Hyperbaric oxygen therapy for non-arteritic central retinal artery occlusion: efficacy of combined treatment with anterior chamber paracentesis

Ozlem Eski Yucel[1], *Muhiddin Fatih Bodur*[2], *Semih Murat Yucel*[3]

ABSTRACT

Purpose: To evaluate the efficacy of hyperbaric oxygen (HBO) for the treatment of non-arteritic central retinal artery occlusion (NA-CRAO, CRAO).

Materials and Methods: The records of patients diagnosed with CRAO between January 2017 and April 2023 at XXX Hospital were retrospectively reviewed. Treatments and detailed ophthalmological examination findings at the baseline and post-treatment follow-up of the patients were recorded. After ocular massage and acute antiglaucomatous treatment; the patients were divided into 3 groups, as group 1 received HBO therapy after anterior chamber paracentesis (ACP), group 2 received only HBO therapy, group 3 received only ACP. Data were analysed with the IBM SPSS Statistics 22 program using non-parametric tests.

Results: Thirty-four patients with a median age of 72 (28-92), 12 (35.3%) women and 22 (64.7%) men, were included in the study. There were 10, 14, and 10 patients in groups 1, 2 and 3, respectively. The groups were similar in terms of age, gender, systemic diseases and time of admission (p >0.05). In groups 1, 2 and 3: baseline median visual acuity (VA) was 2.3 (2.3-3.0), 2.3 (1.3-3.0), and 2.3 (1.3-3.0) logMAR (p =0.573); the median VA at last visit was 1.9 (0.3-3.0), 1.9 (0.3-3.0), and 2.5 (1.3-3.0) logMAR (p =0.624), respectively. Only in group 1, the final VA increased significantly from baseline (p =0.035), while no significant change in VA was observed in the other groups (p =0.138 and p =0.786 for groups 2 and 3, respectively). Final VA was moderately positively correlated with baseline VA (r =0.425, p =0.012) and moderately negatively correlated with time of admission (r =-0.381, p =0.026).

Conclusion: HBO therapy combined with ACP applied in the early period in the treatment of CRAO positively affects the visual prognosis.

Key words: Hyperbaric oxygen, anterior chamber paracentesis, central retinal artery occlusion, CRAO.

INTRODUCTION

Central retinal artery occlusion (CRAO) is an ophthalmological emergency that can cause severe visual impairment.[1,2] Non-arteritic CRAO accounts for the majority of cases, which develops due to thrombosis or embolism resulting in sudden, painless severe vision loss. The main sources for embolus include stenosis and plaques in the carotid arteries. Albeit rare, cardiac embolism is a significant source for retinal emboli[3,4] In addition, it was found that the prevalence of diabetes mellitus, primary hypertension, ischemic heart disease, cerebrovascular events, and smoking were higher than the general population.[3,4] The central retinal artery and its branches supply the inner layers of retinal tissues; and the occlusion in central retinal artery leads to retinal ischemia and infarction. Since the retina is one of the most metabolically active tissues in the body, it is highly susceptible to hypoxia and ischemia.[5] In studies on rhesus monkeys with atherosclerosis and hypertension, it was shown that retinal artery occlusion ≥240 minutes resulted in nerve fiber damage and optic nerve atrophy.[6] Therefore,

1- Doç. Dr., Göz Hastalıkları, Ondokuz Mayıs Üniversitesi Tıp Fakültesi, Samsun, Türkiye

2- Asist. Dr., Göz Hastalıkları, Ondokuz Mayıs Üniversitesi Tıp Fakültesi, Samsun, Türkiye

3- Doç. Dr., Kalp Damar Cerrahisi, Tıp Fakültesi, Ondokuz Mayıs Üniversitesi, Samsun, Türkiye

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Correspondence author:
Ozlem Eski Yucel
Email: drozlem38@hotmail.com

rapid diagnosis and treatment are crucial in minimizing permanent damage in this group of patients.

