Hyperbaric Oxygen in the Treatment of Invasive Fungal Infections: A Single-Center Experience

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Key words: hyperbaric oxygen, mucormycosis, Aspergillus spp., invasive fungal infection

Abstract

Background: Invasive fungal infections by Mucorales or Aspergillus spp. are lethal infections in immune compromised patients. For these infections a multimodal approach is required. One potential tool for treating these infections is hyperbaric oxygen.

Objectives: To evaluate the clinical course and utility of hyperbaric oxygen in patients with invasive fungal infections by Mucorales or Aspergillus spp.

Methods: We conducted a retrospective chart review of 14 patients treated with HBO as part of their multimodal therapy over a 12 year period.

Results: Most patients had significant immune suppression due to either drug treatment or their underlying disorder. Thirteen of the 14 underwent surgery as part of the treatment and all were receiving antifungal therapy while treated with the hyperbaric oxygen. The number of HBO sessions ranged between 1 and 44. Seven of the patients survived the infection. No patient developed complications due to HBO therapy.

Conclusions: HBO is a potentially significant adjunct in the treatment of invasive fungal infections. Evidence on its usefulness as a standard of care in these infections is still lacking. Since it will be difficult to generate conclusive data regarding the importance of HBO in these infections, the value of HBO in these patients should be considered on an individual basis.

IMAJ 2007;9:355–357

For Editorial see page 387

Invasive fungal infections with Aspergillus or Mucorales spp. are rare and often life-threatening infections, afflicting primarily immune compromised patients. Mucormycosis is caused by a group of molds, Mucorales, from the class Zygomycetes, particularly *rhizopus* and *rhizomucor* [1]. These fungi are very common molds to which exposure is probably quite frequent. Still, clinical disease is rare and affects severely immunocompromised patients or patients with diabetes mellitus. There are several clinical presentations of mucormycosis, the most common being rhino-orbital-cerebral mucor. Other presentations include pulmonary [2], cutaneous, gastrointestinal, and central nervous system. Aspergillus is a mold that can cause disease in both immunocompetent and immunocompromised patients. The most severe forms of infections with Aspergillus are invasive, which typically afflict immunocompromised individuals. The pathophysiology of invasive infections due to the different types of molds is similar in that both groups have a propensity to invade vascular structures and cause necrosis of soft tissue and bone. The outcome of invasive fungal infections is very poor. The mortality rate of immune compromised patients with either mucormycosis or Aspergillus infections is reported to be 60–100% [3,4].

Optimal therapy for these infections requires a multimodal approach with the mainstay being aggressive antifungal drugs combined with extensive surgical debridement. Hyperbaric oxygen has been used in cases of invasive fungal infections, but its role in the multimodal treatment of the disorder has not been defined. We describe our experience with 14 patients treated with HBO in conjunction with antibiotics and surgery.

HBO = hyperbaric oxygen

Patients and Methods

We retrospectively reviewed the charts of all patients with a diagnosis of mucormycosis or invasive Aspergillus infection treated in the Hyperbaric Chamber of the University of Iowa Hospital and Clinics. We assessed the information regarding the initial diagnosis and presenting symptoms and the therapeutic approach taken by the primary team. Information was collected from the hospital computerized patients' records and from the patients' paper records as well as from the Hyperbaric Chamber facility database. Data were retrieved from the charts using a structured form.

Results

Fourteen patients were treated with repeated HBO therapy as part of their treatment over a 12 year period. The patients' initial diagnosis and presenting infection are given in Table 1. Seven patients survived the infection (50%). Among the non-survivors, therapy was withdrawn from one patient because of progression of leukemia, one suffered an acute myocardial infarction perioperatively and did not recover hemodynamically, and one did not undergo surgical debridement and had only one HBO session before therapy was withdrawn.

Table 1. Patient characteristics

Patient	Age (yrs)	Gender	Primary disorder	Infection site	Outcome
1	47	Male	Common variable immune deficiency	Rhinocerebral	Survived
			Diabetes mellitus	Brain abscess	
2	14	Female	Osteogenic sarcoma	Rhinocerebral	Survived
3	6	Female	Acute lymphocytic leukemia	Rhinocerebral	Died
4	13	Male	Myelodysplastic syndrome	Pulmonary	Died
5	76	Male	Myelodysplastic syndrome, acute myocardial infarction, congestive heart failure, pulmonary edema	Rhinocerebral	Died
6	12	Male	Chronic granulomatous disease	Pulmonary, chest wall	Survived
7	33	Male	Liver transplant	Chest wall, pleura	Survived
8	14	Male	Leukemia	Rhinocerebral	Survived
9	63	Male	Diabetes mellitus	Rhinocerebral, orbital cellulitis	Survived
10	65	Male	Acute myeloid leukemia	Rhinocerebral, Aspergillus pneumonia	Died
11	82	Male	Neoplasia	Rhinocerebral	Survived
12	20	Male	Acute lymphocytic leukemia	Pulmonary aspergillosis	Died
13	44	Male	Diabetes mellitus	Rhinocerebral	Died
14	76	Male	Liver transplant	Abdominal wound	Died

All patients but one underwent a number of surgical procedures, usually multiple wide excisions. HBO treatment consisted of a 90 minute session at 2 ATA with three 10 minute air breaks. The number of HBO sessions ranged from 1 to 44 (mean 21, median 18). Time from diagnosis to HBO treatment ranged from 4 to 26 days. There was no correlation between time to HBO treatment and outcome. All patients received antifungal therapy. Medication was as follows: amphotericin B was given to 11 patients, liposomal amphotericin to 2 patients, caspofungin to 2, and itraconasole and voriconazole to 1 each. The choice of antifungal agents probably reflects the time period of 15 years, during most of which the newer agents were not available.

