Preliminary report on the effect of hyperbaric oxygen on cystoid macular edema

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ABSTRACT

The treatment of established cystoid macular edema has been enigmatic. This is a preliminary study of five patients treated by intermittent hyperbaric oxygen with an intensive regimen of 1.5 hours two times per day for seven days and two hours per day for an additional 14 days. Visual acuity improved within 14 days in all five patients: One patient improved from 20/40 to 20/15, one from 20/50 to 20/25, one from 20/200 to 20/40, one from 20/70 to 20/25, and one diabetic patient improved from 20/70 to 20/25. Vision has tended to regress with time.

Key Words: cystoid macular edema, fluorescein angiography, hyperbaric oxygen

Cystoid macular edema (CME) is a degenerative change in the neural retina that arises following any one of a large number of ocular maladies. Cystoid macular edema may result from a variety of inflammatory, infectious, degenerative, hereditary, traumatic, and surgical conditions.[1-12] The clinical pathophysiology of this disorder has remained obscure despite extensive study, and to date no animal model that adequately parallels the clinical syndrome has been found.

Evidence suggests that multiple processes lead to the clinical observation of CME. These include fluorescein leakage from perifoveal capillaries,[3,4] macular cyst formation,[5] and a subset of patients with significant visual impairment that may or may not resolve spontaneously.

Hyperbaric oxygen has been shown to be effective in several pathologic processes. These include the treatment of osteomyelitis,[13,14] hypoxic states of tissue such as threatened skin grafts,[15,16,17] air embolism,[18,19] and a growing list of other states.[20] It has the ability to constrict blood vessels and, paradoxically, to hyperoxygenate tissue[21,22,23] which causes a reduction of edema.[21,24,25]

We felt hyperbaric oxygen might beneficially affect CME, and this paper presents the preliminary results in five patients treated with this modality.

SUBJECTS AND METHODS

We selected patients who were seven to 11 months postoperative from cataract extraction or secondary intraocular lens (IOL) implantation with best corrected visual acuity of 20/40 or less. We chose this time window because we wanted subjects who were beyond the usual normal spontaneous resolution period, but were not so severely damaged from their disorder that they could not be helped. Patients had to demonstrate classic CME on a recent fluorescein angiogram. They must not have been treated with steroid or antiprostaglandin medication for three weeks prior to initiation of hyperbaric oxygen treatment, nor could they be treated at any time during the three-month study.

Hyperbaric oxygen was instituted on the following protocol: Total body hyperbaric oxygen in a monoplace chamber at 2.2 atmospheres for 1.5 hours two times per day for seven days, then 2.0 hours one time per day for the next 14 days. Fluorescein angiography was

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performed at the conclusion of treatment. Vision was measured at the conclusion of each treatment with the patient's current spectacle correction or pin-hole correction or both, and the patient was refracted by his or her ophthalmologist at the conclusion of treatment, one week, and three months later.

A control group based on a table of random numbers was established. As patients were enrolled in the study, those who were assigned an even number were treated with hyperbaric oxygen and those who were assigned an odd number were treated with topical prednisolone acetate drops and 0.75% indomethacin drops.

Fluorescein angiograms were evaluated by a method devised by Stephen Petty, M.D. (personal communication). The horizontal extent of edema was divided by the horizontal optic disc diameter and expressed as a number. This is the most sensitive way of evaluating subtle changes in the angiogram as each angiogram automatically is corrected for changes in magnification due to technique. Angiograms were evaluated with a doubleblind method by a vitreoretinal surgeon. Results are listed in Table 1.

Table 1. Fluorescein angiography results.

Case Number	Results*		
	Before Treatment	Conclusion of Treatment	3 Months Post-Treatment
1	2.00	1.75	2.00
2	1.50	1.00	0.75
3	2.50	1.00	1.25
4	1.75	1.75	1.50
5	1.50	1.50	1.50

*Horizontal CME diameter divided by the horizontal disc diameter.

