REVIEW ARTICLE

Treatment outcomes on neovascularization after CRAO treated with hyperbaric oxygen

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ABSTRACT

Central retinal artery occlusion (CRAO) is a condition that causes sudden vision loss due to obstruction of the retinal artery, typically from a thrombotic or embolic source. It is often associated with atherosclerotic risk factors, including cardiovascular disease, diabetes, hyperlipidemia, and a history of cerebrovascular disease. CRAO often leads to a poor visual outcome as well as neovascularization of the iris, retina, and optic disc, which can exacerbate vision loss and cause pain. While there are several treatment modalities for CRAO, few have been proven to be effective in decreasing the effects of neovascularization.

The use of hyperbaric oxygen (HBO_2) therapy is often used in the treatment of CRAO due to its ease of use and relatively benign side effect profile. This study aims to assess the degree of improvement in visual acuity (VA) and neovascularization following HBO_2. Our data ultimately shows that 20% of patients developed neovascularization after HBO_2 compared to 29.8% of those who did not undergo HBO_2 ($p<.05$). Our findings suggest that HBO_2 has a statistically significant protective effect against neovascularization and may improve long-term visual acuity.

INTRODUCTION

Central retinal artery occlusion (CRAO) is a disease of the eye that causes sudden vision loss due to obstruction of the central retinal artery, typically from a thrombotic or embolic source. The source of the thrombus or embolus is thought to be from an atherosclerotic plaque, carotid stenosis, vasculitis, or cardiac abnormality. Occlusion of the central retinal artery, a branch of the ophthalmic artery, results in ischemia of the inner retinal layers, leading to acute and painless vision loss.

The incidence of CRAO is estimated to be 0.85 in 100,000 [1] and it is typically found in individuals with atherosclerotic risk factors including cardiovascular disease, diabetes, hyperlipidemia, and a history of cerebrovascular disease [2]. Upon presentation to a medical provider 74% of patients with CRAO have visual field defects and a visual acuity of 20/200 or worse [2]. CRAO has a low probability of spontaneous recovery, and every effort should be made to reverse occlusion within the first 100 minutes of symptom onset to prevent permanent retinal damage [3]. A study by Hayreh et al. induced a CRAO in hypertensive and atherosclerotic rhesus monkeys by clamping of the central retinal artery. This established that occlusion lasting longer than four hours produced complete and irreversible retinal ischemia [3]. One reason for preservation of vision in a CRAO is the presence of a cilioretinal artery (CA) which supplies the fovea and may be present in up to 49.5% of the population. The CA is typically a branch of the short posterior ciliary arteries as opposed to the central retinal artery, which is a branch of the ophthalmic artery. The presence of a cilioretinal artery, in addition to incomplete occlusion of the central retinal artery, may explain why some patients have more favorable visual outcomes with artery occlusions of more than four hours [4].

Without intervention, 90% of individuals with CRAO will not have significant improvement in their vision [2]. Along with loss of vision CRAO is associated with neovascularization of the iris, retina, and optic disc. Ocular neovascularization is due in part to production of vascular endothelial growth factor (VEGF) from ischemic retinal tissue, often leading to angiogenesis.

KEYWORDS: central retinal artery occlusion; hyperbaric oxygen therapy; neovascularization; visual acuity

Neovascularization can exacerbate vision loss by causing vitreous hemorrhage or lead to pain secondary to neovascular glaucoma. Neovascularization has been reported in 2.5% to 31.6% of cases and can occur between two weeks to two years following artery occlusion [5,6].

One of the most challenging aspects of treating CRAO is the lack of consensus of appropriate treatment protocols. Currently there are several treatment modalities, including ocular massage, hyperbaric oxygen (HBO_2) therapy, inhalation of 10% carbon dioxide, sublingual isosorbide dinitrate, intravenous acetazolamide, intravenous mannitol, corticosteroids, thrombolytics, and a variety of anticoagulants [1]. These treatments have questionable efficacy, along with numerous side effects.

