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Is there a Role for Hyperbaric Oxygen Therapy in Pediatric Infectious Diseases Practice?

Hiperbarik Oksijen Tedavisinin Çocuk Enfeksiyon Hastalıkları Pratiğinde Yeri Var mıdır?

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Question: *Is there a place for hyperbaric oxygen therapy in pediatric infectious diseases practice?* **Rüveyda Şişmen, MD.**

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Answer (Esra Çiftci, MD; Mustafa Kemal Hacımustafaoğlu, MD)

Introduction and general information: Hyperbaric oxygen therapy (HBO) is the administration of oxygen (usually at 100% concentration) at high pressure in a special chamber or cabin. The aim is to deliver higher oxygen to host tissues than can be delivered in normal room air. HBO may be recommended as a primary treatment (e.g., diver's post-deep submersion stranding disease, carbon monoxide intoxication) or as adjuvant treatment (e.g., profound anemia, severe invasive clostridial skin and soft tissue infections, non-healing ulcers, refractory brain abscesses) (Table 1). In this article, only HBO and its use in infectious diseases will be discussed in relation to the question posed.

As is well known, healthy and efficient functioning of tissues requires oxygen, which is transported through the blood and is usually bound to hemoglobin. According to Henry's Law, the ideal amount of gas dissolved in a liquid is directly related to the partial pressure of that gas. In this framework, in a normal person, breathing normal air (20% oxygen) at sea level [1 atmosphere (Atm pressure)], the concentration of dissolved oxygen in plasma is 0.3 ml/dL. The oxygen concentration increases to 1.5 ml/dL by breathing 100% oxygen at sea level and to 6 ml/dl with 3 Atm HBO. In this case, tissue oxygenation is provided independently of hemoglobin level and contributes to tissue oxygenation especially in cases of carbon monoxide poisoning, deep anemia in which tissue nutrition is impaired, acute or chronic ischemia (1,2). In typical HBO treatment (2.5 Atm pressure, 100% oxygen), hyperoxygenated plasma (5.4 ml/dL) meets the basal metabolism of tissues even in the absence of hemoglobin and can also deliver oxygen to places where erythrocytes cannot reach (1).

Physiopathologic/pathogenetic role of HBO in infectious diseases: Reactive oxygen molecules [reactive oxygen species (ROS)] generated by HBO lead to bacteriostatic or bactericidal effects, especially against anaerobic bacteria (3,4). HBO suppresses the release of some cytokines and inflammatory mediators, which both enhances the antimicrobial effect and contributes to wound healing (1,3,4). HBO increases the bactericidal effects of some

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Table 1. Indications for hyperbaric oxygen therapy (1,2)

Not related to infection	Infection-related
• Carbon monoxide poisoning • Hydrogen peroxide poisoning • Air/gas embolism • Decompression sickness • Crush injury, compartment syndrome and other traumatic acute ischemia • For better healing of selected problematic wounds, including diabetic wounds • Anemia of excessive blood loss • Late radiation necrosis of soft tissue and bone • Serious skin grafts and flaps • Hermal burns	• Necrotizing fasciitis, clostridial myonecrosis (gas gangrene) • Treatment-resistant osteomyelitis (usually chronic), • Rhinocerebral mucormycosis • Problematic intracranial abscesses (such as treatment-resistant, immunodeficiency, dominant localization, multiple abscesses, non-surgical abscesses)

antibiotics (such as betalactam, vancomycin, trimethoprim/sulfamethoxazole, aminoglycoside, quinolone) (5,6). In addition, increased full oxygenation leads to a decrease in tissue edema with hyperoxia-induced vasospasm, which indirectly contributes to tissue healing (2,7).

Bactericidal effects of polymorph-nucleated leukocytes may be either oxygen-independent or oxygen-dependent. Oxygen-independent killing function may be inadequate alone, especially in killing wound bacteria, and this inadequacy becomes more pronounced in the presence of hypoxia. Oxygen-dependent killing is relatively increased in the presence of high oxygen concentration (3,7). In animal experiments, killing of gram-positive and gram-negative bacteria such as *Staphylococcus aureus* and *Pseudomonas aureginosa* decreases at tissue pO_2 <30-40 mmHg. In addition, oxygen itself can also cause bacterial inhibition. In an environment with pO_2 <30 mmHg, bacterial growth and cell destruction effect increases (1,8-10). In clostridial necrotizing fasciitis and myonecrosis (gas gangrene), alpha toxin production, which has a very important role in pathogenesis and is responsible for rapid spread, is completely inhibited if tissue pO_2 >250 mmHg, and this level is easily achieved with 3 Atm HBO (1).

