

Multidisciplinary Acute Care of Central Retinal Artery Occlusion with a Stroke Paradigm: A Call to Action

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Received date: July 08, 2021, **Accepted date:** August 09, 2021

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Abstract

Central retinal artery occlusion (CRAO) is an ophthalmologic emergency that can result in permanent vision loss. Over 25% of CRAO are associated with acute cerebral ischemia, and there are many parallels between CRAO and acute ischemic stroke. There are no definitive treatment algorithms for CRAO, however there may be opportunities to treat CRAO as an “eye stroke”. Given the similarities to acute ischemic stroke, multidisciplinary involvement and stroke algorithms should be considered and tested for this disease.

Keywords: Central retinal artery occlusion, Acute ischemic stroke, Intra-arterial thrombolysis, Clinical trial design

Background

Central retinal artery occlusion (CRAO) is a painless ophthalmologic emergency with potential for irreversible vision loss. Similar to ischemic stroke, CRAO occurs when there is sudden obstruction of the central retinal artery, leading to ischemic injury to the retina and subsequent cell death. Continuous occlusion and ischemia of the retina progresses to permanent damage to retinal cells and loss of vision. The incidence of CRAO is approximately 1 per 100,000 patients and most often presents as a unilateral occurrence [1]. Onset of CRAO is usually seen in the sixth decade of life, without evidence that race or other demographic parameter increase risk of CRAO [2].

Central retinal artery occlusion is inextricably linked to embolic disease, of which amaurosis fugax is a classic symptom. This is often a signal of underlying carotid stenosis or cardiac embolic disease. Of all patients presenting for evaluation of CRAO, 25% also show evidence of acute ischemic stroke on MRI, in addition to having an increased risk of ischemic stroke in the first 4 weeks following their presentation [3]. Current treatment

protocols, such as digital ocular massage, anterior chamber paracentesis, IV acetazolamide, mannitol, topical anti-glaucoma agents, vasodilatory agents, steroids, hyperbaric oxygen, and intra-venous or intra-arterial thrombolysis, have been previously used, however, no level 1 evidence for any standardized treatment protocol has yet been determined [4].

Overall, only 17.7% of patients demonstrate any functional visual recovery without treatment, emphasizing that the chance of spontaneous visual recovery in the setting of CRAO is overall very poor [5]. A critical factor influencing visual outcomes is the duration of retinal ischemia, in addition to site of occlusion of the central retinal artery, and residual retinal circulation [2]. Also important when designing clinical trials, is the recognition that there are subsets of CRAO with varying degrees of potential recovery [6]. Of note, arteritic CRAO, such as giant cell arteritis, will not be covered here, as it is a separate physiologic mechanism. Non-arteritic CRAO (NA-CRAO) carries only 22% spontaneous visual recovery, whereas transient NA-CRAO, in contrast, is analogous to a cerebral transient ischemic attack (TIA) of the retina

with 82% spontaneous visual improvement [6]. As part of this variability, approximately 15-25% of patients have a cilioretinal artery that perfuses a portion of the macula, essentially acting as collateral circulation to create “retinal penumbra”, and cilioretinal artery sparing CRAO patients demonstrate spontaneous improvement in 67% of eyes, primarily within the first 7 days [6]. These redundancies in vascular anatomy explain how some patients with CRAO can present with incomplete vision loss, which may provide a therapeutic window to restore blood flow with a better chance of visual recovery.

There is very poor public awareness of this condition and, further contributing to the problem, there are no widespread protocols in place to rapidly triage these patients, nor are there any clear guidelines for preferred treatment practices. The pathophysiology of this disease carries numerous similarities to that of cerebral stroke, as does the severity of disease, scarcity of effective treatment options, and evolution of management. Like acute ischemic stroke (AIS), CRAO is a time-sensitive ischemic event, and given this, there is opportunity to apply lessons learned from stroke trials and systems of care to improve the treatment of CRAO.

Perspectives from Mechanical Thrombectomy for Large Vessel Occlusion

There is no better example showcasing the tremendous benefit to public health as the evolution of mechanical thrombectomy (MT) in the treatment of emergent large vessel occlusions (ELVO). In 2013, three major randomized controlled trials (RCTs) assessed endovascular treatment versus medical management for ELVO (IMS III [7], SYNTHESIS Expansion [8], and MR RESCUE [9]), with all showing no significant benefit to MT in terms of primary outcomes. These trials were met with considerable criticism as each failed properly select appropriate patients; failing to confirm ELVO, withholding medical therapy (IV tPA) in the treatment arm, and/or not reproducing modern standards of revascularization [10]. Subsequent trials corrected for these limitations by using carefully selected enrollment criteria and by using cutting edge revascularization devices in the surgical arm. MR CLEAN [11], ESCAPE [12], EXTEND-IA [13], SWIFT PRIME [14], REVASCAT [15], DEFUSE 3 [16], and DAWN [17] have since unanimously demonstrated the overwhelming benefit of MT in patients with ELVO. In fact, MT is now one of the most efficacious surgical treatments in medicine with a number needed to treat of only 2.6 to prevent disability on one level or more on the modified Rankin Scale (mRS) [18]. The consequences of this paradigm shift have been far-reaching, powering widespread improvements in all facets of stroke care. In the last 5 years, we have seen concomitant advancements in public stroke awareness through public education initiatives, enhanced triage of stroke