Currently, there is no definitive treatment with proven efficacy for CRAO. Conventional non-invasive treatments are based on the principles of theoretical removal of emboli and elevation of retinal vascular perfusion pressure. These treatments include ocular massage, topical anti-glaucomatous drops oral acetazolamide, intravenous mannitol, or anterior chamber paracentesis (ACP) to reduce intraocular pressure; and vasodilation of the central retinal artery (CRA) using methods such as sublingual isosorbide dinitrate, or carbogen inhalation. Invasive methods include intravenous or intra-arterial thrombolysis with recombinant tissue plasminogen activator (tPA) and surgical techniques aimed to remove emboli. In the literature, contradictory outcomes have been reported with various treatment modalities.[4,7,8]

Hyperbaric oxygen (HBO) therapy is a treatment method that involves providing 100% oxygen in a high-pressure environment. In accordance to the indications determined by the Undersea and Hyperbaric Medical Society (UHMS) and the European Committee for Hyperbaric Medicine (ECHM), retinal artery occlusion is among indications for clinical applications involving HBO therapy in our country.[9] In retinal artery occlusion, the rationale underlying HBO therapy is based on the theory that the increased oxygen levels in the choroidal circulation supplying the outer layers of the retina will facilitate the oxygen diffusion from choroidal capillaries to the inner retinal layers, maintaining enabling viability to some extent, when the central retinal artery (CRA) is occluded. However, there is ongoing debates regarding the efficacy of HBO therapy on the final visual outcomes. In this study, we aimed to evaluate the treatment effectiveness in patients who presented with CRAO and underwent HBO therapy.

MATERIALS AND METHODS

This retrospective study was conducted at Ondokuz Mayıs University Hospital. The study was approved by Ethics Committee of Ondokuz Mayıs University on Clinical Research. It was conducted in accordance to tenets of Helsinki Declaration.

We retrospectively reviewed the files of patients who were diagnosed with CRAO at Ondokuz Mayıs University, Medicine School between January, 2017 and April, 2023. The study included the patients with non-arteritic CRAO who had at least one follow-up examination and received HBO therapy after initial assessment. The patients with arteritic CRAO, combined arterial and venous occlusions, and those with incomplete data were excluded.

In all patients, the demographic characteristics , ocular and systemic diseases, treatments received, and the baseline and post-treatment follow-up measurements, including visual acuity (VA, LogMAR), intraocular pressure (Goldmann Applanation Tonometry), anterior segment, and fundus examination findings, were recorded. Then, the patients were classified into three groups based on the treatments given: Group 1, those received Oxygen Concentration Therapy (OCT) followed by Hyperbaric Oxygen (HBO) Therapy; Group 2, those received HBOT alone; and Group 3, those received OCT alone. The final VA and the changes in VA were compared among groups.

HBO Therapy

Before Hyperbaric Oxygen (HBO) therapy, the patients were evaluated for contraindications to the treatment. CBC (complete blood count) and anteroposterior chest X-rays were performed to assess presence of acute infections and pulmonary pathology. The patients eligible who accepted the treatment underwent acute intervention for SRAT (Sudden Retinal Artery Thrombosis) before referral to HBO therapy center. The acute intervention included intermittent ocular massage (every 15 minutes) together with intravenous 20% mannitol infusion (1g/kg over 15 minutes), acetazolamide (500 mg via oral route), topical anti-glaucomatous eye drops, and in some cases, Oxygen Concentration Therapy (OCT) to reduce intraocular pressure (IOP). The patients were transferred to HBO therapy center as soon as possible after acute intervention. The HBO therapy was administered in a multi-place pressure chamber at 2.4 ATA (1 ATA, atmosphere absolute = 760 mmHg) for a total of 20 sessions (one session per day on weekdays). Each session included breathing of 100% oxygen with 5-minute air breaks; overall 90 minutes of oxygen inhalation per session was administered.

Statistical Analysis

Data were analyzed using IBM SPSS version 22.0. The normality of data distribution was assessed using the Shapiro-Wilk test. Non-parametric tests were used due to skewed data. The Kruskal-Wallis and Mann-Whitney U tests were used to assess continuous independent variables while the Chi-square test for categorical variables and the Wilcoxon signed-rank test for dependent variables. Spearman's correlation test and linear regression analysis were used to evaluate the factors influencing final visual

acuity (VA) and changes in VA . The results are presented as median (minimum-maximum) and frequency (%). A p value <0.05 was considered as statistically significant.