HBO_2 is commonly used in the treatment of CRAO due to its ease of use and relatively benign side effect profile. In HBO_2, a pressure chamber delivering 100% oxygen under increased atmospheric pressures is employed. It allows for increased oxygenation of the retina via the surrounding choroidal blood supply. The retina can be subdivided into two layers: the inner and outer retinal layers. The blood supply to inner retina comes from the central retinal artery, while the outer retina is supplied by the choroidal plexus. HBO_2 increases the oxygen delivery to the choroidal plexus until recanalization of the central retinal artery occurs. This increased oxygenation is thought to decrease edema and preserve tissue that borders the ischemic area [5,7]. Increased oxygenation is also thought to downregulate genes related to angiogenesis, including VEGF and erythropoietin, which may subsequently decrease the risk of neovascularization [8].

In addition to CRAO HBO_2 has been used in other forms of ischemic retinopathies, as seen by Ricci and Calogero. This was an experimental study that compared the effects of prolonged normobaric and hyperbaric oxygen on retinal vessels of newborn rats. Rats that were exposed to hyperbaric oxygen at 1.80 atm had no evidence of peripheral retinopathy or neovascularization, compared to the litters that received normobaric oxygen, which had severe retinopathy and extraretinal proliferation. This study by Ricci and Calogero supports the notion that HBO_2 has protective effects against neovascularization [9].

This study aims to assess the degree of improvement of visual acuity and neovascularization following HBO_2 in the setting of a CRAO.

METHODS

This retrospective study was reviewed by an accredited Institutional Review Board (IRB) and granted exempt status according to federal regulations. Health Insurance Portability and Accountability Act compliance was adhered to throughout this study. Using the "SlicerDicer" function of our electronic medical record, EPIC, we identified 123 patients with a diagnosis of CRAO (123 eyes) between August 2012 and August 2017. Of those charts reviewed 62 patients met the inclusion criteria, which was a documented clinical diagnosis of CRAO made by a practicing ophthalmologist. Charts that had incomplete information, unclear diagnosis, presence of neovascularization prior to occlusion, or presence of branch retinal artery occlusion were excluded. Other etiologies for artery occlusion were also excluded, including: vein occlusions, proliferative diabetic retinopathy, ocular ischemic syndrome, and uveitis.

Visual acuity (VA) was measured at various times, but each patient had VA assessed at their initial presentation, a subsequent VA measured within seven days of symptom onset, followed by a measurement within one to 12 months. Patients' subsequent VAs were placed into one of four categories:

1) Significant improvement was defined as vision improved from no light perception (NLP), light perception (LP), hand motion (HM), or count fingers (CF) to a VA of 20/50 or better.
2) Moderate vision improvement was defined as vision that improved to no better than 20/60.
3) Worsening vision was defined as vision that had a decrease in best corrected visual acuity (BCVA).
4) No change in vision was defined as no altered BCVA from symptom onset.

The charts were reviewed for complications of neovascularization of the iris (NVI), neovascularization of the angle (NVA), neovascularization of the optic disc (NVD), neovascular glaucoma (NVG), and time to onset of neovascularization following the diagnosis of CRAO. Neovascular glaucoma was defined as NVI or NVA with an intraocular pressure (IOP) greater than 22 mmHg without any prior history of elevated ocular pressure or glaucoma (Table 1).

A statistical analysis was performed using a chi-squared test to compare the rate of neovascularization in those who received HBO_2 to those without HBO_2.

Table 1: Patient visual acuity and characteristics in those who developed neovascularization

patient number	age	presenting VA	final VA	# HBO_2 sessions	type of NV	time to NV onset
1	50	20/300	20/500	0	NVI, NVD	31 days
2	60	CF	CF	0	NVI,NVA	30 days
3	89	NLP	NLP	0	NVA, NVG	86 days
4	78	HM	HM	0	NVI,NVA, NVG	40 days
5	94	LP	LP	0	NVA, NVG	20 days
6	88	LP	LP	0	NVI, NVA	40 days
7	80	HM	HM	0	NVI, NVA	34 days
8	59	NLP	NLP	0	NVI, NVG	21 days
9	80	20/300	NLP	0	NVI, NVA	28 days
10	75	NLP	NLP	0	NVI	17 days
11	86	20/150	20/200	0	NVI, NVA, NVG	36 days
12	82	20/500	CF	0	NVI, NVD, NVA	29 days
13	67	20/800	HM	0	NVD	131 days
14	56	20/400	NLP	0	NVI	15 days
15	66	HM	CF	3	NVI, NVA, NVG	45 days
16	75	NLP	HM	7	NVI, NVD	25 days
17	76	LP	CF	3	NVI	28 days