RESULTS

Case 1

A 57-year-old white female had cataract surgery without an IOL in her right eye in January of 1978. Subsequently, she suffered from intractable aphakia and peripheral corneal vascularization from a soft contact lens. She desired a secondary implant. On March 20, 1985, an AC21B anterior chamber IOL was implanted. Her visual acuity improved to 20/15 at two months, but declined to 20/40 at five months post-implantation. Fluorescein angiography demonstrated classic CME. She was treated with hyperbaric oxygen, commencing seven months after secondary lens implantation. On day five of treatment, her acuity improved to 20/20. At the conclusion of treatment, her best corrected visual acuity was 20/15, and at three months post-treatment it was 20/25+2.

Case 2

A 72-year-old white female who had insulin-dependent diabetes mellitus and advanced open-angle glaucoma had extracapsular cataract extraction and posterior lip sclerectomy on January 8, 1985. Subsequently, her visual acuity improved from 20/100 preoperatively to 20/70 postoperatively at seven months. Fluorescein angiography showed CME. She was treated with hyperbaric oxygen nine months after cataract surgery. On day seven her acuity improved to 20/25. She was unable to be refracted until one week after completion of hyperbaric oxygen treatment at which time her acuity was 20/40. She stated that she felt that her vision had declined in the week since completing the treatment. Three months post-treatment her fluorescein angiogram had improved and her visual acuity was 20/25.

Case 3

A 69-year-old white female had an intracapsular cataract extraction in April 1985 with the implantation of a Leiske-style IOL by another surgeon. She refused to allow us to contact the other surgeon for information, thus details of the surgery are unknown. She consulted one of us (DSP) at seven months postoperatively. Visual acuity was 20/100. Hyperbaric oxygen treatment was instituted at this time after fluorescein angiography demonstrated classic CME. Subsequently, her acuity improved from 20/50 to 20/30 after six days of hyperbaric oxygen therapy, enabling her to obtain a driver's license. At the conclusion of therapy, her visual acuity was 20/25. Three months after treatment, it was 20/40.

Case 4

A 67-year-old white male had extracapsular cataract extraction with IOL implantation at the Denver Veterans Administration Hospital on June 27, 1985. The surgery was complicated by iridodialysis. Visual acuity declined to 20/200 at seven months postoperatively. Fluorescein angiography confirmed classic CME. He was enrolled in the hyperbaric oxygen study at seven months postoperatively. On day six of treatment, his visual acuity had improved to 20/70. On day 14, it was 20/40, and at the conclusion of treatment his best corrected acuity was 20/60. He is not yet three months post-treatment.

Case 5

A 72-year-old white male had a planned extracapsular cataract extraction with posterior chamber IOL implantation on July 22, 1985. Seven months later his best corrected visual acuity was 20/70 and he demonstrated classic CME on fluorescein angiography. He had hyperbaric oxygen treatment eight months postoperatively. On day three of treatment his visual acuity had improved to 20/30. On day seven, it was 20/25. He had idiopathic CME in the contralateral phakic eye. At the start of treatment, the best corrected visual acuity

of this eye was 20/40. On day 20, it had improved to 20/20. He is not yet three months post-treatment.

Control Case 1

This 78-year-old female had planned extracapsular cataract extraction on May 22, 1985. The surgery was complicated by rupture of the posterior capsule and vitreous loss. Automated vitrectomy was performed. At eight weeks postoperatively the best corrected visual acuity was 20/50. By seven months postoperatively, it was 20/60. Fluorescein angiography showed CME. She was started on prednisolone acetate and indomethacin drops four times daily. Three months later the visual acuity was still 20/60.

Control Case 2

This 85-year-old female had phacoemulsification cataract extraction on July 30, 1985. The procedure was uncomplicated. At eight weeks postoperatively, the best corrected visual acuity was 20/60. Eight months postoperatively it was still 20/60. Fluorescein angiography demonstrated CME. The patient was treated with prednisolone acetate and indomethacin drops four times per day. Three months later the best corrected visual acuity was 20/80.

Control Case 3

This 84-year-old female had uncomplicated phacoemulsification cataract extraction on December 4, 1985. At two months postoperatively, her best corrected visual acuity was 20/40. Fluorescein angiography confirmed CME. The patient had a trial with indomethacin and prednisolone acetate topical drops and was intolerant to the indomethacin. At eight months postoperatively, the visual acuity was 20/40. The patient was continued on prednisolone acetate topical drops four times per day. Three months later the acuity remained at 20/40.

