Review Article

JRAD Journal of Research and Advancement in Dentistry

J Res Adv Dent 2017;6:2s:187-192.

Hyperbaric Oxygen Therapy: A Boon For Oral Lesion

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ABSTRACT

Background: Worldwide, oral cancer is one of the most prevalent cancers and is one of the 10 most common causes of death. It has been established that virtually all oral cancers are preceded by visible clinical changes in the oral mucosa usually in the form of white or red patches termed as precancerous lesions and conditions. Numerous treatment modalities ranging from various drugs to behavioral therapy have been tried with inconsistent results with varying degrees of success reflecting low predictability, requiring further evaluation and standardization.

"HYPER" means increased and "BARIC" means pressure. Hyperbaric Medicine is the clinical specialty using pressure higher than local atmospheric pressure (>1atm) to treat diseases or injuries inside a hyperbaric chamber, to derive therapeutic benefit from breathing gases, usually O_2.In 1662 hyperbaric air was used by Henshaw for the treatment of "affections of the lung". (Lung diseases).

Keywords: Hyperbaric oxygen, OSMF, Hypoxia, Oxidative stress.

INTRODUCTION

Head and neck cancers account for approximately 5% of the overall cancers treated in the United States and ranked the 8th most expensive cancer in the United States today. There are five primary sites that make up this group of cancers: larynx, pharynx, oral cavity, salivary glands, and paranasal sinuses. It has been established that virtually all oral cancers are preceded by visible clinical changes in the oral mucosa usually in the form of white or red patches termed as precancerous lesions and conditions.

However, in World Health Organization (WHO) Workshop, held in 2005, the term "potentially malignant" was preferred above "premalignant" or "precancerous". Furthermore, it has been recommended to abandon the distinction between potentially malignant lesions and potentially malignant conditions and to use the term "potentially malignant disorders" (PMD) instead. Of all the PMD, Leukoplakia, Oral submucous fibrosis, Oral lichen planus are the most common lesions.

HYPERBARIC OXYGEN THERAPY (HBOT)

Hyperbaric Oxygen Therapy (HBOT) is achieved when the patient is breathing 100% O2 intermittently, in a closed chamber (hyperbaric chamber), while being inside a chamber at a pressure higher than the pressure of the sea level (more than 1 atm). Exposing some parts of the body to 100% oxygen or breathing 100% O2 at 1 atm of pressure does not constitute HBOT.

Received: Apr. 19, 2017: **Accepted:** May. 30, 2017
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pISSN 2278-0076
eISSN 2321-9270

THE HISTORICAL EVOLUTION OF HBOT

The use of air and oxygen under increased atmospheric pressure is distinguished in time "pre-scientific" and "scientific period". Aristotle in 300 BC, described the ruptured eardrum as a complication of undersea diving . During the 17th century in England, metallic vessels strong enough to hold air under pressure, combined with the production of pumps capable of compressing air. Resulted in the treatment of patients with a variety of medical problems with hyperbaric air treatments. In the 19th century, in various European countries hyperbaric chambers, were initially created for exposing patients to ambient air under modest pressure and eventually became health spa accoutrements and were used empirically to treat a variety of maladies.

Among all the first scientists who studied the diver's disease, was the Greek professor Michael Katsaras (1888), who after many clinical and experimental studies, described in detail the pathogenesis and clinical types of the disease. He suggested the slow emergence of the diver and stopping at regular time intervals as a prevention method. Since the beginning of the 20th century Hyperbaric Medicine enters a period of doubt. In Kansas City in 1921, Dr. Orville J. Cunningham built a multiplace hyperbaric compressed air chamber to treat patients with a wide variety of ailments. Supported by a wealthy industrialist, Cunningham later constructed the biggest hyperbaric chamber in the world (a five storey, 20 meter diameter, hyperbaric building, on the top floor of which, there was a smoking room), which had the potential to reach up to 3 atm pressure.