VA - visual acuity; HBO_2 - hyperbaric oxygen therapy; NV - neovascularization;
NVI - neovascularization of the iris; NVD - neovascularization of the disc; NVG - neovascular glaucoma;
NVA - neovascularization of the angle; CF - count fingers; NLP - no light perception; HM - hand motion

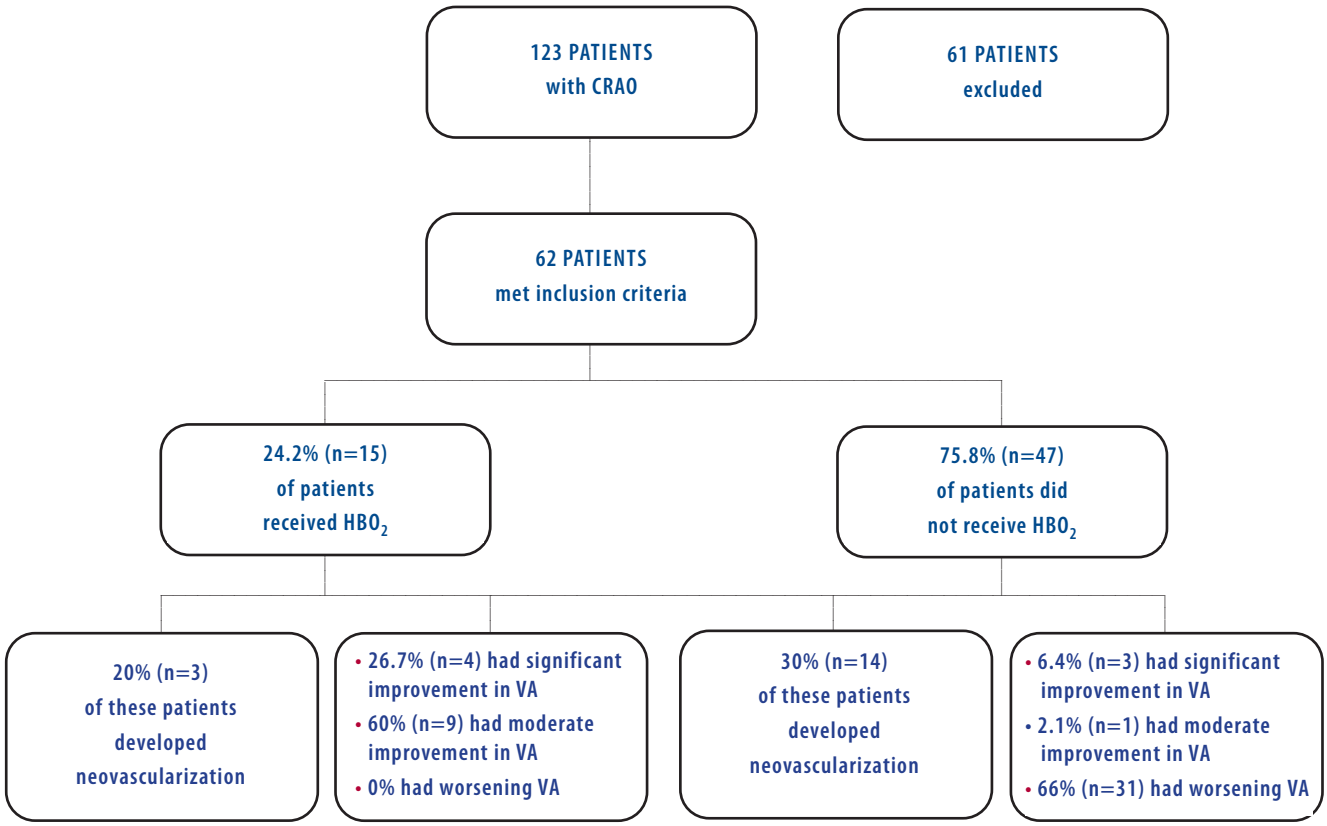
RESULTS

A total of 62 of 123 patients with the diagnosis of CRAO met the inclusion criteria. The mean age at presentation was 67 years old, ranging from 31 to 94 years of age; 27% (n=17) of patients meeting the inclusion criteria had ocular neovascularization (Figure 1). Of the patients with neovascularization 82.4% (n=14) had NVI, 58.8% (n=10) had NVA, 35.3% (n=6) had NVG, and 23.5% (n=4) had NVD. The average time for onset of neovascularization secondary to CRAO was 38.59 days, ranging from 15 to 131 days from the date of presentation (Table 1). In our cohort, 76% (n=47) had a history of hypertension, 50% (n=31) had a history of diabetes mellitus, 69% (n=43) had a history of hyperlipidemia, 32% (n=20) had greater than a 10 pack year smoking history, 26% (n=16) had a history of a cerebrovascular accident, and 34% (n=21) had a prior history of carotid artery stenosis.

Of the patients diagnosed with CRAO, 24% (n=15) underwent HBO_2 treatment. Of the patients who underwent HBO_2, 20% (n=3) had neovascularization, with an average time to onset of 32.7 days. All three patients had NVI, one patient had NVD, and one patient developed NVA and NVG. Of the patients who received HBO_2 26.7% (n=4) had significant improvement in VA, 60% (n=9) patients had moderate improvement in VA, 0% (n=0) patients had worsening VA, and 13.3% (n=2) of patients had no change in their VA when compared to their initial presentation (Figure 1, Table 2).

A total of 75.8% (n=47) of patients diagnosed with CRAO did not undergo HBO_2. Of these patients 6.4% (n=3) had significant improvement in VA, 2.1% (n=1) had moderate improvement in VA, 25.5% (n=12) had worsening VA, and 66% (n=31) had no change in VA between 1 and 12 months. Of the patients who did not undergo HBO_2, 29.8% (n=14) developed neovascularization, with an average time to onset of 39.9 days. Of the patients who had neovascularization and no HBO_2 78.6% (n=11) had NVI, 64.3%(n=9) had NVA, 35.7% (n=5) had NVG, and 21.4% (n=3) had NVD. Overall, 20% of patients developed neovascularization after HBO_2 compared to 29.8% of those who did not undergo HBO_2 ($p<.05$).

