Current Approaches in the Management of Central Retinal Artery Occlusion

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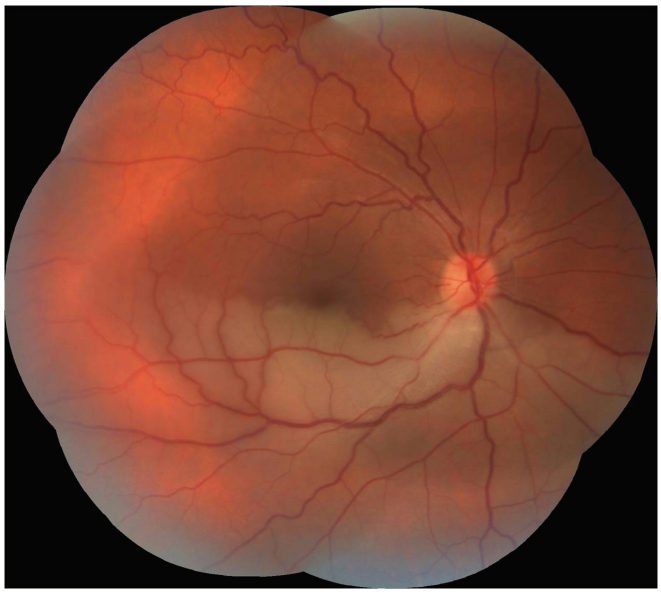
ABSTRACT

Central retinal artery occlusion (CRAO), an ophthalmological emergency, is a condition that progresses with acute, severe vision loss. Although there are different modalities in the treatment of acute CRAO, these treatment options aren't supported by prospective, controlled studies and outcomes are not satisfying. In recent years, there have been increasing numbers of publications suggesting that patients with acute CRAO carry a significant risk for cardiovascular and cerebrovascular events and that risk factors diagnosed timely could be life-saving. Based on literature, in CRAO, which is considered as a medical emergency, the patient should be referred for neurological and cardiologic examination as soon as possible after diagnosis. Here, we discuss current approaches in the management of central retinal artery occlusion, emphasizing acute ischemic event with high mortality which may develop following CRAO in the shed of current literature.

Key Words: Retinal artery occlusion, Ischemia, Cerebrovascular event, Cardiovascular event.

INTRODUCTION

The central retinal artery occlusion (CRAO) is an entity that is considered as an ophthalmological emergency and progresses with acute, painless, unilateral loss of vision. The CRAO was first defined by retinal ischemia occurred in a patient with endocarditis in 1859. The central retinal artery (CRA) originates from ophthalmic artery which is first branch of internal carotid artery. The CRA and its branches supply whole inner retina. The occlusion in one branch of central retinal artery results in branch retinal artery occlusion (BRAO) (Picture 1). In the 15-30% of population, there is a cilioretinal artery that arises from posterior ciliary artery system and supplies macula. As the cilioretinal artery does not originate from CRA, it preserves fovea in case of CRAO (Picture 2). Among retinal artery occlusions, CRAO is the one that affects visual acuity at most. In BRAO, visual acuity is relatively better but recurrent cases can cause severe vision loss.[1-4]



Picture 1. *In the color fundus image (right eye), retinal artery branch occlusion that involves inferior part of eye is seen. It is seen that retina was whiten at areas compatible to trace of occluded artery and superior part of fovea was spared.*

Any condition that impairs blood flow in retinal arteries can lead retinal artery occlusion. However, the most common cause is embolus from internal carotid artery or heart in CRAO and BRAO (non-arteritic CRAO and