FINDINGS

Overall, the study included 34 patients (12 women [35.3%], 22 men [64.7%]) with a median age of 72 (28-92). There were 10, 14, and 10 patients in groups 1, 2 and 3, respectively. The groups were comparable regarding age, gender, systemic diseases and time of presentation (p >0.05). The time from onset of vision loss and presentation was shorter in group 1 when compared to Group 2 and 3; however, the difference did not reach statistical significance (p=0.099). Table 1 presents demographic and clinical characteristics in the study groups.

It was found that the baseline median VA was 2.3 (2.3 - 3.0), 2.3 (1.3 - 3.0), and 2.3 (1.3 - 3.0) logMAR in the groups 1, 2, and 3 respectively (p = 0.573). At the final visit, the median VA was 1.9 (0.3 - 3.0), 1.9 (0.3 - 3.0), and 2.5 (1.3 - 3.0) logMAR in the groups 1, 2 and 3 respectively (p = 0.624). Only in group 1 was the final VA significantly improved compared to the baseline (p = 0.035), while no significant changes were observed in the other groups (p = 0.138 and p = 0.786 for groups 2 and 3, respectively). When all patients who underwent HBO therapy were pooled, it was found that the difference between the baseline (2.3 logMAR) and final (1.9 logMAR) VA remained to be statistically significant (p = 0.015). The proportion of patients with improved VA was 70% in group 1, 57.1% in group 2, and 30% in group 3 (p = 0.077).

The final VA showed a moderate positive correlation with the baseline VA (r = 0.426, p = 0.012); however, there was no significant correlation between the final VA and age (p = 0.937), gender (p = 0.957), or time to presentation (p = 0.752). The change in VA showed a moderate negative correlation with the time to presentation (r = -0.314, p = 0.040) but there was no significant correlation between the change in VA and age (p = 0.874), gender (p = 0.802), or initial VA (p = 0.097). Since there was a correlation between the final and initial VA, the initial VA was included to linear regression model as the most important predictor variable (Table 2, Model 1). In addition, age, gender, and time to presentation were added to the model as other independent variables potentially related to final VA (Table 2, Model 2). It was found that the initial VA was a prognostic factor for the final VA [0.79 (0.29-1.28), p = 0.03] but the time to presentation, age, and gender had no influence on visual prognosis (Table 2).

At final visit, the median intraocular pressures was 14 (10 - 22) mmHg, 12 (8 - 16) mmHg, and 13 (9 - 17) mmHg in groups 1, 2, and 3, respectively (p = 0.436). No adverse effect related to HBO therapy were reported.

DISCUSSION

Table 1: *Baseline demographic and clinical characteristics. Results are presented as median (min-max) or n (percent).*

	Group 1 n =10	Group 2 n =14	Group 3 n =10	p
Age (years)	68,5 (44 - 81)	69,5 (28 - 83)	79,5 (63 - 92)	0,076
Sex (F/M)	4 (40) / 6 (60)	4 (28,6) / 10 (71,4)	4 (40) / 6 (60)	0,790
Systemic disease				
HT	5 (50)	6 (42,9)	4 (40)	0,897
DM	3 (30)	3 (21,4)	1 (10)	0,540
HL	1 (10)	3 (21,4)	1 (10)	0,651
CAD	2 (20)	4 (28,6)	4 (40)	0,615
CaD	1 (10)	3 (21,4)	2 (20)	0,749
CA	3 (30)	1 (7,1)	1 (10)	0,262
Time of presentation (days)	1 (1 - 2)	1 (1 - 5)	1,5 (1 - 6)	0,099
VA (logMAR)	2,3 (2,3 - 3,0)	2,3 (1,3 - 3,0)	2,3 (1,3 - 3,0)	0,573
OT (mmHg)	15,5 (11 - 22)	12 (7 - 16)	12 (7 - 22)	0,055
Follow-up duration (months)	5 (1 - 12)	2 (1 - 22)	1,5 (1 - 70)	0,601

F =Female; M =Male; HT =Hypertension; DM =Diabetes Mellitus; HL =Hyperlipidemia; CAD =Coronary artery disease; CaD =Carotid artery disease; CA =Cancer; VA =Visual acuity; OT =Ocular Tension; p =Kruskal-Wallis Test or Chi-Square Test.

