR). As this group was included as controls to thrombolytic therapy, it cannot be concluded that conservative treatments altered the natural history.

Conclusion

There is a paucity of evidence to support the use of "conservative" treatment options for CRAO. The available evidence for all treatments outlined in this review is insufficient to conclude that any treatment will influence the natural history of the disease. Given this lack of effective treatments to reverse visual loss, the highest priority currently for patients with acute, nonarteritic CRAO is to reduce the risk of subsequent recurrent cerebral and cardiovascular events. Emerging treatments such as HBO and thrombolysis to reverse permanent retinal ischemia should only be considered within a short time window after the onset of visual loss, likely within 4 h if one extrapolates from the cumulative knowledge gained from studying and treating cerebral ischemia. Therefore, efforts at educating the medical community and patients regarding the need for emergent evaluation of patients with acute visual loss related to acute retinal ischemia are essential.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

Search strategy

Data for this review were identified by searches of MEDLINE, PubMed, and references from relevant articles using the search terms: "acetazolamide," "anterior chamber paracentesis," "branch retinal artery occlusion," "carbogen," "central retinal artery occlusion," "enhanced external counterpulsation," "hemodilution," "hyperbaric oxygen," "isosorbide dinitrate," "laser embolectomy," "Nd: YAG laser embolysis," "ocular massage," "pentoxifylline," "retinal vascular occlusions," and "thrombolysis." Articles published in English between 1960 and 2020 were included.

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