The scientific period of HBOT actually begins in the late '50s. When in Amsterdam in 1956, the professor of surgery Boerema (1902- 1978), having studied experimentally the effects of hyperbaric oxygen (HBO), used HBOT to extend the duration of disruption of cardiac function in cardiac surgery (before application of extracorporeal circulation). Brummelkamp in the Netherlands demonstrated the therapeutic effect of HBO in anaerobic infections in general; however, perhaps the greatest achievement of HBOT was the treatment of gas gangrene. Before the use of HBOT, gas gangrene was treated with extensive debridement of damaged tissue or amputation. HBO was presented in 1960 as a possible treatment for gas gangrene and it was observed that the mortality rate sharply declined from 66% to 23%.

Definition

The Committee on Hyperbaric Medicine defines HBOT therapy as "A mode of medical treatment in which the patient is entirely enclosed in a pressure chamber and breathes 100%. Oxygen at a pressure >1 atmosphere absolute (ATA)." ATA is the unit of pressure and 1 ATA is equal to 760 mm of mercury or pressure at sea level.

Mechanisms of action

The clinical benefits of hyperbaric oxygen can be explained by the

1. Mechanical effects of pressure,
2. Physics of gas laws
3. The physiological and biochemical effects of hyperoxia and
4. Through the reversal of local hypoxia in target tissues

When we normally breathe air (with 21% O2) at sea level pressure, most tissues need of oxygen are met from the oxygen combined to hemoglobin, which is 95% saturated. 100 ml blood carries 19 ml O2 combined with hemoglobin and 0.32 ml dissolved in plasma. At the same pressure if 100% O2 (oxygen) is inspired, O2 combined with hemoglobin increases to a maximum of 20 ml and that dissolved in plasma to 2.09 ml (fig 1)

HBOT causes increase in the diffusion of more oxygen under raised atmospheric pressure into solution i.e., plasma component of the blood. The amount of O2 dissolved in plasma raises from 4.4 ml/dL to 6.8 ml/dL with increase in 1 ATA. This raised O2 levels in plasma are responsible to meet oxygen demand in hypoxic areas irrespective of blood hemoglobin levels and amount of Oxyhemoglobin, this forms the rationale of this therapy in treating certain hypoxic conditions such as Carbon monoxide poisoning, etc and hemoglobin pathologies such as anaemias, cyanosis, etc.

EFFECTS OF HYPEROXIA:

1. Improved leucocytes killing activity.

2. Promotion of angioneogenesis in problem wounds, flaps and irradiated tissues.
3. Reduced falls in adenosine triphosphate (ATP) and phosphocreatinine levels in burns.
4. Decreased white cell adherence to capillary walls.
5. Vasoconstriction in normal blood vessels.
6. Decreased post-traumatic tissue oedema.
7. Decreased lipid peroxidation.

Availability and administration

Multiplace chambers are available in a few NHS hospitals (Aberdeen, Craigavon, and Newcastle upon Tyne), Royal Navy centers, private units, police diving units, professional diver training schools, and sites associated with the North Sea oil industry. The United States has over 250 facilities.

INDICATIONS FOR HBOT

- Carbon monoxide (CO) poisoning complicated by cyanide poisoning
- Air or Gas embolism
- Clostridia myositis and myonecrosis (gas gangrene), anaerobic cellulitis and necrotizing fasciitis
- Crush injury, compartment syndrome and other acute traumatic ischemia
- Decompression Sickness (DCS)
- Arterial Insufficiencies: i) central retinal artery occlusion ii) the
- enhancement healing of selected problem wounds (chronic ischemic ulcers)
- Severe anemia
- Adjunctive therapy in intracranial abscess (ICA)
- Necrotizing soft tissue infections
- Refractory osteomyelitis
- Delayed radiation injuries (soft tissue and bony necrosis)
- Compromised grafts and flaps
- Acute thermal burn injury

Idiopathic Sudden Sensor neural Hearing Loss (ISSHL) other indications under investigation are perinatal asphyxia, anoxic encephalopathy (acute-chronic), CNS injuries, myocardial, Ischemia and Miscellaneous Sports Injuries.

