

Hyperbaric oxygen therapy and age-related macular degeneration

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ABSTRACT

Age-related macular degeneration (AMD) is a significant cause of visual loss in the United States and Western Europe. As the population ages, the prevalence rate of advanced AMD is expected to double by 2030. A one-hour session of hyperbaric oxygen therapy (HBO₂) was used to treat a group of 14 patients with advanced AMD. Eight patients were treated at 1.75 ATA, and six patients were treated at 1.5 ATA for one hour. Significant improvements in visual acuity and/or visual field, with improvements in the activities of daily living were observed.

INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of visual loss in the developed world (1-5). AMD is characterized by degeneration of the macula, the area of the retina responsible for fine central vision. The earliest clinical feature of AMD is the development of drusen, which are extracellular deposits of glycoprotein, lipid and cellular debris inside Bruch's membrane of the retina and beneath the retinal pigment epithelium.

More than 1.8 million Americans have the advanced stage of AMD, which is defined by the Age-Related Eye Disease Study (AREDS) into two forms: a "wet," or neovascular form, characterized by the development of aberrant choroidal neovascularization, and a "dry" type, termed geographic atrophy (GA), characterized by the loss of photoreceptors and retinal pigment epithelium. The prevalence rates of advanced AMD are expected to double by 2030.

Approximately 70-80% of severe vision loss, defined as vision of 20/200 or worse (legal blindness), is caused by the neovascular type and 20-30% by GA. The term "legal blindness" is a government definition used for compensation purposes and does not necessarily reflect functional loss, including inability to read, contrast sensitivity loss, depression and the need for rehabilitative training.

Risk factors for the development of AMD are age, ethnicity, smoking, hypertension, diet and family history. Genetic studies have explained approximately 50% of the attributable risk of AMD. Recent studies have suggested an immunologic process in AMD pathogenesis, which includes the development of extracellular deposits, recruitment of macrophages, complement activation, microglial activation and accumulation, and effects of chronic inflammation by *Chlamydia pneumoniae*. Oxidative stress and hypoxia have also been implicated in the development of AMD (6-10).

Hyperbaric oxygen therapy (HBO₂) has many biologic effects including activation of endogenous antioxidants, decrease in lipid peroxidation, microbicidal actions, and as a regulator of inflammation (11), which may theoretically affect the development and/or progression of AMD. As hyperoxia has been shown to restore retinal oxygenation (12,13) and supplemental normobaric oxygen has resulted in improvements in vision in some cases of retinal artery occlusion (12,14), a lower pressure (1.5 or 1.75 ATA) rather than the UHMS-recommended 2.0 ATA for central retinal artery occlusion (12) seemed reasonable to use in this preliminary study. In addition, the retina is a neural tissue, and Holbach et al (15) reported that 1.5 ATA resulted in a nearly balanced cerebral glucose metabolism, whereas 2.0 ATA increased cerebral glycolysis considerably

and caused a disturbed oxidative energy formation. The lower ATAs and the one-hour treatment duration also minimized the risk of discomfort and complications in this elderly population of patients.

MATERIALS AND METHODS

Fourteen patients with a history of advanced AMD underwent an ophthalmic examination that included best-corrected visual acuity, intraocular pressure, biomicroscopic and dilated fundus examinations and ancillary testing, as indicated. Following medical screening for hyperbaric oxygen therapy (HBO₂) and informed consent, eight patients underwent one 60-minute session of HBO₂ at 1.75 ATA each day for four days, and six patients underwent one 60-minute session of HBO₂ at 1.5 ATA for six days. One patient from the 1.5 ATA group underwent an additional course of six HBO₂ treatments. All patients received 100% oxygen in a monoplace chamber.

Case 1. A 92-year-old woman with a three-year history of legal blindness having undergone one ranibizumab (Lucentis®) injection, (a vascular endothelial growth factor, or VEGF, inhibitor) in the right eye (OD) 13 months prior to this visit and laser photocoagulation 10 months earlier OD presented with a visual acuity of count fingers at 6 feet in each eye (OU). She underwent 4 HBO₂ sessions at 1.75 ATA and 2 days later her visual acuity had improved to 20/400 OU. Four months after the last HBO₂ treatment the visual acuity was 20/200 OD and 20/400 in the left eye (OS), which remained stable three months later (seven months after the last HBO₂ treatment).

