



Hyperbaric Oxygen for Invasive Fungal Infections

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Key words: hyperbaric oxygen, fungal infection, mucormycosis, Aspergillus, hyperoxia

IMAJ 2007;9:387–388

In this issue of *IMAJ* Segal and colleagues [1] report their experience with the use of hyperbaric oxygen to treat invasive fungal infections. They summarize retrospective data on 14 immunosuppressed patients with mucormycosis or invasive *Aspergillus* infection who received HBO treatment in addition to conventional therapy with antifungal drugs and surgery. Fifty percent of the patients in this cohort survived the infection. Exact data on the causating agents in each case are not clearly provided. However, based on the site of infection at least nine of their patients had mucormycosis. Based on their own data and previously reported information in the literature, the authors suggest that adjuvant HBO therapy should be considered in immunosuppressed patients with invasive fungal infections.

Exposure to oxygen at high ambient pressures of more than 1 atmosphere is within pressure chambers. The main effect of this treatment is a marked increase in oxygen delivery to peripheral tissues and a striking increase in oxygen pressure gradient across capillary membranes, which augments cellular oxygenation. HBO is easily tolerated and is associated with a very low risk of adverse effects (such as oxygen toxicity and middle ear barotrauma) [2]. Currently accepted indications for HBO therapy include carbon monoxide intoxication, gas gangrene, crush injuries, non-healing hypoxic wounds, radiation necrosis, decompression sickness, and air embolism [3-5].

HBO has been studied and used in a variety of infections for over 40 years. Early demonstrations of its beneficial effects in gas gangrene [6] and chronic refractory osteomyelitis [7] were followed by a large body of experimental data on the *in vitro* effects of increased ambient oxygen partial pressures on microorganisms, and by a substantial number of reports on *in vivo* effects of HBO in animal models of infection and in clinical studies in humans [8,9]. HBO exerts direct bacteriostatic and bactericidal effects mostly on anaerobic microorganisms. These effects have been attributed to deficient defense mechanisms of anaerobic microorganisms against increased production of free radicals in hyperoxic environments. In addition to its direct activity against microorganisms, HBO has been shown to reestablish defense

mechanisms that are critically impaired by the typically hypoxic microenvironment in infectious sites [10]. Both phagocytosis and microbial killing by polymorphonuclear leukocytes are severely impaired in hypoxic environments. By increasing tissue oxygen tensions HBO therapy restores phagocytosis and augments the oxidative burst that is needed for leukocyte microbial killing. Furthermore, the activity of a number of antibiotics is impaired in hypoxic environments and is restored and even augmented during exposure to HBO. Other important beneficial effects of hyperoxia in infection are attributed to enhancement of key components of tissue repair such as necrotic tissue proteolysis, fibroblast proliferation, and collagen deposition, as well as angiogenesis, migration of epithelial cells and bone remodeling by osteoblastic/osteoclastic activity [11]. Altogether, direct activity on bacteria, enhancement of cellular defense mechanisms, synergistic effects on antibiotic activity, and augmentation of mechanisms of tissue repair form the basis for the use of HBO in combination with antibiotics and surgery as adjunctive therapy for treating tissue infections involving both anaerobic and aerobic microorganisms in hypoxic wounds and tissues [8-11].

Hyperoxia has also been shown to inhibit the growth of some fungi [12-14]. It has been suggested that membranal damage, enzyme inactivation, and reduced protein synthesis caused by increased production of oxygen-based free radicals during exposure to HBO is a key mechanism of its antifungal effects [15]. The importance of this mechanism has been indicated by increased susceptibility of fungal mutants lacking antioxidant enzymes to killing by HBO [16], and by the protective effects of induction of antioxidant enzymes [17]. Furthermore, it has also been suggested that HBO may potentiate the antifungal effect of amphotericin B [13].

However, information on the clinical effects of HBO in invasive fungal diseases in humans is limited. A number of single [18,19] or double case descriptions [20] reported alleged benefits of the use of adjunctive HBO treatment together with amphotericin B and surgery in invasive rhinocerebral mucormycosis. A retrospective summary of 13 patients with rhinocerebral mucormycosis, 6 of whom received HBO therapy in addition to amphotericin B and surgery reported better survival after HBO [14]. A more

HBO = hyperbaric oxygen

recent report on nine patients with rhino-orbital-cerebral mucormycosis also claimed a somewhat better outcome with the combination of amphotericin B, surgery and HBO [21]. Yohai and colleagues [22] compared their data on six patients afflicted by rhino-orbital-cerebral mucormycosis with those of 139 patients previously reported in the literature and concluded that HBO exerted favorable effects on the prognosis.

Overall, advocates of adjunctive HBO therapy in mucormycosis base their recommendations on data from single case reports, small groups of patients, and compiled retrospective literature surveys that strongly support a claim that in mucormycosis HBO may be of value in deterring progression and improving survival. Unfortunately, prospective controlled studies that support a significantly better outcome with HBO are unavailable.

The level of evidence on the effects of HBO in invasive aspergillosis is less compelling. Only a few case reports and small group studies demonstrating beneficial effects of HBO in this condition are available [23-25]. Based on the current level of evidence it is impossible to come up with a straightforward conclusion regarding the exact role of HBO in mucormycosis and invasive aspergillosis. The cumulative impression from the available literature and the high fatality rate in these conditions as well as the relative ease of application and the very low rate of adverse effects of HBO promote the use of this modality in invasive fungal infections. The moderate reported effect of HBO on survival does not present a significant ethical restraint on a much-needed adequately powered prospective controlled multicenter study to define its role in invasive fungal infections. Yet, since funding for such an effort is unlikely, it is feasible that HBO therapy should be viewed as a reasonably substantiated safe adjuvant therapy that should be considered in invasive mucormycosis.

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My play was a complete success. The audience was a failure

Ashleigh Brilliant (1933-), British-born US author, syndicated cartoonist and epigramist