Table 2: *Linear regression analysis of factors influencing on final visual acuity.*

Model		B	Standard Deviation	β	t	p	95% confidence interval for B	
							Lower limit	Upper limit
1	Constant	.563	.558		1.009	.321	-.574	1.700
	Baseline visual acuity	.627	.236	.425	2.656	.012*	.146	1.107
2	Constant	-.516	1.040		-.496	.624	-2.642	1.611
	Başlangıç Baseline visual acuity	.786	.244	.533	3.223	.003*	.287	1.284
	Age	.005	.009	.086	.511	.613	-.014	.024
	Sex	.037	.247	.024	.151	.881	-.469	.544
	Time of presentation	.189	.105	.308	1.798	.083	-.026	.405

R^2 =0.181 (p =0.012) for Model 1; R^2 =0.286 (p =0.253); Constant =Final visual acuity

In this study, the efficacy of Hyperbaric Oxygen Therapy (HBO) therapy added to conventional emergency treatments such as ocular massage and the use of anti-glaucomatous agents to reduce intraocular pressure was evaluated in cases of Sudden Retinal Artery Thrombosis (SRAT). Since some patients also received (OCT) in our study, the cases that received OCT alone were considered as the control group while the cases received HBO therapy were divided into two groups: those who received OCT plus HBO therapy, and those received HBO therapy alone. It was found that the baseline and final visual acuity (VA) were similar across all cases. While the change in VA was not statistically significant in patients received either OCT or HBO therapy alone, it was found to be significantly increased only in patients who received the HBO therapy plus OCT.

Hayreh et al. evaluated CRAO cases in different subgroups, reporting that that VA was hand motion or worse in 49% of the eyes diagnosed with AO-CRAO in the absence of cilioretinal artery, with some cases having potential of complete loss in light perception.[8] There is ongoing research efforts for an effective treatment for the condition with very poor visual prognosis. Based on fundus photography and fluorescein angiography, it has been reported that one or more cilioretinal arteries are present in 32% of all eyes, and in most cases, these arteries contribute to the perfusion of the fovea and perifoveal area.[11] Such cases have a relatively better visual prognosis.[4-8] None of the cases had a cilioretinal artery in our study.

It has been suggested that HBO therapy may limit ischemic retinal damage in the period between the onset of CRAO and retinal artery recanalization occurring within 72 hours. The HBO therapy exerts its effect via provision of effective oxygen diffusion by increasing the oxygen concentration and partial pressure in the blood and all tissues in the body. A vasoconstriction of 20% occurs in the boy with HBO therapy. Although the blood amount supplied to the tissues decreases, the tissue oxygenation is enhanced due to the increase in dissolved oxygen in the plasma. Vasoconstriction also reduces edema due to hypoxia and ischemia.[12] The restoration of hypoxia as early as possible will prevent tissue damage by reducing ischemia and edema. The major effect HBO therapy on retinal artery occlusion may also manifest in such way. A prospective study including serial imaging with optical coherence tomography may be helpful to evaluate the effect of treatment on ischemic edema. However, there was no images obtained between HBO session in our patients due to retrospective nature of our study. Although tissue damage has been occurred due to acute, severe ischemia, damage to adjacent tissue areas affected partially from hypoxia can be prevented.[12] Masters et al. reported a trend to better visual outcome in patients who received HBOT within the first 12 hours after the onset of symptoms in CRAO. Authors suggested that there is a “penumbra” of salvageable marginal retinal tissue during this period and that rapid treatment may help to protect this tissue.[13] It has been shown that the partial oxygen pressure gradient is quite steep in choroid during hyperoxia, and that the choroid can deliver oxygen to the wider retinal areas under these conditions when compared in normoxic conditions.[14]

In recent years, retrospective case series have been published about HBO in the treatment of retinal artery occlusion. Masters et al. reported somewhat VA improvement in 28 (72%) of 39 patients with CRAT following HBO therapy twice a day over 5 days.[13] Complications such as barotrauma of middle ear and claustrophobia were