patients, development and refinement of stroke center accreditations, a surge in stroke technological innovation, and an explosion of MT studies and ongoing research. MT procedural volumes continue to increase [19,20] as more studies have demonstrated the benefits to MT even in marginal candidates [21]. It is likely that future trials will provide even more justification for MT in more diverse patients. In just 10 short years, MT for ELVO has evolved from a rare, unproven procedure to an almost daily, highly protocolized, overwhelmingly efficacious treatment. This transformation was predicated on: 1) the recognition of a public health need to improve outcomes; 2) identification of limitations from early failed trials; 3) persistence and excitement among the neurointerventional community around emerging treatments; and 4) and refinement of patient selection criteria to allow for trial success.

CRAO is an “Eye Stroke”

CRAO parallels acute ischemic stroke in etiology and pathophysiology and should be considered the ocular equivalent of a cerebral infarct. First and foremost, CRAO is a time-dependent ischemic event. In animal studies, retinal injury was detected 97 minutes following the clamping of the central retinal artery. After this time point, increased duration of ischemia was directly associated with the degree of injury to the ganglion cell layer, with massive irreversible retinal damage occurring after 240 minutes [22]. As such, early recognition, efficient triage, and proper intervention are all important factors, much like when managing ELVO. Second, reperfusion of the ischemic tissue is paramount [23,24]. Refinements in reperfusion will be integral in improving the poor prognosis seen with this condition. The presence of a potential viable retinal tissue irrigated by vascular collaterals such as a cilioretinal artery, or “retinal penumbra”, underscores the importance of recognizing this subset of patients for potential for extended time to intervention. While vision loss with CRAO even in the presence of a cilioretinal artery would still be disabling, a cilioretinal artery or equivalent collaterals in patients with incomplete vision loss may keep retinal tissue alive to create a time window in which to reopen the central retinal artery and restore vascularization to the entire retina, with overall less damage and decreased future risk of neovascularization. Third, patients with CRAO have near identical vascular risk factors as patients with a history of coronary artery disease and cerebrovascular accidents: diabetes mellitus, hyperlipidemia, hypertension, and tobacco use. Of all these factors, hypertension seems to be most indicative of retinal ischemia [25] with hyperlipidemia closely following, which is also the most commonly undiagnosed vascular risk factor occurring concurrently with a CRAO diagnosis [26]. Finally, concomitant extracranial internal carotid artery stenosis of at least 70% has been demonstrated in up to 40% of patients with a diagnosis of CRAO [27]. CRAO is

almost always caused by emboli, and it is essential that a full embolic work-up is performed, including cardiac imaging, when CRAO is discovered [2]. As a community, neurointerventionalists, neurologists and neurosurgeons are well-positioned given our involvement with stroke to manage and treat patients with CRAO in an attempt to avoid devastating visual loss and subsequent disability.

Current Treatments for CRAO

As noted, patients presenting with CRAO often do so in a delayed fashion, which is likely in part to the painless unilateral nature of the vision loss, lack of public and provider awareness, and the lack of organized treatment practices and protocols. Most often, the approach to the management of CRAO in the acute setting is medical management with therapies including digital ocular massage to dislodge the embolus, anterior chamber paracentesis or pharmacologic agents (IV acetazolamide, mannitol, or topical anti-glaucoma agents) to reduce intraocular pressure and increase retinal artery perfusion, vasodilatory agents, or steroids to address retinal edema, but their use lacks uniformity as well as proven efficacy. In a retrospective analysis of 91 patients that presented at our center with non-arteritic CRAO, only 21% of patients presented within 4 hours of symptoms, whereas 38.5% of patients presented greater than 24 hours after symptom onset [28]. Patients presented initially to ophthalmology clinics (29.7%), non-ophthalmology clinics (5.5%), or the emergency department (57.1%). Half (52.7%), received no treatment for CRAO.

Paralleling stroke, both IV thrombolysis and intra-arterial therapies (IAT) have been studied for patients with non-arteritic CRAO. A meta-analysis involving 5 retrospective case-controlled studies and 1 prospective RCT (the European Assessment Group for Lysis in the Eye – EAGLE trial) evaluated the safety and efficacy of IAT [29]. Targeted infusions of urokinase (200,000-1,300,000 IU) or tPA (maximum of 80 mg) were given into the ipsilateral ophthalmic artery within 24 hours of symptom onset. While all 5 retrospective studies showed significant visual outcome improvement with IAT [30-34], the EAGLE trial, which was the only prospective randomized controlled trial and enrolled patients within 20 hours of symptom onset, found no differences in visual improvement between the medical management protocol (60.0%) and the IAT group (57.1%) [35]. Notably, the EAGLE trial did not include a medical management plus IAT arm, a similar issue seen in the 2013 ELVO trials, which withheld IV tPA in the surgical arm. Further, there was no distinction of patients with complete versus incomplete NA-CRAO, no inclusion of IAT within 4.5 hours, and no recanalization results reported. Prior studies involving the clamping of central retinal arteries in animals, as previously described, demonstrated irreversible damage to the retina occurs