Case 2. The 92-year-old mother-in-law of a local optometrist had a seven- to eight-year history of legal blindness OU secondary to AMD. The visual acuity at presentation was 20/200 in the OD and 20/400 OS. She underwent four HBO₂ sessions at 1.75 ATA, and though the visual acuity was unchanged three days later, the patient reported “brighter” vision in each eye. Her aide and her son-in-law both confirmed that the patient was now able to read large-print books and road signs and see her wristwatch for the first time in many years. They also noted that the patient was able to walk with

more confidence and was less afraid of stepping off a curb or a step. The reported visual improvement was stable seven months after the last HBO₂ treatment.

Case 3. This 81-year-old male was unaware that he had lost vision OD until he underwent an eye examination and was discovered to have a visual acuity of 20/200 OD secondary to GA. The visual acuity OS was 20/25. He underwent four HBO₂ treatments at 1.75 ATA, and two days later the visual acuity OD had improved to 20/70. There was no change in the visual acuity OS. One month later, the visual acuity had further improved to 20/60 OD and 20/20 OS.

Case 4. A 95-year-old woman with an 18-month history of legal blindness OU secondary to GA presented with a visual acuity of 20/400 OD and light perception vision secondary to an acute vitreous hemorrhage OS. She underwent four HBO₂ treatments at 1.75 ATA, and when she returned one week later the visual acuity had improved to 20/200 OD and was unchanged at light perception OS. The visual acuity OD remained stable 11 months later.

Case 5. A 92-year-old man with 20/400 acuity and a stable macular scar status-post-Lucentis® injection nine months earlier OD and 20/400 visual acuity secondary to anterior ischemic optic neuropathy OS underwent four HBO₂ treatments at 1.75 ATA. Though the visual acuity was unchanged at 20/400 OU, he reported an improvement in the quality of vision. The patient also stated that he experienced improvement in his daily activities, including reading the newspaper headlines and ambulation. These improvements were independently confirmed by his son. Four months after the last HBO₂ treatment the visual acuity had improved to 20/200 OD and was unchanged at 20/400 OS. There was no change in the vision five months later (nine months after the last HBO₂ treatment).

Case 6. A 92-year-old woman who had undergone injections for neovascular AMD had bilateral macular scars. Injections included pegaptanib (Macugen®), bevacizumab (Avastin®) and Lucentis® (all VEGF inhibitors) OD, with the last injection five months prior to this examination and one Avastin injection OS four months prior to this examination.

The macular scar was stable OD, there was persistent subretinal fluid OS, and the visual acuity was count fingers at 6 feet OD and 20/400 OS. The patient refused any further intravitreal injections and decided to undergo four HBO₂ treatments (1.75 ATA). Following the last treatment the visual acuity was unchanged OD and had improved 1 line to 20/200 OS, though subretinal fluid was still present by ocular coherence tomography. Two months later, the visual acuity was 20/400 OU.

Case 7. An 81-year-old female with 20/30 visual acuity in each eye and progressive GA with paracentral scotomas by visual field testing bilaterally underwent four HBO₂ treatments at 1.75 ATA. The visual acuity OS improved one line to 20/25, and there was an improvement in the visual field OD. The visual improvements were stable 17 months later.

Case 8. An 84-year-old woman with 20/30-2 visual acuity OD, 20/80-2 vision OS and significant visual field changes OS more prominent than OD secondary to GA underwent four HBO₂ treatments at 1.75 ATA. The visual acuity improved to 20/30+2 OD and to 20/60-2 OS. The visual field OS was unchanged, but there was significant improvement in the visual field OD. The patient relocated, and no follow-up information is available.

Case 9. An 86-year-old woman with 20/70-2 visual acuity OD, having received an intravitreal injection of Avastin three months earlier and a visual acuity of 20/20-2 OS, underwent six HBO₂ treatments at 1.5 ATA. There was no improvement in visual acuity, but there was a significant improvement in the visual field OD. Six weeks after the last HBO₂ treatment, the patient experienced a macular hemorrhage OD (unrelated to the HBO₂ treatment), with a reduction in visual acuity to 20/200+1.

Case 10. An 88-year-old man with 20/60-2 vision OD secondary to GA and a visual acuity of count fingers at 6 feet with a disciform scar OS underwent six HBO₂ treatments at 1.5 ATA. There was a significant improvement in the visual field in each eye. There was a further improvement in the visual field OS two months later.

Case 11. A 79-year-old female with a visual acuity of 20/40-2 OD and 20/50-2 OS secondary to GA underwent the prescribed course of six HBO₂ treatments at 1.5 ATA. The visual acuity OD was unchanged, the visual acuity OS improved to 20/40-2 OS and the visual field of each eye improved. She has not returned for subsequent examination.