observed in patients.[15] Vincenzo et al. found that the mean VA was increased from 1.5 logMAR to 0.9 logMAR after HBOT therapy (twice a day for at least 15 days) given to 28 patients diagnosed with CRAO and retinal artery branch occlusion (RADT) presented within 7 days ($p = 0.001$). In addition, authors also reported high blood pressure and low baseline VA as poor prognostic factor in agreement with our study. Baglı et al., reported that the mean VA improved from 3 LogMAR to 1.8 LogMAR after 20 sessions of HBO therapy in 10 patients diagnosed with CRAO, ($p <0.05$).[16] Rozenberg et al. compared data from 121 patients diagnosed with AO-CRAO who received HBO therapy with those from 23 patients who received standard care at two distinct facilities.[17] Authors reported that the mean VA improved from 2.89±0.98 logMAR to 2.15±1.07 logMAR in patients received HBO therapy ($p <0.001$); however, there was no significant improvement in VA in patients received standard treatment. After adjusting for age, gender, and duration of symptoms, the final VA remained to be better in the in the HBO therapy group compared to the controls ($p = 0.023$). Although no significant VA improvement was achieved in the groups received HBO therapy alone and the OCT alone as standard treatment, a significant increase in VA was observed in the group received OCT plus HBO therapy in our study. However, lack of significant difference in VA change among groups might have been resulted from relatively small number of cases in the groups. When all patients received HBO therapy were assessed regardless of prior OCT, a significant increase in VA was found after HBO therapy.

In their meta-analysis on oxygen therapy in retinal artery occlusion, Wu et al. reported that the likelihood of visual improvement was 5.61 folds higher in patients who received oxygen therapy compared to those who did not.[18]Authors suggested that the type of artery occlusion (CRAO or BRAO), methods of oxygen inhalation, and whether combined treatment was applied had no influence on visual acuity (VA), but 100% oxygen or HBO therapy and duration of treatment (>9 hours) significantly improved VA. On contrary, in their meta-analysis, Rasignoli et al. reported that they observed no such effect although some individual studies indicated that early treatment with HBO in CRAO patients improved visual outcomes.[10] Authors also emphasized the need for large, randomized studies about systemic adverse effects.

In all CRAO cases, a comprehensive systemic evaluation, including carotid Doppler ultrasound/angiography and echocardiography, should be performed to reduce the risk for additional morbidity and mortality. One must investigate conditions such as hypertension, diabetes, hyperlipidemia, carotid artery disease, cardiovascular, and cerebrovascular diseases. However, such investigation should be performed after initiating treatment to avoid delaying therapy. Appropriate treatment should be recommended to reduce the risk of potential ischemic disease. Hayreh reported that VA improvement largely occurred within first 7 days in CRAO cases, with no additional improvement thereafter.[2,8] Authors reported spontaneous VA improvement in 22% of eyes with VA at finger count or worse in AO-CRAO. In our study, the VA improvement rate was slightly higher than the spontaneous improvement rate observed in the natural course of the disease (30%) in ACP group while it was markedly higher in the HBO therapy groups (70% and 57.1%), suggesting that HBO therapy can be considered as an effective treatment option.

Anterior chamber paracentesis is performed, aiming to increase SRA perfusion pressure by enabling an immediate, profound reduction in IOP. It is a straightforward procedure that can be performed an ophthalmologist using a syringe or knife via biomicroscopy in outpatient setting. Due to its invasive nature, there is a rare risk for complications such as traumatic cataract, hyphema, and endophthalmitis.[7] In our study, it was found that ACP alone led no significant change in VA with smaller proportion of patients who achieved VA improvement compared to the HBO therapy groups.

No adverse effect related to HBO therapy was observed in any patients included. Although the efficacy of HBO therapy is still controversial in retinal artery occlusion, it should be kept in mind that it has a more favorable side effect profile compared to invasive approaches such as fibrinolysis and surgical interventions and that it can be safely employed once contraindications are ruled out.

This study has some limitations due to its retrospective design: the time from onset of symptoms to treatment initiation was heterogeneous among patients; and no examinations or imaging study was performed between treatment sessions. Although the follow-up period was relatively long in the ACP and HBO treatment groups, there was no statistically significant difference in follow-up durations between the groups. Since no addition effort was planned to question treatment side effects, we solely reviewed data in patient files. The study included limited number of patients due to relatively low incidence and HBO therapy is employed in relatively smaller number of patient.

Our results support that HBO therapy, particularly when combined with ACP, had favorable effects on visual prognosis in the treatment of AO-CRAO. Initial VA is the most important determinant for final VA. The increase in visual acuity is positively correlated with the time from symptom onset to treatment, shorter duration means better visual acuity. We think that there is a need for multicenter, prospective studies with larger sample size.

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