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MAJOR REVIEW

The Use of Hyperbaric Oxygen Therapy in Ophthalmology

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Abstract. Hyperbaric oxygen therapy is a primary or adjuvant therapeutic method used in treatment of various acute or chronic disorders. Currently, eye diseases are among the off-label use of hyperbaric oxygen. However, there is an increasing body of evidence showing its safety and efficacy in retinal artery occlusion, cystoid macular edema secondary to retinal vein occlusion, scleral thinning and necrosis faced after pterygium surgery, orbital rhino-cerebral mucormycosis, nonhealing corneal edema, and anterior segment ischemia. Its potential to treat some blinding disease has also been pointed out in recent studies. This article consititutes an up-to-date summary of knowledge and therapeutic use of hyperbaric oxygen, and aims to contribute understanding of current and potential use of hyperbaric oxygen therapy in ophthalmology. (**Surv Ophthalmol 53**:112–120, 2008.

Key words. cellular effect • cost • evidence-based medicine • eye diseases • hyperbaric oxygen therapy • side effect

I. Introduction

In 1930s hyperbaric oxygen (HBO) therapy was first applied in the navies of United States of America and Great Britain to treat decompression sickness (Neumeister M: Hyperbaric oxygen therapy. http://www.emedicine.com/plastic/topic526.htm. Accessed 15 January 2007). After 1950, a more complete examination of blood gases and understanding the detailed physiology of gas exchange led the physicians to employ HBO therapy as a treatment of choice.[37,70]

HBO therapy can be managed either by direct respiration in the cabins, including one or more patients, or by endotracheal tube, mask, or a firm cap. Instead of using a monoplace chamber for a particular disease in each treatment session, the usage of a multiplace chamber, serving two or more patients who need that particular treatment session, reduces the cost of treatment and preferable in the most clinical settings (Table 1) (Neumeister M: Hyperbaric oxygen therapy. http://www.emedicine.com/plastic/topic526.htm. Accessed 15 January 2007).[46] Each session of HBO therapy takes about 45 minutes to 5 hours, with most averaging roughly 90 minutes. Several sessions are required, depending on the properties of the disease being treated. Often, early treatment is essential for maximum benefit from HBO therapy. Intensive care conditions should be readily available in the centers where HBO therapy is applied.

The Undersea and Hyperbaric Medicine Society (UHMS) approves use of hyperbaric oxygen for 13 conditions for which there is thought to be reasonable scientific evidence or well-validated clinical experience (Table 2) (http://www.uhms.org/Indications/indications.htm, Accessed 15 January 2007). In these

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TABLE 1

Comparison of Monoplace and Multiplace Hyperbaric Oxygen Chambers

Monoplace
Advantages
• Portable
• Lower cost
• Treatment protocol specific to patient
• No risk of iatrogenic decompression sickness in patient or staff
Disadvantages
• Claustrophobic environment
• Limited access to patient
• Whole chamber contains hyperbaric oxygen, increasing fire
• Limited pressure capability (3 atmosphere absolute)
Multiplace
Advantages
• Hyperbaric oxygen via tight fitting mask-chamber gas can be air, reduced fire risk
• More room; Attendants able to enter and exit during therapy, assistant can enter to deal with acute problems of patient
• Greater working pressure
• Ability to use a variety of electrically generated signals during therapy
Disadvantages
• Risk of cross infection
• Higher operating costs
• Uncertain oxygen delivery tension at patient with face mask
• Severe maxillofacial and/or head and neck involvement possibly making effective delivery of oxygen difficult

TABLE 2

Indications of HBO Therapy

1. Air or gas embolism
2. Carbon monoxide poisoning
3. Clostridial gas gangrene
4. Crush injury, compartment syndrome, and other acute traumatic ischemias
5. Decompression sickness
6. Enhancement of healing in selected problem wounds
7. Acute exceptional blood loss (anemia)
8. Intracranial abscess
9. Necrotizing soft tissue infections
10. Refractory osteomyelitis
11. Radiation injury, osteoradionecrosis, soft tissue damage
12. Compromised skin grafts or flaps
13. Thermal burns

Defined by the Hyperbaric Oxygen Therapy Committee and approved by the Undersea and Hyperbaric Medicine Society.

conditions early referral is essential. Currently, eye diseases are among the off-label uses of HBO. However, several reports support its use in ophthalmology. These are particularly impressive in the context of alternative intervention for some potentially blinding eye diseases. In this article, we scrutinize the evidence available to provide recommendations for the use of HBO in ophthalmology.