Figure 1: Patient status after initial presentation



CRAO - central retinal artery occlusion; VA - visual acuity; HBO2 - hyperbaric oxygen therapy

DISCUSSION

CRAO often leads to sudden monocular vision loss that can be further complicated by neovascularization of the iris, retina, optic disc, and anterior chamber angle. While numerous treatment modalities exist for CRAO, few have been shown to reduce subsequent neovascularization.

Neovascularization is an important prognostic factor, as it may further worsen visual acuity and induce pain secondary to neovascular glaucoma [5]. In this study neovascularization occurred in 27% of the patients diagnosed with CRAO, which falls in the reported frequency of 2.5% to 31.6% [6]. In our cohort, evidence of neovascularization occurred on average within 38.0 days and in the range of 15 to 131 days, which is comparable to other studies that have an average onset of 30.7 to 59.5 days ranging from the date of presentation to 137 days [6,10].

Of the patients diagnosed with CRAO there was a predisposition to those who were middle-aged or older (average age of 66) and those who had vasculopathic risk factors including: hypertension, diabetes, hyperlipidemia, and an extensive smoking history. These risk factors are comparable to a study done by Callizo et al., which identified 84 patients with a CRAO with a mean age of 62.2 years, 67% of whom had cardiovascular risk factors in their medical history, 73% had hypertension, and 40% had carotid artery stenosis of at least 70% [11].

In our cohort 24.1% (n=15) of the patients diagnosed with CRAO who met the inclusion criteria received HBO_2. Of those patients only 20% had ocular neovascularization compared to 29.8% of patients who did not receive HBO_2. Of the patients who received HBO_2 86% had moderate to significant improvement in VA compared to 8.5% patients who did not receive HBO_2. Also,