Discussion

Invasive fungal infections caused by molds from the Zygomycetes or Aspergillus class are uncommon lethal infections. These infections occur in immune compromised patients and only an aggressive multimodal therapeutic approach can increase survival rates. The occurrence of Mucor and Aspergillus sinus infections in five immunocompetent patients was recently described [5].

The role of hyperbaric oxygen in patients with invasive fungal infections is unclear. Some reports of patients with mucormycosis have described HBO as part of the therapeutic regimen, mostly as a salvage therapy in patients who were unresponsive to other therapeutic modalities or could not undergo extensive surgery. There are only a few reports on the use of HBO in patients with invasive Aspergillosis [6].

Anecdotal experience with HBO for invasive mucormycosis has been reported. Couch et al. [7] treated two patients whose infection penetrated the central nervous system and caused brain abscess. Both of these patients demonstrated significant improvement after initiation of HBO therapy and remained free of disease for almost 2 years following hospital discharge. Price and Stevens [8] added HBO to the therapeutic regimen of a patient with rhino-orbital-cerebral mucormycosis who refused extensive surgery. They noted that while infected tissue before HBO therapy grew large amounts of fungi, tissue samples taken after HBO grew bacterial contaminants only and no fungi. The patient did well until he developed a bacterial infection which led to his demise.

Bentur and colleagues [9] report the case of a young diabetic patient with a skin infection due to zygomycosis. The wound on her hand had not responded to surgical debridement and amphotericin B. HBO therapy was administered and proved successful in healing the wound.

Several larger series refer to the value of HBO in mucormycosis. In their retrospective series, Guevara et al. [10] reported that five patients survived out of nine receiving HBO as part of the multimodal therapeutic approach. They ascribe the increased survival to early diagnosis of the infection by use of frozen section in the initial surgical procedure. Yohai and co-workers [11] reviewed 139 patients with rhino-orbital mucormycosis reported in the literature and found a number of risk factors for poor outcome. These were a) delayed diagnosis and treatment, b) hemiparesis or hemiplegia, c) bilateral sinus involvement, d) leukemia, e) renal disease, and e) treatment with deferoxamine. They concluded that hyperbaric oxygen treatment of this infection has a favorable effect. Talmi et al. [12] reported their experience treating 19 patients suffering from mucormycosis of the rhino-orbital-cerebral area, and also reviewed a large number of publications dealing with the infection. Although their group had a 47% survival, and the survival of the 240 patients described in their literature review was 52%, there were two studies that used HBO as a part of the multimodal therapy and the survival in both was 67%.

There are not many reports of HBO being used in the treatment of invasive Aspergillus infections. A retrospective series in one institution reported the survival of 6 of 10 patients in whom HBO was part of the therapeutic approach [6]. In our patient group, HBO was beneficial in the context of a multimodal approach that included surgery, antifungal agents and supportive care. In the patients who did not survive, death was primarily due to progression of their underlying condition or the late application of HBO.

The pathophysiological basis for the efficacy of HBO in invasive fungal infections such as mucormycosis and Aspergillus is unclear. These molds are obligate aerobes, which means that a toxic effect by oxygen is unlikely. Other possible mechanisms are probably related to the pathophysiology of the infectious process. Once fungi from these groups start proliferating in tissues, the hyphae have an affinity for blood vessels leading to thrombo-

sis, tissue ischemia and necrosis. It may also be that acidosis promotes the infectious process. In fact, relief of acidosis can help resolve the infection. Mendoza-Ayala et al. [13] described a diabetic patient with pulmonary mucormycosis whose infection resolved after adequate treatment of his diabetic ketoacidosis without specific antifungal care. The mechanism of action may be that HBO decreases acidosis of the ischemic tissues, thereby improving the body's capacity to resolve the infection. By increasing the partial pressure of oxygen in ischemic tissues, anaerobic metabolism is reduced, and local pH may improve to a degree that promotes the killing of fungi in white blood cells.

HBO may also have an effect on the function of antifungals. HBO and amphotericien B have been shown to inhibit the growth of *Candida albicans* [14]. Bornside [15] has shown that hyperbaric oxygen can kill many types of fungi and yeasts. On the other hand, Brown and team [16] demonstrated that the usual clinical protocols of hyperbaric oxygen did not have a bacteriostatic or bacteriocidic effect on either bacteria or fungi. It would appear from the above that the mechanism by which hyperbaric oxygen impacts fungal growth is not yet understood.

In a murine model of mucormycosis induced by intravenous and intrasinus injection of the fungus *Rhizopus arrhizus* into immune compromised mice, the addition of HBO was not associated with any benefit over antibiotics alone [17].

We recognize that due to the small size of our patient group and the retrospective nature of this study we cannot generalize to larger population groups. At the same time, the lack of controlled studies in this field precludes the making of decisions based on sound evidence.

Conclusions

In patients with invasive fungal infections the use of HBO as part of a multimodal therapeutic approach may be beneficial. Studies directed at patients with these infections are necessary to enable better patient selection.

Acknowledgment. We thank the staff of the Hyperbaric Chamber for their ongoing commitment and efforts to patient care.

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Capsule

Bacterial lethal injection

Pathogenic bacteria can inject into host cells virulence factors via the so-called type III machinery. Li and colleagues describe a family of bacterial virulence factors that have a previously unknown phosphothreonine lyase activity that can remove the phosphate from signaling mitogen-activated protein kinase family members involved in innate immunity. This family of effectors is important in the virulence of a variety of animal and plant bacterial pathogens, including Shigella, Salmonella, and *Pseudomonas syringae*.

Science 2007;315:1000

Eitan Israeli