Two patients were eliminated from the control group. One had a suspected bilateral toxic optic neuropathy secondary to cancer chemotherapy, and one patient died of carcinoma of the lung while being followed.

No hyperbaric-oxygen-treated patient's visual acuity declined from pretreatment levels. All five improved by four Snellen lines at some time during treatment. Virtually every patient noted subjective improvement in visual acuity after one week of treatment. This was confirmed by objective testing in subsequent days. Figure 1 summarizes the visual course during treatment.

The vision of control patients did not improve over the three-month post-treatment with topical prednisolone acetate and indomethacin drops.

DISCUSSION

Although the number of patients in this study is small, we felt that the time relationship between the onset of treatment and improvement was too coincidental to have been chance. Case 4 was particularly instructive, as the patient demonstrated the poorest vision and the most improvement with treatment. Because of the gravity of this condition and the prolonged time required to carry out a study, these preliminary findings are submitted to the ophthalmic community prior to statistical significance so that others can participate in the collection of data and treatment.

Gass and Norton[4] have shown that the primary cause of CME is leakage of fluid that is low in lipid and protein from the perifoveal capillaries. By light microscopy, it was seen that fluid escaped into the extracellular space of the retina. In 1985, Gass[3] again reported on the light and electron microscopic appearance of CME, demonstrating a leakage from the perifoveal capillaries. He was, however, unable to demonstrate the junctional complexes of the capillary endothelium with his methods. He stated that the absence of lipids in the edema fluid was probably explained by the relatively small openings in the vasculature, which allowed only low molecular weight substances to pass.

Hyperbaric oxygen promotes collagen formation,[26] constricts blood vessels,[21,22] hyperoxygenates tissue by plasma loading of oxygen independent of oxyhemoglobin,[23] and reduces edema.[21,24,25] Cystoid macular edema has been demonstrated to involve leakage from perifoveal capillaries with resultant characteristic edema formation and subsequent reduction in neural function. We therefore felt that hyperbaric oxygen might be an effective treatment for this condition. Over the short term, this appears to be true. We may conclude that this disorder is ameliorated.

Cystoid macular edema may be due to breakdown of the junctional complexes of the perifoveal capillaries by the action of prostaglandins or other mediators, allowing leakage of fluid that results in localized edema formation in most cases. Miyake[1] has demonstrated increased levels of PGE and PGF_{2alpha} in patients with CME undergoing vitrectomy. In a study by Sebag and Balazs,[27] vitreous fibers could be seen coursing from the anterior vitreous posteriorly to a set of holes in the posterior vitreous, one over the macular area and the other over the optic nerve head. This orientation may represent a conduction pathway for inflammatory mediators to penetrate from the anterior surgical site to the posterior site of effect, not only in the macular area but also to the optic disc, another not uncommon location of leakage of blood vessels in CME. Constriction of the perifoveal capillaries by hyperbaric oxygen may allow these complexes to reform with adjacent endothelial cells, which would prevent further leakage. If a certain percentage of these bridges were to reestablish attachment with hyperbaric oxygen treatment, a smaller percentage would lose attachment at