In osteomyelitis, HBO increases osteoclast activity that cleans the tissue (microscopic debridement), osteoblastic activity that provides new tissue and collagen production, as well as angiogenesis and neovascularity. Thus, it contributes to the reduction of subsequent bone destruction (1,11).

Recommendations and use of HBO in infectious diseases: There are no randomized controlled studies on the efficacy of HBO in infectious diseases. The studies conducted are generally on adults. Considering the clinical studies, HBO has been given especially in gas gangrene, rhinoserebral mucormycosis, intracranial abscesses (cerebral, subdural, epidural) unresponsive to treatment, and chronic refractory osteomyelitis (1,2,12,13). Recommendations for application as adjuvant treatment in these types of infections are summarized in Table 2.

Table 2. HBO application recommendations (1)

	HBO application recommendations *			
Clinical Condition (infection type)	**Pressure (Atm)**	**Session Duration**	**Frequency of Application; Daily**	**Total Number of Applications (mean)**
-Necrotizing fasciitis -Clostridial myonecrosis (gas gangrene)	2-2.5	90-120′	Day 1; 3x Days 2-5; 2x After stabilization 1x	10-30 (after the tenth session, evaluation is necessary)
Rhinocerebral mucormycosis	2-2.5	90-120′	1-2x	40-80
Intracranial abscess	2-2.5	60-90′	1-2x	13-20
Kr refractory OM**	2-2.5	90-120′	1x	15-40

*: Adult recommendations; in children, may vary according to specialist recommendation and clinical situation and characteristics. The number of sessions can be adapted according to the patient's response to treatment and clinical condition.
**: May be considered in cases not responding to 4-6 weeks of appropriate antibiotic treatment.

Practice, contraindications and complications of HBO application: HBO application can be performed in single or multi-patient rooms. Multiple rooms may allow closer monitoring of critically ill patients. HBO can be administered at pressures of 2, 2.5, 3 Atm (usually 2.5-3 Atm) and usually 100% oxygen. The duration of each application can last 45-300 minutes. While 1-3 sessions may be required in treatments of acute events (such as carbon monoxide intoxication, deep diving stricken disease), 10-40 sessions and more may be required in chronic medical conditions (such as clostridial necrotizing fasciitis/myonecrosis, rhinoserebral mucormycosis, intracranial abscesses, refractory chronic osteomyelitis) (1). While HBO sessions continue, the patient should be evaluated and the frequency of sessions should be adjusted and/or reconsidered according to the response. Necessary precautions should be taken in terms of infection control, especially in patients receiving HBO in multiple rooms and especially in risky patients.

Contraindications and complications of HBO: HBO is generally safe. The only absolute contraindication is untreated pneumothorax. Relative contraindications include asymptomatic pulmonary air bullae/cysts (detected on chest radiography), recent ear and thoracic operations, obstructive lung diseases, upper respiratory tract infections, sinusitis. Complications due to increased CNS toxicity due to high oxygen may occur in patients with a history of convulsions. However, relative contraindications should not be accepted as absolute contraindications; HBO may be given on an individual patient basis, by discussing the indications and, if necessary, by closely monitoring the patient (1,2).

The most common complications are middle ear barotrauma (approximately 2%) and sinus barotrauma. Nasal decongestant, nasal corticosteroid spray or antihistamine administration may be useful before HBO treatment. Reversible myopia may develop due to direct oxygen toxicity of HBO to the lens. Myopia resolves within days to weeks after HBO is discontinued. Pulmonary barotrauma is a rare condition and may lead to pneumotrax. Rarely, pulmonary oxygen toxicity may occur. This is characterized by chest tightness, cough and transient decrease in pulmonary function. Convulsion due to CNS oxygen toxicity is rare (1,2).

In the light of the information given above, the answer to the question can be briefly summarized as follows: HBO therapy may be recommended as an adjunctive treatment to antibiotics and other treatments (including surgical treatments) in infectious diseases in some cases (Table 1). However, this decision should be made rationally and early in order to obtain optimal benefit from the treatment. HBO treatment should be evaluated individually on the basis of pediatric patients in the light of recommendations for adults, and appropriate management should be ensured by taking necessary precautions for possible side effects.

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