Case 12. An 81-year-old female with a visual acuity of 20/60-2 secondary to GA OD and count fingers at 2 feet OS with a breakthrough vitreous hemorrhage from neovascular AMD underwent six HBO₂ treatments at 1.5 ATA. The visual acuity improved to 20/50+1 OD, with a significant improvement in the visual field OD. She underwent six additional HBO₂ treatments, and only a slight improvement in the visual field OD was noted. At the two-month follow-up visit, the visual acuity OD had slightly improved to 20/40-2.

Case 13. An 89-year-old female with a visual acuity of 20/100+1 OD and 20/400 OS secondary to GA underwent six HBO₂ treatments at 1.5 ATA. The visual acuity OD improved to 20/60+1 and OS improved slightly to 20/200-1, with a significant improvement of the visual field in each eye. The improvement was maintained at the six-week follow-up visit.

Case 14. An 89-year-old male with a visual acuity of 20/200 OU status – post one Avastin injection OD four years ago and four Avastin injections OS, with the last injection eight months prior to this examination – underwent six HBO₂ treatments at 1.5 ATA. An improvement in the visual field OD was noted. He has not yet returned for follow-up evaluation.

DISCUSSION

There were no complications, and the visual improvements appeared similar in the four treatments at 1.75 ATA group, compared to the six treatments at 1.5 ATA group. The improvement, whether in visual acuity or visual field, was maintained at subsequent follow-up visits. This is a preliminary study; it is possible that a greater number of HBO₂ treatments and a different ATA may have resulted in better visual results.

Vascular endothelial growth factor (VEGF) inhibitors are effective in the treatment of choroidal neovascularization and are injected directly into the eye (intravitreal injection). Though the optimal injection schedule for the best visual results has yet to be determined, early studies used four- to six-week dosing. Patients undergoing intravitreal injections understandably report discomfort and are at an increased risk of developing inflammation, retinal detachment and intraocular infection (endophthalmitis). Unfortunately, there has been no effective treatment to slow or halt the progression of GA.

With the advent of the VEGF inhibitors it has become apparent that converting the neovascular, or “wet,” type of AMD to the non-neovascular, or “dry,” type may not prevent the progressive loss of vision. There are several studies now under way to treat GA (16). In one study, AREDS2, lutein and zeaxanthin are added to the current AREDS formulation (vitamin/mineral supplement), which was shown to reduce the risk of progression to advanced AMD by 25 percent and the risk of moderate visual loss by 19 percent. Other work has centered on aberrant complement activity that may lead to inflammation, tissue damage and upregulation of angiogenic factors such as VEGF (6-10).

Visual loss from dry AMD is probably underestimated because the areas of atrophy resulting in central, ring and paracentral scotomas are not assessed. Patients may be able to read small letters on the eye chart, but not the larger letters that are lost in areas of retinal atrophy. In addition to the loss of central vision, patients complain of difficulty seeing in dim environments and of reduced contrast sensitivity. As expected, a reduction in visual acuity in this elderly population increases the risk of falls/fractures and contributes to a diminished sense of well-being and self-reliance.

This preliminary study raises several questions. If HBO₂ is effective in reactivating the “idling” cells at the margins of the atrophic lesions and possibly stimulating the remaining retinal cells to a higher level of function, would it also slow or prevent the cellular apoptosis that leads to a progression or to the development of focal retinal atrophic areas?

Since hypoxia stimulates VEGF production, could HBO₂, in combination with VEGF inhibitors, be more effective in restoring or maintaining vision than in using the VEGF inhibitor alone? But the most important question is this: Can HBO₂ treatment prevent or delay the development of AMD or the progression of dry AMD into wet AMD? A positive answer to this last question would have immense public health implications for the more than 7 million individuals in the U. S. at high risk for visual loss from AMD.

There are many proposed mechanisms for the development of AMD. While there is a genetic predisposition, environmental factors, such as tobacco usage, vitamin/mineral supplementation and heavy alcohol usage play a role. These factors should be controlled in any prospective study of this modality.

Klein, *et al.* (17) reported a 6.6-year period from baseline to the initial appearance of GA (4-11 year range). Large drusen and hyperpigmentation was followed by the regression of drusen and hypopigmentation and the development of GA. The slow and identifiable antecedents to GA and to choroidal neovascularization as well offer a large time window of treatability.

CONCLUSION

In the present off-label study, 14 patients with visual loss secondary to AMD underwent HBO₂ treatment and achieved improvements in their visual acuity and/or visual field in cases considered untreatable by presently accepted methods. There were no complications, and the visual benefits achieved appear to be maintained at follow-up visits. A controlled clinical study is necessary to determine whether HBO₂ is valuable in the treatment of AMD.



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