II. Physiologic Basis of HBO Therapy

The primary effects of HBO therapy are hyperoxygenation and decreased gas bubble size. Oxygen, which is the most essential substrate for metabolism, makes up 21% of the air we breathe. HBO therapy includes application of 100% oxygen with an atmospheric pressure that is two- to three-fold of that found in the air at sea level. During HBO therapy arterial oxygen pressure and tissue oxygen pressure can increase up to 2000 mm Hg and 400 mm Hg, respectively. Application of oxygen at this pressure, which increases the gradient (or the transfer of oxygen into tissues) twenty-fold, has many biochemical, cellular, and physiological useful effects.[46,70] Oxidants may serve as cellular messengers to promote healing.[65] Thus, tissues receiving higher amount of oxygen increase their capacities of reparation. Hyperoxia induced by HBO therapy has beneficial effects through molecular, cellular, and biochemical changes that result in effective oxygen consumption at the tissue level. The value of HBO therapy depends on the physical properties of the gases.

The volume of a gas in an enclosed space is inversely proportional to the pressure exerted on it (Boyle's law). At 300 kPa, the bubble volume, which is reduced by about two thirds, moves into the smaller vessels and reduces extravascular tissue damage.

Secondary effects of HBO are vasoconstriction, fibroblast proliferation, leukocyte oxidative killing, toxin (clostridial) inhibition, and antibiotic (fluoroquinolones, amphotericin B, and aminoglycosides) synergy.[46]

Nitric oxide synthesis seems to be one of the probable mechanisms of action in HBO therapy. Hypoxia decreases nitric oxide synthesis in cells from pulmonary and systemic circulations, probably as a result of enzyme O_2 requirement.[64] Elevated O_2 tensions above ambient increase nitric oxide production by pulmonary endothelial cells and intact lungs.[64] In the central nervous system, elevated partial O_2 pressures increase the steady-state concentration of nitric oxide by stimulating neuronal nitric oxide synthesis activity.[69] HBO can modify the nuclear factor-kappaB activation in the intestinal mucosa and attenuate the sequential nitric oxide

overproduction and myeloperoxidase activation. Hence, bacterial translocation could be potentially decreased, which would improve survival rates.[62] In rats, HBO treatment showed a beneficial effect on renal dysfunction in sepsis by increasing the antioxidative capacity.[19] Also, no impairment of the innate human host defense in exposure to hyperoxia has been shown.[40] These factors might explain the beneficial effects of HBO in treatment of sepsis.

There has been a considerable debate on the relationship between HBO therapy and free radical production in tissues. Studies on ischemia-reperfusion injury showed that hypoxia, not oxygen, was causative agent for free radical–mediated damage.[17,81] HBO therapy affects many of the components involved in ischemia-reperfusion injury, including polymorphonuclear leukocyte function, endothelial cellular adhesion molecule expression, nitric oxide production, nitric oxide synthase expression, cellular energetic, lipid peroxidation, and microvascular blood flow. It is likely that the sum of many of these effects is responsible for the final outcome in ischemia-reperfusion injury.

A study on the effect of HBO on Na^+ transport across the isolated toad (Bufo marinus) skin during steady state conditions showed that free radicals were involved in the HBO-induced inhibition of short-circuit current.[56] Further studies searching the site(s) of radical generation as well as the site(s) of toxic action have been conducted to investigate the cellular and molecular mechanism(s) of HBO toxicity.[12,56,61]

III. The Use of Hyperbaric Oxygen Therapy in Systemic Diseases

The main indications of HBO therapy are decompression sickness, arterial gas embolism, and severe carbon monoxide poisoning.[46] Decompression sickness occurs when a diver ascends to the surface of water very quickly. The effects of pressure, which is affected by several factors, in addition to rate of ascent manifests as decompression sickness or caisson disease through bubble formation after decompression due to great excess of intrabody pressure.[37] A hyperbaric chamber is used to provide recompression in these circumstances. In carbon monoxide poisoning, HBO therapy provides an alternative source of tissue oxygenation through oxygen dissolved in the plasma; it also facilitates dissociation of carbon monoxide from hemoglobin and myoglobin. Hyperoxia also constitutes the basic mechanism of action in treatment of severe blood loss (anemia), crush injury, flap improvement, prolonged failure of wound healing, prevention and treatment of osteoradionecrosis, and nonhealing diabetic wounds such as diabetic foot ulcers.

