Acute management of Central Retinal Artery Occlusion

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ABSTRACT

CRAO has been linked to ischaemic cerebral stroke as the same atherosclerotic risk factors can contribute to both processes. Hypertension, diabetes, carotid and coronary artery disease, and smoking tobacco have all been associated with non-arteritic CRAO.[1] While there are clear evidence-based protocols widely in use for the management of cerebral stroke there continues to be debate concerning the acute management of CRAO. Many clinicians feel that the available treatment options are ineffective and that the inherent risks outweigh the potential benefits. The goal of this paper is to provide the most updated summary of the current literature on this topic.

Key words: CRAO, Hypertension, diabetes, embolus.

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INTRODUCTION

CRAO can have devastating visual consequences. First described by von Graefe in 1859[2] the estimated annual incidence rate is 1 in 100.000[3] and it leaves most patients with profound permanent visual impairment.[4] The loss of vision affects quality of life especially in the older population, the group in which CRAO is the most common. In addition the disorder can result in increased healthcare costs due to falls and other associated complications. Given the severity of outcomes an effective treatment for CRAO has long been sought and a wide variety of treatments have been attempted.

In 1881 the use of inhaled amyl nitrite to dislodge a presumed embolus via vasodilation was reported by Samelsohn.[5] Seven years later Mules described a patient who had a central embolus pass into a smaller more peripherall vessel after anterior chamber paracentesis.[6] In 1926 Oppenheimer boldly recommended temporary detachment of the inferior rectus to gain access for direct massage of the optic nerve to attempt to displace an embolus.[7] Other proposed and attempted measures have included full body hot baths, immersion of the arms and legs in freezing water, retrobulbar injections and intravenous application of cobra venom.[8] More recently there have been reports on the use of ocular massage to manually dislodge emboli, carbogen sublingual, isosorbide dinitrate, hyperbaric oxygen and hyperventilation to dilate retinal vessels and increase blood oxygen content, intravenous acetazolamide or mannitol and topical intraocular pressure lowering agents to increase the perfusion pressure, gradient and systemic oentoxifylline or aspirin, intravenous

platelet inhibitor and intra-arterial recombinant tissue plasminogen activator for thrombolysis.[9]

Patients with CRAO usually present with sudden painless severe visual loss with a relative afferent pupil defect without disc swelling. A cherry red spot and macular oedema are often observed although may not be present immediately.[10] The putative pathogenesis of CRAO is embolism from the carotid arteries in the setting of atherosclerosis. Emboli can also originate from the heart.[11] It is not certain where CRAO occurs. A site often implicated in embolic occlusion is the narrowest portion of the central retinal artery located at the point where it pierces the dural sheath of the optic nerve. The vast majority of retinal arterial emboli are thought to consist of cholesterol with smaller proportions made of fibrin or calcific material[12] although it has been argued that this distribution does not necessarily apply to central retinal arterial emboli which are not visible on fundoscopic examination.[13] CRAO can also result from trauma or arteritis. Occlusive thrombi are thought to occur predominantly in the region of the vessel immediately posterior to the lamina cribrosa.[11]

Monkey studies have shown that time is of the essence for establishing re-perfusion and preventing retinal infarction. The exact amount of time is not clear but it seems to be less than four hours.[14] Heyreh and Zimmerman studied a cohort of 244 consecutive patients with CRAO to determine the natural history.[4] They found that the initial visual acuity differed significantly by type of occlusion. Arteritic CRAOs fared the worst followed by permanent non-arteritic, then transient non-arteritic and finally non-arteritic with cilio-retinal sparing. For all comers initial visual acuity was 20/200 or worse for 84.6% of patients and final visual acuity generally measured greater than 30 days after onset was 20/200 or worse for 81% of patients. They reported that 82% of eyes with transient occlusion, 67% of eyes with cilio-retinal artery supply and 22% of eyes with permanent non-arteritic occlusion, experienced some degree of improvement in vision but it is not possible to tell from their paper the degree of improvement in specific cases. They also examined visual field loss and recovery and concluded that marked improvement in both visual field and acuity can occur without treatment although the potential for and degree of visual improvement is dependent on a number of factors, including length of occlusion, residual retinal circulation, site of occlusion within the artery, presence of cilio-retinal artery supply, cause of the occlusion and perfusion pressure. While a very small percentage of patients with CRAO enjoy significant improvement most patients are left with profoundly impaired vision. There is obvious need for an effective treatment.