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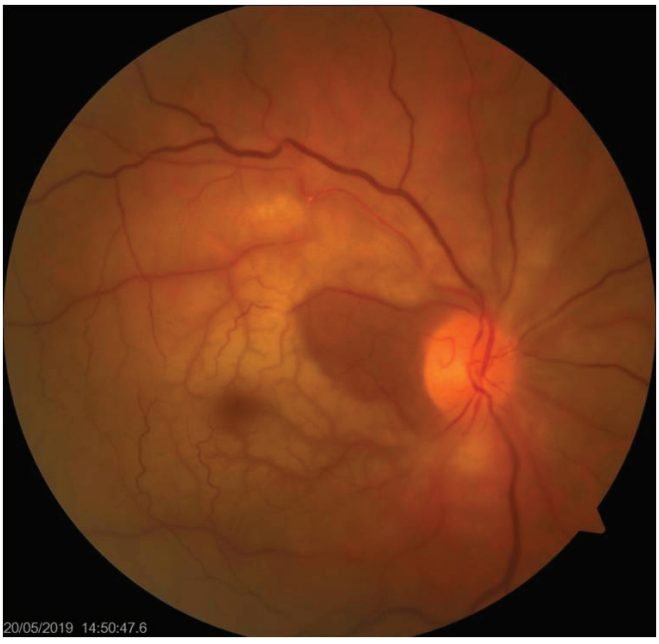
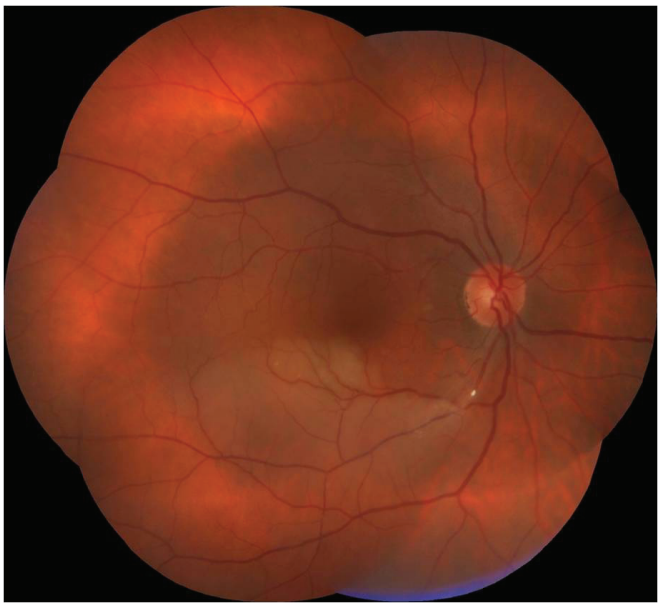


Picture 2. *In the color fundus image (right eye), central retinal artery occlusion accompanied by cilioretinal artery is seen.*

BRAO) (Picture 3). Blood dyscrasias that cause hyper-coagulation and vasculitis are less commonly involved in the etiology. The giant cell vasculitis in a cause of arteritic CRAO.[5-8] The incidence of non-arteritic CRAO is 1-2: 100,000 but it is increased by advancing age and reaches up to 10: 100,000 in 80 years of age.[9,10] In patients with CRAO, the frequency of cardiovascular risk factors such as hypertension, atherosclerosis and diabetes mellitus



Picture 3. *In the color fundus image (right eye), embolus in inferotemporal retinal artery and resultant retinal artery branch occlusion is seen.*

is high as similar to patients with cerebral infarct.[11-14] In 2011 and 2013 consensus statements published by National Stroke Society and American Heart Association, the definition of central nervous system infarct (stroke) is revised as "ischemia-related death of brain, spinal cord and retina cells".[15-17] This definition emphasizes that acute arterial ischemia is equivalent with stroke and that it represents both medical and ophthalmological emergency. The CRAO is considered to be similar to ischemic stroke in many instances; however, it is controversial whether it would be managed as an equivalent of stroke. Moreover, in recent studies, it has been reported that patients with CROA carry a significant risk for future cardiovascular and cerebrovascular events and that risk factors diagnosed timely could be life-saving.[18-26] The morbidity and mortality of CRAO is high since it does not only cause severe and permanent loss of vision directly but it is also associated to long-term systemic risk factors. The risk for cerebrovascular event following CRAO is highest within first week.[11-14,25] Thus, it should kept in mind that CRAO may be a preceding event for a potentially mortal ischemic event and treatment should be planned accordingly.

Approach to patient with CRAO

Although the CRAO is currently considered as equivalent to stroke, most patients do not receive any emergent intervention other than ophthalmologic treatment. In a survey (2019), it was reported that only one-third of ophthalmologists refer patients diagnosed as CRAO to emergency department for further evaluation.[27] Although optimum management differs based on settings, the patients should have to be referred to emergency department and examined by a neurologist at a minimum. In all patients, cranial magnetic resonance imaging (MRI) or diffusion MRI should be performed, if not contraindicated, regardless of presence of neurological symptom. [2,7,25,26,28-30] In 3 retrospective studies, it was reported that small, acute cerebral infarct areas were observed on simultaneous cranial MRIs in 23-24% of patients with acute retinal ischemia (CRAO, BRAO or transient monocular vision loss).[28-30] In majority of patients included to these studies, no focal neurological deficit suggestive of acute cerebral ischemia was detected. It is well-known that such quiescent infarcts are risk factors for future stroke. Again, in these studies, significant findings that can lead stroke in the future and require emergent treatment were detected in the patients with acute renal ischemia and acute quiescent infarcts.