According to the best clinical evidence available, HBO is likely to be beneficial in air embolism, hydrogen sulfide toxicity, non-healing diabetic wounds such as diabetic foot ulcers, severe thermal burns, fractures impossible to knit, acute crush injury, neurological disorders (paralysis, intracranial abscess, brain edemas, and focal ischemia and stroke), hematological disorders (cycle cell crisis), and Clostridial myonecrosis in refractory osteomyelitis).[13,15,20,27,30,37,75] Recent reports on hyperoxia-mediated mobilization of bone marrow–derived endothelial progenitor cell is intriguing because it has potential to improve healing in chronic, nonhealing wounds affected by diabetes and peripheral arterial disease.[25] Moreover, a recently announced potential application of HBO as a drug in myocardial infarction may have clinical implications in the future.[79]

The beneficial effects seen in experimental studies suggest some clinical merits; this is particularly important for diseases under investigation for effective treatment. In experimental allergic encephalomyelitis in myelin-induced guinea pigs model, HBO treatment suppressed the encephalomyelitis and prevented the development of arthritis.[58,76,77] On the other hand, evaluation of all randomized, controlled trials involving a comparison between HBO therapy and a sham therapy in multiple sclerosis patients clearly demonstrated no clear benefit of HBO therapy.[7] This underscores the importance of evidence-based evaluation of HBO therapy for the daily management of patients.

IV. Current and Potential Use of Hyperbaric Oxygen Therapy in Ophthalmology

Understanding current and potential use of hyperbaric oxygen therapy in ophthalmology is of great importance. This is particularly important in the context of limited efficacy or inefficacy of conventional interventions for potentially blinding diseases. The indications for HBO therapy in ophthalmology are listed in Table 3.

A. VASCULAR DISEASES OF THE RETINA

HBO therapy was reported to be useful in the treatment of ocular vascular diseases.[43,44] Vasoconstriction of the retinal vessels is probably a direct response to the interaction between free oxygen radicals and nitric oxide, together with the autoregulation in this treatment. After 10 minutes of

TABLE 3

Indications for HBO Therapy in Ocular Diseases

A. Recommended as primary treatment
1. Occlusive vasculopathies (central retinal artery occlusion, branch retinal artery occlusion)
2. Cystoid macular edema of vascular origin (central retinal vein occlusion, branch retinal vein occlusion, retinitis pigmentosa)
3. Scleral necrosis of avascular origin (scleral thinning after pterygium surgery)
4. Orbital infections of mycotic and anaerobic origin (rhino-orbito-cerebral mucormycosis)
5. Nonhealing corneal edema
6. Anterior segment ischemia

B. Recommended as adjuvant therapy
1. Proliferative vitreoretinopathy due to Sickle cell disease
2. Primary open-angle glaucoma
3. Visual field defect after macular hole surgery
4. Macular detachment
5. Optic neuropathies of vascular origin

HBO treatment, vasoconstriction occurs significantly. On the other hand, the increased nitric oxide and free oxygen are used promptly after the treatment and therefore, rapid vasodilatation occurs after ending of hyperbaric oxidation.[74] Despite vasoconstriction of retinal vessels during HBO therapy, oxygen saturation rises up to 23% and retina is not damaged.[13]

HBO therapy in patients with retinal vein obstruction improved visual prognosis and in patients who had retinal vein obstruction associated with cystoid macular edema, HBO therapy improved macular edema and visual acuity.[43,44] In most cases, the diabetic macular edema showed no morphologic change and photocoagulation was necessary.[44] Cystoid macular edema resistant to other therapy modalities was shown to respond to HBO therapy and to improve visual acuity.[38] HBO therapy was successfully used in treatment of central retinal artery occlusion[5,78] and branch retinal artery occlusions, including Susac syndrome.[1,49] HBO therapy should be applied as early as possible in these circumstances.

HBO therapy was reported to be useful in the treatment of diabetic retinopathy;[18] an experimental study demonstrated that HBO therapy ameliorated the blood–retinal barrier breakdown. Hence, it can prevent and treat persistent macular edema due to blood–retinal barrier breakdown in patients with diabetes.[14] However, the effects of HBO therapy in treating this common ophthalmic disorder have not been extensively studied. The beneficial effect of HBO therapy in treating retinal vascular diseases is the result of hyperoxia-dependant improvements in retinal and macular oxygenation, especially in areas with deficient perfusion and interstitial edema or thickened basal membrane, and from vasoconstriction which prevents fluid leakage leading retinal edema.[43,44] Although the current clinical evidence supports use of HBO in retinal vascular occlusions with macular edema, questions involving the production of surplus free radicals and the placebo effect still persist. Additional well-designed controlled clinical trials are required.