STUDIES

A Cochrane review in 2009 examined the relevant literature to date addressing the management of acute CRAO.[9] At that time there were a number of case reports and series and other retrospective non-randomized, non-controlled studies, describing a wide variety of treatments including **anterior chamber paracentesis, ocular massage, carbogen acetazolamide, aspirin, intravenous tirofiban and intra-arterial urokinase or recombinant tissue plasminogen activator**. There were only two randomised controlled trials available for review. Both of these were small single centre studies that are summarised in the paragraphs that follow.

One of the studies reported on the use of haemodilution as well as enhanced external counter-pulsation, a technique which involves intermittent compression of the legs in synchrony with the cardiac cycle in order to increase cardiac preload, decrease cardiac after load and improve cardiac output and presumably end-organ perfusion.[15] In addition to patients with CRAO this study included patients with BRAO. Half of the twenty study subjects received haemodilution and two hours of enhanced external counter pulsation. The other half received only haemodilution. No adverse effects of treatment were reported. Scanning laser Doppler flowmetry was used to assess changes in retinal perfusion. A significant increase in perfusion of ischaemic areas was noted immediately after enhanced external counter pulsation in the group receiving that therapy as well as forty-eight hours later in both the control and non-control groups, without a significant difference between them. Some of the increase in perfusion may be attributable to the haemodilution used in both groups. While this increase in perfusion was noted, there was no difference between control and non-control groups after 48 hours and more importantly there was unfortunately no concurrent improvement in visual acuity. While the authors suggest that the treatment may have application, it thus seems to miss the mark in terms of outcome goals.

The other randomised controlled trial[16] described treatment

with **oral pentoxifylline** a competitive non-selective phosphodiesterase inhibitor that is thought among other actions to increase the deformability of red blood cells and decrease blood viscosity and the potential for platelet aggregation and thrombus formation.[17] This study included ten patients with CRAO with decreased retinal blood flow compared to the fellow eye as assessed by duplex scanning. These patients were randomized to either treatment with pentoxifylline or with placebo for four weeks. No adverse effects were observed. The authors reported a significant increase in flow velocity in both groups but this was much greater for the group treated with pentoxifylline. Still while they conclude that the treatment improved retinal flow better than placebo and should be considered as an important option, they too did not report any corresponding improvement in vision.

At the time of publication of the Cochrane review there were also a number of observational studies[13,18,19] and two major reviews[20,21] examining the role that thrombolysis might play in the treatment of CRAO. The reviews concluded that a prospective randomised multi-centered controlled trial was needed to further evaluate this possibility. Such a trial was in fact in progress at the time run by The European Assessment Group for Lysis in the Eye (**EAGLE**).[22] To be included in this study patients had to have a CRAO for less than 20 hours and a poor presenting visual acuity. A total of 84 patients were randomised to either conservative treatment (ocular massage, topical beta blocker, acetazolamide, aspirin, heparin and/or hemodilution) or local intra-arterial thrombolysis using recombinant tissue plasminogen activator injected directly into the ophthalmic artery through a micro catheter by a neuro-radiologist. The primary endpoint in this study was visual acuity at one month compared to the time of presentation. The mean best corrected vision improved significantly in this time frame in both groups and did not differ significantly between them. Clinically significant visual improvement was noted in 60% of the patients treated conservatively and 57.1% of patients who received thrombolysis. Two patients in the conservative measures group and 13 patients in the thrombolysis groups experienced a complication including severe complications such as cerebral and cerebellar haemorrhage in the thrombolysis group. The authors concluded that in light of similar outcomes between the two groups intra-arterial thrombolysis is not worth the risk of such adverse outcomes. The study was in fact discontinued after the first interim analysis because of these adverse effects.[23]

In 2014 there were no further large randomised controlled trials but there were a few additional publications that reported on the acute management of CRAO. Fieb et al retrospectively analysed 74 patients with CRAO 15 of whom were managed conservatively and 59 of whom received anterior chamber paracentesis.[24] They found no significant difference in improvement of best-corrected visual acuity at day three between patients with and without paracentesis. They also found no significant difference by time from symptom onset to paracentesis even when stratified into presentation times less than six hours. Additionally one patient suffered a lens injury due to the paracentesis with subsequent need for cataract surgery. They concluded that the procedure provided no additional benefit and should not be used given the risk it carries for such complications as well as infection and bleeding and the apparent lack of efficacy.