In the support for above-mentioned evidence, Chodnicki et al. reviewed 300 patients with CRAO followed over 15 years period and reported that the risk for symptomatic stroke was 5% during 30 days period of CRAO (15 days before and 15 days after).[25] In addition, in a meta-

analysis by Fallico et al., it was reported that acute cerebral ischemia-related findings were noted on MRI in 30% of patients with acute CRAO and 25% of patients with acute BRAO.[26]

Also, simultaneous head and neck MR angiography and cranial MRI involving carotid arteries and aortic arc should be obtained since source of embolus is usually carotid system in patients with CRAO. In addition, cardiovascular risk factors should be assessed thoroughly using electrocardiogram, echocardiogram, blood pressure and cardiac monitorization. Hypercoagulability states such as factor V Leiden deficiency, prothrombin gene mutation, protein C or S deficiency, anti-thrombin III deficiency, hyper-homocysteinemia, excessive factor VIII, anti-phospholipid antibody or hyperviscosity; vaso-occlusive conditions such as sickle cell anemia; systemic inflammatory disease; and drug and substance use should be questioned in young patients with no established etiology.[12,31,32] Giant cell arteritis should be ruled out in patients aged >50 years presenting with CRAO. The patient should be questioned about jaw claudication and headache and erythrocyte sedimentation rate and C-reactive protein should be studied.[2,3] If there is clinical suspicion, temporal artery biopsy should be performed regardless of laboratory results. If giant cell arteritis is confirmed, high-dose intravenous steroid treatment should be initiated, followed by gradually tapered oral steroid treatment in order to prevent progression of vision loss and systemic complications.[33,34]

Treatment in non-arteritic CRAO and BRAO

The treatment in CRAO can be classified as acute therapies aiming to improve visual acuity and secondary therapies targeting to prevent subsequent ischemic events (acute myocardial infarction, acute cerebral infarction. There is no single treatment modality proven to improve visual acuity after CRAO. However, approaches ranging from ocular massage to intra-arterial tissue plasminogen activator (tPA) have been used in attempt to restore ocular perfusion and improve visual acuity.[2,3,5,6,35] Theoretically, the likelihood for improvement in visual acuity is increased by retinal perfusion as soon as possible after CRAO.[36, 37] Although optimal timing is controversial, primate studies revealed outcomes similar to cerebral ischemia. It seems that acute treatment within 3 hours after insult can prevent permanent retinal ischemia. Although this period may be prolonged up to 6-12 hours, treatment beyond 12 hours will have no effect. Thus, treatment options discussed below have limited value in the acute treatment of CRAO since they are mostly given 12-24 hours after onset of vision loss. Since there is no acute treatment modality proven to improve visual acuity in CRAO, secondary protection against systemic ischemic events are more important given outcomes of such ischemic events.

Conventional therapies

Mobilization of embolus

-*Ocular massage:* Ocular massage is performed by applying digital pressure to globe through eyelids for 15-20 minutes. The aim is to increase retinal artery pressure and to displace embolus occluding arterial lumen by achieving arteriolar dilatation and reduction in intraocular pressure.[8,38,39] Although ocular massage alone or in combination with IOP-lowering agents is employed, it does not lead a significant alteration in the natural course or CRAO.[8,38,40]

-*Laser embolectomy:* In CRAO, physical mobilization of visible embolus in the artery lumen by Nd-YAG laser has been reported in limited number of studies. Although an improvement is observed in retinal perfusion and visual acuity following breakage of embolus, vitreous hemorrhage has been reported in the 50% of cases. Nd:YAG laser in the treatment of CRAO is controversial and has not been accepted as standard therapeutic option.[41,42]

Increasing retinal artery perfusion pressure

IOP-lowering therapies: Both classical topical and systemic agents (oral or intravenous acetazolamide or intravenous mannitol) are also used in order to increase retinal arterial pressure in CRAO treatment.[36,43] However, there are no definitive evidence that they improve vision.[38,44]

Anterior chamber paracentesis: Anterior chamber paracentesis is performed by draining somewhat humor aqueous using a fine-needle attached to injector directed to anterior chamber through limbal cornea. It causes a sudden decrease in intraocular pressure and increase in retinal artery perfusion pressure. Although it is used frequently, no effect on improvement in visual acuity has been shown.[35,40,45]

Vasodilatation

-*Hyperventilation or carbogen inhalation:* Both techniques lead respiratory acidosis by increasing CO_2 concentration in the blood. The elevated blood CO_2 concentration prevents vasoconstriction in retinal vessels caused by oxygen, resulting in improved retinal perfusion.[45-48] However, no marked difference was observed in vision outcomes in CRAO patients received hyperventilation or carbogen inhalation when compared to untreated patients at acute period.[45]

-Therapies enhancing vasodilatation or erythrocyte flexibility: Sublingual isosorbide dinitrate causes vasodilatation of retinal vessels and mild decrease in intraocular pressure. As similar to above-mentioned treatments, improvement in vision could not be shown in CRAO patients.[38] Oral pentoxifylline is an agent that enhances erythrocyte flexibility, decreases blood viscosity and improves tissue perfusion.[49,50] In a randomized-controlled study, it was reported that pentoxifylline significantly increased CRA blood pressure but no data was provided regarding its effect on visual acuity.[49]