Table 2: Initial and final visual outcomes in CRAO patients who received HBO_2

patient number	age	sex	presenting VA	final VA	# HBO_2 sessions	type of NV
1	66	M	HM	CF	3	NVI, NVA, NVG
2	75	F	NLP	HM	7	NVI, NVD
3	76	F	LP	CF	3	NVI
4	60	M	HM	20/100	2	none
5	76	F	HM	CF	1	none
6	86	M	HM	CF	8	none
7	76	F	HM	CF	2	none
8	69	F	CF	20/80	2	none
9	70	M	NLP	CF	3	none
10	73	M	CF	CF	9	none
11	61	M	CF	CF	7	none
12	41	M	CF	20/25	5	none
13	51	M	HM	20/40	4	none
14	56	F	CF	20/20	5	none
15	74	F	HM	20/50	5	one

VA - visual acuity; HBO_2 - hyperbaric oxygen therapy; NV - neovascularization; NVI - neovascularization of the iris; NVD - neovascularization of the disc; NVG - neovascular glaucoma; NVA - neovascularization of the angle; CF - count fingers; NLP - no light perception; HM - hand motion

0% of patients who received HBO_2 had worsening VA compared to 66% of patients who did not receive HBO_2 (Figure 1). This suggests that HBO_2 is more likely to improve long-term VA. Our study suggests that HBO_2 reduces the risk for neovascularization and is protective against worsening VA as compared to patients who do not receive HBO_2.

There are numerous reports of HBO_2 effectively treating CRAO [1,12]. Weinberger et al. present a retrospective study of 21 patients with CRAO who underwent HBO_2. They found that 19 patients had a subjective improvement in VA and an objective improvement in 13 patients. None of the patients had a worsening VA following HBO_2 as compared to initial presentation [12]. This is similar to the patients in our cohort who underwent HBO_2, as their VA either improved or remained the same, but did not worsen.

Cope et al. present a case series of 51 patients with a retinal artery occlusion treated with HBO_2: 74% of patients had improvement in VA, with 53% of patients improving two lines or greater on a modified Snellen value. Improvement in visual acuity was seen between eight hours and six days following HBO_2 [13]. Our data show a slightly greater amount of improvement, with 86.7% of patients who received HBO_2 having an improvement in their VA. The range of time to visual acuity improvement in our cohort was significantly greater, ranging from 12 hours to 60 days.

While our data show that HBO_2 is somewhat protective against neovascularization, it does not fully prevent it, as 20% of our patients subsequently had neovascularization following HBO_2 treatment. Tang et al. present a case report of a patient who had neovascularization following HBO_2. The patient presented to the emergency department with a CRAO. Gonioscopy indicated that the right eye angle was open to trabecular meshwork without neovascularization. Later, 24 hours after the patient was discharged he returned to his ophthalmologist complaining of ocular discomfort. Gonioscopy indicated neovascularization of the iris and angle [5]. While HBO_2 may help prevent neovascularization, subsequent follow-up is still necessary to monitor for any change in the vasculature of the affected eye.

While our data support the notion of HBO_2 leading to a better visual prognosis, there are complications associated with treatment. Systemic side effects of

HBO_2 include: barotrauma to organs such as the cranial sinus or the lung; seizures secondary to oxygen toxicity; and temporary lung dysfunction. Ophthalmologic complications are rare but include: narrowing of visual fields, nuclear cataract formation due to oxidative stress, and retinal toxicity from hyperoxia [14].

Limitations

The limitations of this study include lack of consistency in HBO_2 protocol, including time to initiation of treatment following diagnosis of CRAO and total number of treatments of HBO_2, which make it difficult to fully assess the effectiveness of HBO_2. While each patient had a unique treatment protocol, all patients received HBO_2 within 15 hours of symptom onset, which follows the current protocol by the Undersea and Hyperbaric Medical Society of initiating therapy within the first 24 hours [15]. In addition, the time to onset of neovascularization is dependent on frequency of follow-up visits scheduled by an ophthalmologist as well as patient compliance with follow-up and treatment protocol. The documented "days to onset of neovascularization" is most likely an overestimate, as daily visual acuity assessments are not performed. This is a non-randomized, non-controlled study and a single-center or multicenter trial could be considered.

This study is unique in that it is the largest of its size to analyze the effects of HBO_2 on neovascularization. Our data support the notion that HBO_2 has some protective effect against neovascularization and may improve long-term VA. While not all patients will have a significant improvement in their vision with HBO_2, the likelihood of worsening VA is much lower as compared to individuals who do not undergo therapy.

Conflict of interest statement:
The authors have declared no conflicts of interest.

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