after 4 hours of occlusion. With that said, patients that present with incomplete visual loss and/or those with cilioretinal arteries may have a “retinal penumbra” and be more amenable to visual improvement with delayed time to reperfusion. The EAGLE trial, in fact, demonstrated increased visual improvement in patients treated less than 12 hours from onset compared to those who presented less than 20 hours from onset [35]. It is also important to note that the EAGLE trial did demonstrate a significant number of adverse events, though the vast majority were mild and resolved such as headache and facial pain. There were two major adverse events in each group: 2 intracranial hemorrhages in the thrombolysis group (complete symptom resolution), and in the medical management group, one ischemic stroke and one death within 3 days from endocarditis. Other adverse events seen, such as epistaxis, eyelid edema, and groin site complications may be mitigated with controlled tPA doses, directed infusion into the ophthalmic artery without external carotid artery infusions, and by employing radial access instead of femoral access to enhance procedural safety, mirroring safety changes seen between the 2013 and 2015 stroke trials to mimic current best practices. Perhaps most importantly, visual outcomes in the medical group in EAGLE improved to 60%, compared with less than 30% chance of spontaneous visual improvement without medical therapy [6]. This is of significant importance as a potential model for protocolizing multimodality therapy within a rigorous timeframe to impact outcomes. The medical arm of the EAGLE trial included a single eye-drop of timolol 0.5%, IV acetazolamide 500mg, 3-5 minutes of ocular massage, and hemodilution for patients with a hematocrit >40% [35].

IV thrombolysis with tPA has also shown to be feasible within 4.5 hours with improved functional recovery (reading ability) compared with the conservative standard treatment in the EAGLE trial (6/20 (30%) versus 1/39 (3%)) [36]. This may be another arm of multimodality therapy and importantly, also highlights the necessity of defining a pragmatic functional endpoint, such as finger counting or reading, akin to modified Rankin scale 0-2.

These studies highlight important corollaries to our recent experience with ELVO. First, patient selection for IAT is critical and these studies can assist us in refining enrollment criteria to optimize outcomes with IAT in CRAO. Second, establishing protocolized guidelines for CRAO medical treatment is paramount, as patient outcomes with a regimented protocol were better in the EAGLE trial compared to other retrospective studies that did not use regimented medical therapies. Third, establishing IAT protocols will help to standardize treatment, aid in reporting of reperfusion outcomes, and will help to prevent systemic complications from overdosing of tPA. Importantly, the EAGLE trial should not be

seen as a failure, but instead as a learning experience with important lessons that can help us refine methodology to better select and treat patients.

Areas of Opportunity

Prior studies as well as our institutional data illustrate clear areas for improvement in the management and treatment of CRAO. First, 42% of our patients presented to a health care provider >24 hours after symptom onset, with only 19% of patients presenting within 4 hours of symptoms. This delay in patient presentation stems from many contributing factors: a) lack of public awareness of symptoms and severity of CRAO is unestablished; b) transportation of patients between facilities; and c) referral and consultation patterns. To achieve expedited CRAO diagnosis and treatment, providers must understand the presentation of this disease along with its urgency to be seen in the ED. Patient education via a public health initiative is also important to spread knowledge of CRAO. For example, expanding stroke education from “FAST” (facial droop, arm weakness, speech difficulty, time to call 911) to BE FAST (blindness of eye as “BE”) [37] can accelerate triage and time from onset to presentation, along with an established “Code Eye Stroke alongside current “Code Stroke” protocols to improve systemic multimodal treatment.

Additionally, variable results are seen with the currently applied conservative medical management regimes. These treatment variabilities can be addressed by the utilization of a uniform professional treatment guideline similar to those developed for AIS. This change would mimic the improved visual outcomes seen in the EAGLE trial when a multimodal model was implemented. Further, extrapolating improvements in minor stroke and TIA patients with short-term use of dual antiplatelets may offer an additional important opportunity to enhance multimodality therapy for CRAO patients [38].

Further study and development of therapies for CRAO, such as IAT and IVT, is critical due to the significant morbidity of vision loss. 37% of adults would accept the risk of stroke and death for a threefold increased chance to regain 20/100 visual acuity in one eye when binocular [39]. With CRAO thrombolysis offered in greater than 50% of academic centers [40], there exists clinical equipoise along with opportunities for prospective randomized control trials to successfully explore the efficacy of IAT in the setting of CRAO.

Conclusion

Given the similarity to stroke in etiology and pathophysiology, as well as the significant number of patients with concomitant stroke risk factors and

symptoms, current multidisciplinary stroke algorithms should be applied to CRAO. Improvements towards the handling of CRAO are contingent upon a) establishing public awareness of symptoms and severity of CRAO; b) multi-specialty education of medical professionals; c) a standardized multi-disciplinary treatment guideline; d) implementation of stroke system protocols; and e) establishing IAT efficacy of CRAO treatment via clinical trials.

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