Therapies directing to increase blood oxygen pressure

Hyperbaric oxygen: Hyperbaric oxygen is directed to improve oxygenation of ischemic retinal tissues by elevating concentration of soluble oxygen in the blood.[51,52] In general, it is used as a supportive until spontaneous restoration of retinal reperfusion.[3] Although some cases have been reported to achieve improvement in vision by hyperbaric oxygen therapy after CRAO, the difference in visual acuity did not reach statistical significant when compared to those not received hyperbaric oxygen therapy.[53,54] In a study by Menzer-Severing et al., majority of patients not received hyperbaric oxygen therapy showed similar visual acuity outcomes when compared to those underwent hyperbaric oxygen therapy.[54]

Thrombolysis

Based on positive effects in acute cerebral ischemia, thrombolytic agents such as urokinase, streptokinase and tPA are being used in acute CRAO treatment. The thrombolytic agents lead resolution of fibrin clots implied in CRAO pathogenesis by converting plasminogen into plasmin.[5,8,11] Since there is no established procedure regarding thrombolytic use in CRAO, most clinicians follow stroke protocols. However, current literature based on randomized, controlled clinical trials draws no definitive conclusion regarding localization for thrombolytic therapy. In most studies, thrombolytic agents could be given as early as 12 hours after onset of vision loss. In addition, it was reported that intra-arterial thrombolytic agents are associated with high complication. Thus, thrombolytic use in CRAO treatment should be given in an individualized manner by taking risk: benefit ratio into consideration.

Intra-arterial or intravenous tPA

There are retrospective studies reporting improvement in visual acuity in CRAO by tPA; however, there are also studies reporting no effect.[55-64] For instances, in a retrospective study on 42 patients with CRAO, it was reported that significant improvement in visual acuity was achieved by combined used of tPA with conventional therapy given at maximum dose of 20 mg within 15 hours after onset of symptoms. At least 1-order improvement was achieved in 76.2% of patients received intra-arterial tPA plus conventional therapy whereas in 33.3% of patients received conventional therapy alone.[55] In multicenter, randomized, controlled EAGLE study (Europe), intra-arterial tPA was compared with conventional therapy including hemodilution, ocular massage, IOP reduction, intravenous heparin and daily aspirin regarding effectiveness in 82 CRAO patients with symptom duration less than 20 hours.[65] Intra-arterial tPA was given via ophthalmic or external carotid artery at initial dose of 15 mg (maximum 50 mg). At least 3-orders visual gain was observed in 57.1% of the patients in the thrombolysis group and 60% of the patients in the conventional therapy group, indicating no significant difference. However, complications including intracranial hemorrhage, hemiparesis, headache, dizziness, epistaxis, oral hemorrhage and post-procedural hemorrhage were observed in 4.3% and 37.1% of the patients in the conventional therapy and thrombolysis groups, respectively. The study was prematurely stopped due to lack of significant difference in visual acuity and high complication rates in the thrombolysis group.

As similar to EAGLE study, no significant effect of intravenous tPA was detected on visual acuity in CRAO in placebo-controlled study.[66] Intravenous tPA (via infusion over 1 hour) was given to 8 patients within 6 hours after symptom onset while intravenous saline infusion was given to controls. At week 1, at least 3-orders visual gain was detected in 2 of 8 patients (25%) in tPA group while no such gain was recorded in the control group. However, it was seen that visual gain did not persist on month 6 and visual acuity was comparable to those at baseline in all patients in the thrombolysis group. In addition, in one patient, intracranial hemorrhage occurred on minute 45 of tPA infusion.

tPA infusion hasn't been included in CRAO treatment guidelines due to uncertainty about its effectiveness in retrospective and observational studies, high risk for adverse effect, lack of definitive dose and duration.[67] Although studies reporting visual gain in CRAO by early use of tPA (within 6 hours after symptom onset) have been published in the literature, there is a need for further studies to confirm effectiveness of intravenous or intra-arterial tPA.[52,66-68] Unfortunately, it is challenging to conduct these studies due to rarity of CRAO and delayed presentation of patients.

CONCLUSION

Although effects of acute treatments used in CRAO on visual acuity could not be demonstrated, thrombolysis

remains to be promising. However, based on current literature, one should focus on acute cerebral infarct that may accompany to CRAO and investigate cardiovascular risk factors in a patient with CRAO. In order to prevent events that may occur in early phase such as acute myocardial infarction, acute cerebral ischemia or vascular death, most important step is to approach CRAO patients as a medical emergency. Thus, the most appropriate approach to management of CRAO patient is to refer a neurologist as soon as possible and follow patient for retinal ischemic complications which may occur in the course of disease.

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