ARTERY OCCLUSION AND GIANT CELL ARTERITIS

For those occlusions attributed to giant cell arteritis the literature seems to suggest that the chances of restoring vision are practically nil. Because there is a great risk that the other eye will suffer an imminent infarction of the retina or optic nerve the focus should turned to the immediate treatment of the arteritis in the hopes of preventing vision loss in the fellow eye. Time should not be wasted with localised treatment to the affected eye. Corticosteroid therapy should be started expeditiously. The natural history of patients with what has been referred to as transient non-arteritic CRAO and of patients with perfusion from a cilio-retinal artery seems to be much less severe visual consequence. In these patients vision is usually preserved to such an extent that the potential benefit of therapy is likely outweighed by the risks. For the rest of the patients with non-arteritic CRAO although the outcomes are usually visually devastating and it is frustrating to both doctors and patients a number of hurdles remain to the effective treatment of this disease. The most favourable argument for intervention so far seems to be the study by Aldrich et al.[13] They reported significant improvement in visual outcomes of patients treated with aliquoted intra-arterial tissue

plasminogen activator over standard therapy, without any catastrophic complications. Still the patients in that trial who were treated with thrombolysis presented in a much shorter time window than those who were treated with traditional therapy and the authors themselves conclude that due to the non-randomized nature of the study the therapy can not be recommended as a standard practice.

OPHTHALMIC FOLLOW UP

Although the visual acuity is unlikely to improve more than one week after an acute obstruction of a retinal artery, follow up by an ophthalmologist is essential because of possible retinal and iris neovascularisation. The pathogenesis of ocular neovascularisation after these acute vascular occlusive events remains poorly understood, but there is a general consensus that chronic retinal ischaemia plays an important aetiological part.[25] The incidence of ocular neovascularisation after CRAO lies between 16.6% and 18.75%, and the majority of these go on to develop rubeotic glaucoma (67.5% to 83.3%).[25-28] The time interval between the occlusive event and the development of neovascularisation ranges from 10 days to 10 months, but the vast majority occur within three months of the arterial obstruction.[28] Panretinal photocoagulation has been shown to reduce the risk of rubeotic glaucoma and a painful eye, and close ophthalmic follow up is therefore recommended for a minimum period of three months after the occlusive event.[27]

NON-OPHTHALMIC FOLLOW UP

Systemic management in cases of CRAO and BRAO is aimed at reducing morbidity and mortality associated with predisposing and related conditions. Measures recommended in all cases include cessation of smoking, appropriate dietary advice, managing blood pressure and oral aspirin therapy. Otherwise, associated disorders should be treated on their own merits, and specialist referral is indicated in the presence of systemic vasculitis, significant carotid artery stenosis, hypercoagulable states, valvular heart disease and complex arrythmias.

CONCLUSION

We still lack definitive data from a large well-designed multi-center randomised controlled trial to guide our practice in the acute management of CRAO. Even if such data were available and suggested for example that local intra-arterial thrombolysis was a safe and effective technique for clearing an offending embolus, one must consider the reality of the timing of presentation in these patients. It is unlikely given the brief time window within which ischaemic retinal tissue must be re-perfused to remain functional, that a patient would present be diagnosed and be able to receive such an invasive therapy. Thus short of a public service campaign for this 1 in 100.000 individual occurrence to alert at risk patients who experience sudden painless profound monocular visual loss to call an emergency response line and ask to be taken by ambulance to the nearest tertiary or quaternary care facility with an on-call ophthalmologist and interventional neuro-radiologist, the reality of timely treatment for most of these patients remains limited. As with all modifiable disease processes we should continue to focus on primary prevention for the most contributory risk factors.

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