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Hyperbaric oxygen as an adjunctive treatment for zygomycosis

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ABSTRACT

Zygomycosis is a rare but emerging mycosis. Because of the sub-optimal efficacy of the standard antifungal treatment for this disease, hyperbaric oxygen (HBO) has been used occasionally as an adjunctive therapeutic modality. A review of 28 published cases of zygomycosis indicates that adjunctive HBO may be beneficial in diabetic patients (94% survival), whereas its benefit in the small group of patients with haematological malignancies or bone marrow transplants is doubtful (33% survival; p 0.02). Prolonged courses of HBO were associated with a higher survival (100% survival; p 0.003). Additional studies are required to assess the optimal timing and dose for HBO treatment.

Keywords Antifungal therapy, hyperbaric oxygen, immunocompromised patients, Mucorales, zygomycosis

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Zygomycetes are important fungal pathogens of humans [1]. Zygomycosis is caused by fungi of the order Mucorales, most commonly *Rhizopus*, *Mucor*, *Absidia* and *Rhizomucor* spp. [1]. These organisms cause acute angioinvasive infections in patients with a variety of immunosuppressive conditions, including poorly controlled diabetes mellitus (especially diabetic ketoacidosis), neutropenia, malignancies, transplants, burns and chronic renal failure, as well as those receiving chronic immunosuppressive therapy and deferroxamine therapy. The most common manifestations of zygomycosis are sinusitis, pneumonia, rhinocerebral infection, soft tissue infection and disseminated disease [1]. In contrast, entomophthoromycosis, the infection caused by zygomycetes of the order Entomophthorales, mainly *Basidiobolus* and *Conidiobolus* spp., manifests typically as chronic, subcutaneous infection; angioinvasion is not prominent and the prognosis is good [2]. It should be noted at this point that recent developments in fungal taxonomy have resulted in the creation of a new order, Basidiobolales, containing the single genus *Basidiobolus*, while *Conidiobolus* forms part of a phylogenetically distinct group that is related closely to other zygomycetes such as Mucorales [3,4].

Zygomycosis has emerged as an increasingly common invasive mould infection, particularly among leukaemia patients and bone marrow transplant (BMT) recipients [5]. Zygomycetes are inherently resistant to most antifungal agents [1]. Amphotericin B is the only licensed antifungal agent with activity against zygomycetes [1], but amphotericin B therapy is often combined with surgery because of the tissue infractions caused by zygomycetes.

Since the 1970s, the successful use of hyperbaric oxygen (HBO) as an adjunctive treatment for zygomycosis has been documented in several patients [6–10]. HBO inhibits fungal growth *in vitro* at pressures greater than 10 atmospheres absolute (ATA) [11]. It also corrects lactic acidosis, thus promoting the oxidative action of amphotericin B [12]. In addition to its antifungal activity, HBO contributes to tissue healing by several mechanisms. It can elevate tissue oxygen levels significantly, which increases the rate of tissue healing, and it enhances leukocyte-mediated phagocytosis. It can also elevate significantly the levels of growth factors, which promotes angiogenesis and healing [12]. During HBO treatment, 100% oxygen is provided to patients in chambers through facemasks, hood tents or endotracheal tubes [13].

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A review of the literature identified 28 cases in which zygomycosis was treated adjunctively with HBO. Patients were diagnosed with zygomycosis if zygomycetes were grown in culture from the site of infection and/or histopathological examination of infected tissue revealed broad, branching, non-septate hyphae. There was a predominance of male patients (n = 17; 61%), and the mean age of the patients was 31 years (range, 5 months to 74 years). *Rhizopus* (n = 11) was the most common species isolated, followed by *Apophysomyces* (n = 3), *Mucor* (n = 2) and *Absidia* (n = 2). Of three patients with entomophthoromycosis, two were infected with *Conidiobolus coronatus*, and one with *Conidiobolus incongruous*. Diabetes mellitus was present in 17 (61%) patients, of whom ten (36%) also had ketoacidosis. Five (18%) patients developed zygomycosis after trauma, two (7%) had alcoholic liver disease, and one was receiving systemic corticosteroids. Three (11%) patients had haematological malignancies or BMT. Three (11%) patients had no known risk factors for zygomycosis. The most common site of infection was sino-orbito-cerebral (n = 21; 75%). Other less common sites of infection included soft tissue (n = 4; 14%), lung (n = 2; 7%), kidney (n = 1; 4%), and sclera (n = 1; 4%). There was one case of disseminated infection. Most of the patients received two sessions of HBO/day, each lasting 90–120 min, at a pressure of 2–3 ATA. The median number of sessions was 22 (range, 2–85). HBO was administered postoperatively to most (23/25; 92%) patients who also had surgery. Amphotericin B was used in all except two cases.

The overall survival rate was 86% at the end of treatment, with a survival rate among diabetic patients of 94%. Two of three patients with an underlying haematological malignancy or BMT died (p 0.02; OR 48), compared with no deaths among patients who developed the infection following trauma or among patients with no predisposing factors. Two of four patients with fatal zygomycosis were infected with *Rhizopus*, while one was infected with *Apophysomyces*. All patients who died had sino-orbito-cerebral disease; there were no deaths in patients with infection at other sites. Survivors received significantly (p 0.009) more sessions of HBO therapy than non-survivors (median 24 (range, 9–85) and six (range, 2–9) sessions, respectively). Treatment with nine or fewer sessions of HBO was associated with a greater risk of mortality (p 0.003; OR 225).

The review revealed a high rate of survival among HBO-treated patients. Importantly, most of the patients identified had correctable predisposing conditions, such as diabetes or trauma, rather than haematological malignancies or BMT, which are associated with a greater risk of mortality. It is also possible that patients who did not respond to HBO treatment were under-reported, so the high response rate may represent publication bias. The improved survival rate among patients who received more sessions of HBO probably represents a survival bias, since those who responded to treatment were more likely to continue HBO, while those who died early during therapy would have had fewer sessions.

Previous small case series, comparing the mortality rate of patients with sino-orbito-cerebral zygomycosis, treated with or without HBO, have concluded that patients treated with standard therapy (amphotericin B and surgery) and HBO were more likely to survive than patients treated only with standard therapy [7,8]. In contrast, a study of deferroxamine-induced zygomycosis in mice failed to show a survival benefit in the group of mice treated with HBO and amphotericin B, compared to the group treated with amphotericin B alone [14]. However, the hyperacute type of infection caused by intravenous inoculation of fungal spores, and the relatively low pressure of the HBO administered, may account for this study's negative results.

In conclusion, HBO offers a theoretically promising approach for the treatment of zygomycosis. However, current knowledge does not allow definitive conclusions regarding the efficacy of HBO, since individual case reports do not often take into consideration the benefit of concomitant correction of underlying metabolic factors or the timing and extent of surgery. In the absence of control groups for comparison, it is not yet possible to define a group of patients who are most likely to benefit from HBO.

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