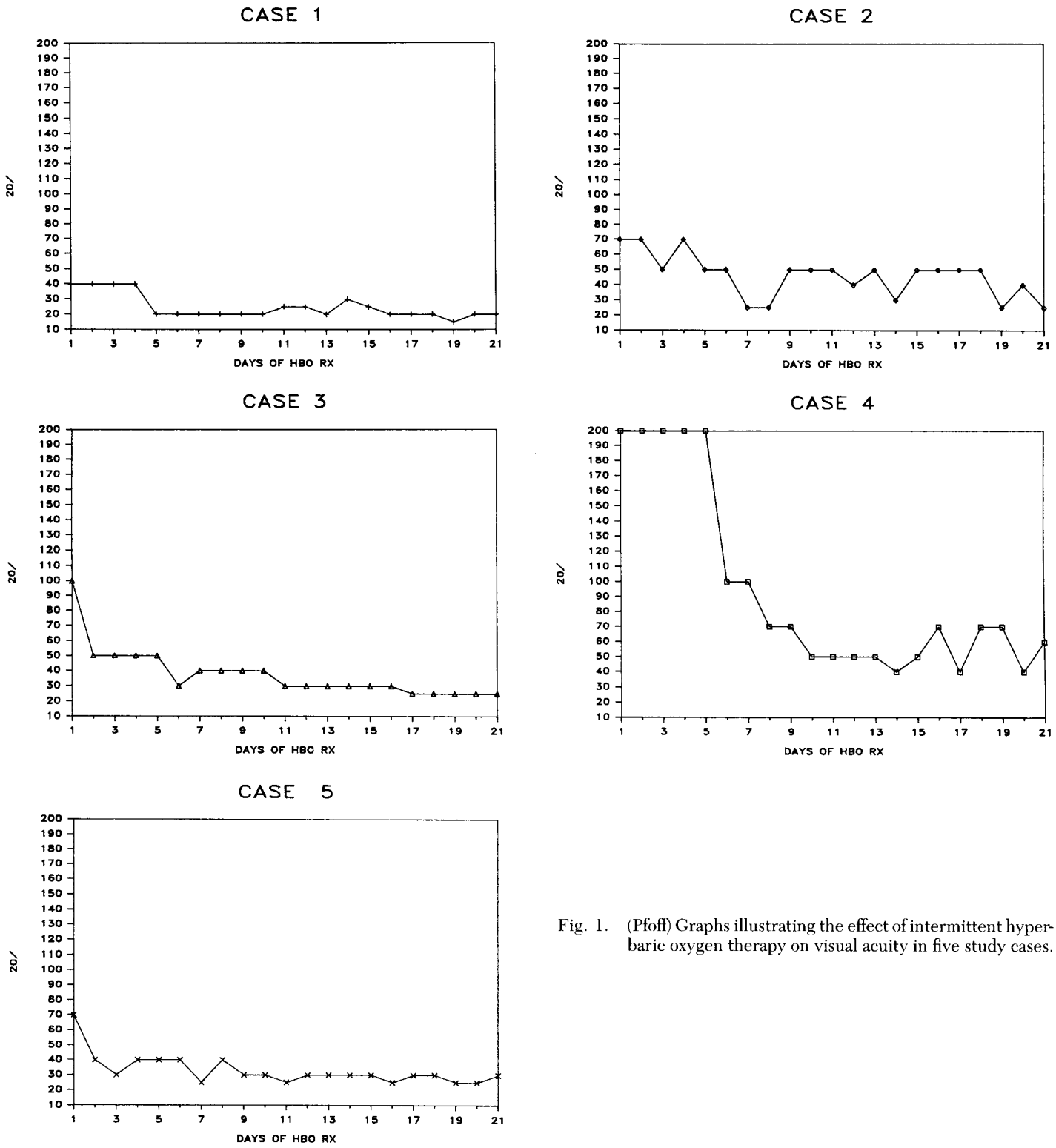

Fig. 1. (Pfoff) Graphs illustrating the effect of intermittent hyperbaric oxygen therapy on visual acuity in five study cases.

the end of a treatment session. With subsequent treatments, a greater and greater number would remain intact. This would reduce edema fluid formation.

Hyperoxygenation of tissue does provide needed oxygen and therefore neural function would be restored or at least maintained at current levels. The fovea may provide 20/20 acuity with only 40% of the macular photoreceptors intact.[6] Thus, there may be significant reduction in macular photoreceptors even with good Snellen vision. Miyake[1] as well as Jampol, Sanders, and Kraff[2] have shown that pretreatment and post-treatment with topical indomethacin in cataract extraction patients results in a statistically significant

reduction of CME. One can infer that at least one of the inciting agents is a prostaglandin that is affected by indomethacin. If the inciting agent can be eliminated, the mechanical reduction of CME by hperbaric oxygen may prove to be curative.

Cystoid macular edema has not been demonstrated to be treatable, once established, with the exception of a report by Yannuzzi[5] in which 40 consecutive patients with established CME were treated with a combination of topical corticosteroids and indomethacin. Eighty percent of the patients improved by two or more Snellen lines. Fifty percent of the patients who improved had residual angiographic edema. When medication was stopped, vision declined, but with resumption vision improved. We plan a study of 25 to 50 patients. Should the treatment prove effective over a long period, alone or in adjunct with other modalities, a tremendous benefit would be established.

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