Multiple sessions of HBO therapy have been associated with an improvement in visual function and retinal appearance in patients with Purtscher retinopathy.[50]

Early HBO therapy is recommended for bilateral blindness during hemodialysis.[42]

B. SCLERAL MELTING AND NECROSIS

Beta-irradiation is employed to prevent recurrence in patients with pterygium.[39,71] The popularity of this technique had waned, but it has seen a recent resurgence. Nevertheless, this method may cause a necrotic or thin sclera. Mitomycin C, an antimetabolite agent used to prevent recurrence, also may cause scleral melting and scleral necrosis.[52] This complication is a serious problem for both the physician and the patient, because endophthalmitis, perforation, and permanent visual loss may occur. In these cases, HBO therapy has helped the patients to gain the optimum episcleral blood flow and scleral thickness.[3,4,28] Hyperoxia and induction of angiogenesis and fibroblast proliferation seem to be responsible for the benefit from HBO therapy in cases with scleral melting or scleral necrosis. In the context of alternative interventions, mechanism of action, and higher benefit/risk ratio shown in clinical studies, HBO therapy in scleral melting seems to be a good candidate for randomized controlled clinical trial (RCT).

C. OCULAR INFECTIONS

Mucoracea, a species of fungi microorganisms, causes rhinocerebral mucormucosis in immune compromised patients. This agent can involve the orbit and rhino-orbital-cerebral mucormycosis may occur. The principal therapy of the disorder is intravenous amphotericin B and debridment of the necrotic tissues. Nevertheless, the mortality rate is high. HBO therapy employed in this disorder prevents both hypoxias in the tissues affected by the fungi and residing of mucor hyphes in the blood vessels, by increasing the oxygen saturation in the vessels. Price and Steves were the first to employ HBO therapy in a patient with rhinocerebral mucormucosis who had not responded to medical treatment and had refused surgical intervention.[57]

Later, others reported that amphotericin B and surgical intervention along with HBO therapy had better results.[6,22,41] In a detailed review of cases with rhino-orbital-cerebral mucormycosis, Yohai et al found that HBO therapy had a favorable effect on prognosis.[80] HBO might be a treatment of choice in ocular and periocular infections of anaerobic origin.[33] In addition, HBO is a therapy of choice in rhino-orbital-cerebral mucormycosis, a rare, life-threatening condition, because of its efficacy in leukocyte-mediated oxidative killing of certain anaerobes and its clinical benefits that have been shown in uncontrolled studies.

D. CORNEAL EDEMA AND ANTERIOR SEGMENT ISCHEMIA

There are good physiologic reasons that may account for why HBO therapy may have beneficial effects on certain ocular diseases. Corneal edema with various etiologies and anterior segment ischemia especially when associated with sickle-cell anemia seem to be proper indications for HBO therapy.[16,59] Although it is not clinically proven, transcorneal delivery of oxygen was suggested for treatment of anterior segment necrosis and rubeosis iridis.[36]

E. PROLIFERATIVE VITREORETINOPATHY DUE TO SICKLE-CELL DISEASE

It was shown that proliferative vitreoretinopathy due to sickle-cell disease also benefits from HBO therapy.[24] A few case reports or a case series, of course, are not enough to claim HBO therapy as a treatment of choice in these conditions. Further research is warranted unless more fruitful alternatives appeared for these troublesome conditions.

F. GLAUCOMA

HBO therapy has been associated with a reduction of intraocular pressure.[26] In other studies, HBO therapy, employed in patients with glaucoma, improved visual field loss without any significant alterations in intraocular pressure.[9,10] The vascular theory in glaucoma seems to be a scientific rationale for application of HBO; however, further well-designed randomized clinical trials are required to determine the role of HBO in glaucoma, an expensive life-time disease to treat.

G. OPTIC NEUROPATHY

HBO therapy can improve the visual loss from optic neuropathies that occurred after radiotherapy of tumors located on the head or the neck. In these patients HBO therapy may prevent visual loss. In one study, treatment administered in the first 72 hours of visual loss improved the visual acuity to the baseline level. On the other hand, HBO therapy administered at week 2 to 6 of visual loss did not improve the visual acuity.[29] Conversely, the visual acuity improved for a patient who received HBO therapy for radiation-induced optic neuropathy for 17 weeks after the onset of optic neuropathy.[11] However, in a review by Levy and Miller, no beneficial effect was shown for cases with radiation-induced optic neuropathy.[48] HBO therapy provided significant improvement of visual acuity and field in patients with non-arteritic anterior ischemic optic neuropathy.[8] As was reported by the authors, beneficial effect in these two patients might be coincidental. Arnold et al in a controlled clinical trial showed that HBO was not effective in therapy of non-arteritic anterior ischemic optic neuropathy.[2] This was confirmed by a recent review by Mathews.[51] Studies in healthy volunteers proved HBO therapy improved contrast sensitivity.[53] In ischemic or non-ischemic type of optic neuropathies, lack of well-designed RCT, a preferred level of evidence, and limited source of data for meta-analysis prevent us from concluding on the value of HBO in optic nerve disorders. HBO therapy temporarily improves visual symptoms in patients with multiple sclerosis. Nevertheless, as suggested by Bennett and Heard, HBO therapy is not recommended in these patients until more advanced and well-designed studies are reported.[7]

H. RETINITIS PIGMENTOSA

Poor blood circulation is a well-known component of retinitis pigmentosa. HBO therapy in patients with retinitis pigmentosa improved the macular edema and visual acuity.[67] HBO therapy in these patients improved the electroretinogram responses and metabolism of retinal photoreceptor cells as well.[73] All these results are source of hope for the treatment of retinitis pigmentosa; earlier intervention is recommended in this kind of progressive disease. Further controlled experimental and clinical studies are needed.

I. MACULAR DETACHMENT

Ischemia, inflammation, and dystrophy or degeneration in the retina is closely associated with tissue hypoxia. Hypoxia-related events leading to apoptosis in the photoreceptor layer have been demonstrated.[68] Recent studies indicating the relation between functional failure and height of macular detachment in retinal detachment cases seem to be of considerable interest since hypoxia-related apoptosis can be managed by HBO in the preoperative and postoperative period.[47,60] HBO

therapy was also shown to reduce visual field defects after macular hole surgery.[45] These results are intriguing, although the achieved improvement could be coincidental. Therefore, well-designed controlled clinical trials are essential to reach a definite conclusion.

V. General Side Effects Of Hyperbaric Oxygen Therapy

General side effects of HBO therapy are oxygen convulsion;[31] middle ear, cranial sinus, and lung rupture presenting with mild to moderate ache as the result of barotrauma effect caused by sudden pressure alteration; and claustrophobia existing in cabins for single patient. Moreover, squeezing sensation in chest, retrosternal burning sensation, and temporary lung dysfunctions such as dry cough may be visible (Neumeister M: Hyperbaric oxygen therapy. http://www.emedicine.com/plastic/topic526.htm. Accessed 15 January 2007). These side effects can be prevented by timely intervention and consultation. The only absolute contraindication to HBO is an untreated tension pneumothorax. Relative contraindications include impaired pressure equalization and cardiac disease. Clinical and experimental evidence show that HBO is safe when used in pregnancy.[72] Caution is mandatory in HBO therapies because hyperbaric and hypobaric chamber fires causing to death was reported.[66]

VI. Ophthalmologic Side Effects of Hyperbaric Oxygen Therapy

HBO therapy has been reported to be safe, as long as the treatment protocols with each section are less than 120 minutes and oxygen pressure below 3 atmospheres are employed. During the fourth hour some patients begin to experience narrowing of their visual field. Eyelid twitching is the most commonly seen manifestation of oxygen toxicity and usually is a warning that full-blown seizure is imminent (Diving and the Eye. http://www.scuba-doc.com/diveye.htm. Accessed 15 January 2007). Retinal toxicity from hyperoxia at very high levels has been shown in experimental studies. A case with the retinal vascular changes and the other with transient unilateral visual loss has been described. Both had multiple sclerosis as well.[32,37]

In order to avoid severe intraocular pressure (IOP) rise, HBO therapy is contraindicated in patients with therapeutic intraocular gas.[35]

Recent studies showed HBO therapy does not cause any significant alteration in refraction.[21,23] Conversely, in another study, this treatment method was shown to cause reversible myopia.[55] In addition, exposure to acute hyperbaric stress in patients undergoing corneal refractive surgery does not cause any alteration in refraction.[34] Induction of fibroblastic proliferation and unstable refraction may lead unsatisfactory results in keratorefractive surgery procedures, especially for photorefractive keratectomy. Therefore, all keratorefractive surgeries should be postponed unless otherwise indicated for those patients undergoing HBO therapy.

Although they are rare, HBO therapy may cause complications to ocular tissues. The most important complication, nuclear cataract formation by oxidative stress in lens proteins, is more prevalent in the long-term use of HBO, particularly among adults of advanced age.[54,55] Palmquist et al studied the effect of the prolonged HBO therapy on human lens.[55] In that study, 150 or more exposures to the HBO therapy sessions induced myopia in all of the 25 patients (100%). Of the patients, 15 had clear lens before the treatment. Seven of these patients (46.6%) developed nuclear cataract during the HBO treatment.[55] Nuclear vacuoles were reported in 11 out of the 25 patients (44%) treated with HBO therapy in another study of Palmquist et al.[54] Both nuclear cataract formation and nuclear vacuoles were reversible to some extent.[54,55] In the study of Schaal et al bovine lenses were exposed to four different combinations of ambient pressure and oxygen concentration in an organ culture for 7 days. They concluded that high oxygen load had a toxic effect on bovine lenses and added that the higher the oxygen partial pressure and the greater the number of exposures, the more severe the changes in the lens. They suggested a role of oxygen in human cataract formation.[63] Fledelius et al applied standard hyperbaric oxygen treatment protocol consisting of a 95 min session at >95% oxygen at 2.5 atmospheres given daily Monday to Friday, to a total of 30 sessions. The results, however, were given for 17 patients. Myopia was induced in all of the 17 patients (100%).[23]

In fact, with the pressure and duration of exposures used in clinical practice, ocular complications do not seem to be a problem in HBO therapies. The most noticeable complication, which is reversible, is induction of myopia.

VII. The Costs of Hyperbaric Oxygen Therapy

Considerable differences exist among the countries with regard to the cost of HBO therapy. In the USA, each 90-minute session (mean) of HBO therapy costs 50–250 US dollars (Hyperbaric Oxygen

Chamber Treatment Centers. http://www.geocities.com/aneecp/hbocent.htm. Accessed 15 January 2007). In Turkey, however, a single session of HBO therapy costs approximately 16–20 US dollars (Ministry of Finance General Directorate of Budget and Fiscal Control. http://www.bumko.gov.tr/Mevzuat/ButceM/Teblig/2006buttalimatlari/sirano6/EK8/ek8.xls. Accessed 15 Janauary 2007). HBO therapy seems cost-effective when the alternative treatment modalities are considered for debilitating or otherwise untreatable diseases. Since the indications have become clearer, the numbers of hyperbaric chambers are growing faster in the world today.

VIII. Conclusion

There is growing interest in the use of HBO therapy in medicine in general, and in ophthalmology in particular. Recently, the indications for its use have become clearer, and newer indications have appeared in the literature. Now, the number of HBO therapy-cabins available throughout the world continues to increase.

Currently, HBO is used for some blinding, otherwise untreatable diseases in ophthalmology. Our recommendations for the current indications of HBO therapy in ophthalmology were mostly derived from physiologic considerations, uncontrolled studies, and some reported cases, but not from randomized controlled trials. Therefore, well-designed trials are warranted in the future. Knowledge about basic principles of HBO therapy and close collaboration with HBO therapy specialists are essential parts of success in use of HBO in ophthalmic practice.

IX. Method of Literature Search

We conducted a search (January 1970–January 2007) of Medline with the PubMed search engine. Search words included *hyperbaric oxygen therapy, eye diseases, cellular effect, side effect, cost* and various combinations of these words. Articles written in English were given preference. References within these articles were also obtained for review. A Turkish publication was translated to English. For those in other languages than English, the English abstract was utilized. We included all articles and case reports that evaluated the clinical application of HBO in various ocular conditions. Criteria for inclusion of the articles were the originality of the research, a major contribution to the understanding of HBO, and critical judgment of different findings of HBO therapy. They were appraised in an evidence-based fashion. The preferred level of evidence was RCT and meta-analysis of the articles. However, other sorts of evidence were accepted, particularly when RCTs are not available or practicable to conclude.

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