CONTRAINDICATIONS OF HBOT

Absolute contraindications

- Untreated pneumothorax
- The use of Doxorubicin (Adriamycin), Cisplatin, Disulfiram (Antabuse), Mafenide acetate (Sulfamylon)

Relative contraindications

- Claustrophobia
- Chronic obstructive pulmonary disease (COPD)
- Upper respiratory infections (Otitis and Sinusitis)
- Non-reasoning pulmonary opacities on chest radiograph
- Pregnancy
- History of optic neuritis
- Previous thoracic surgery or ear surgery
- Uncontrolled high fever
- Epileptic seizures
- Congenital spherocytosis
- Cardiac pacemaker

Indications of HBOT in dentistry:

Osteoradionecrosis

- Post radiotherapy cases
- Mandibular Osteomyelitis, Chronic Refractory Osteomyelitis
- Periodontal disease
- Infected Implants

ADVERSE EFFECTS

- Middle ear barotraumas is the most common complication of HBOT therapy, with an incidence of about 2%. Inner ear barotraumas is a very rare occurrence .
- Sinus squeeze is the second most common complication of HBOT therapy.
- Tooth pain can occur during compression or decompression and this typically follows dental treatment that has created an air space under a dental filling.
- Pulmonary oxygen toxicity can occur in patients if exposed for prolonged periods.
- Fire is the most common fatal complication of hyperbaric oxygen therapy.

GENERAL SAFETY RULES:

- When the main compartment is in use, the outer lock should be brought back to the surface ready for use.
- The chamber should be cleaned after every use and when it is not in use the doors should be dogged.
- All dirty overalls, footwear and static risk clothing should be removed and pockets should be checked for lighters, matches or any forbidden items.
- During surface decompression procedures the main chamber should be pressurized to the required depth before the dive so that the diver can be pressurized efficiently and quickly in the outer lock.
- An attendant should be available with all therapeutic treatments and the attendant will have knowledge of the symptoms and treatment of oxygen poisoning with the ability to carry out neurological checks following the check list.
- Oxygen rich mixes delivered via the BIBS system require the chamber oxygen percentage to be continuously monitored and flushed as appropriate ensuring levels do not approach the maximum specified.

Recommended screening method for patients undergoing HBOT:

(a) Complete Clinical Examination.
(b) Investigations: Complete Blood Count

Urine analysis
Blood Biochemistry to include renal function test
Lipids profile
ECG
Chest roentgenogram
Spirometry.

(a) Additional Investigations if Required: HRCT chest (if individual unable to perform Spirometry), Reticulocyte count & Peripheral blood smear (to rule out hemolytic anemia).

Follow up Investigations during HBOT runs: Hb estimation and Spirometry at 10 day interval in suspected cases. As most tumors grow, cells undergo nutrient deprivation and oxygen deficiency due to the unregulated growth and insufficient vascular supply. A hypoxic microenvironment is reported to induce cellular responses, trigger major molecular and immunological processes, and thus drive tumors to malignancy. However, research into the influence of hyperbaric oxygen on OPMDs is still unreported. In spite of various therapies for OPMDs, determination of effectiveness is far from satisfactory, because of recurrence and malignance. HBO increases oxygen tension, enhances the amount of dissolved oxygen in the plasma, and raises oxygen delivery to the oxygen-deficient tissue. Moreover, Inamoto et al suggested that reduction of interleukin-1 (IL-1) production may play a pivotal role in the immunosuppressive effect of HBO. Benson et al. found an inhibitory effect of HBO on pro-inflammatory cytokine at the transcription and translation level.

Relation of HBO on OPMD at the cellular level

Inhibition of T-cell proliferation

A study by Gaetano et al. demonstrated that CD4+ T cells showed a lower proliferation rate than the control after HBO, on the non obese diabetic mouse. In addition to increased resting CD4+ T cells, a significant reduction in antigen-presenting cell activation was also observed following 100% HBO. Furthermore, Xu et al. studied the influence of HBO on the immune system of normal and autoimmune mice and found the cell population in the lymphoid tissue decreased at 2.8 atmospheres (atm) with 100% oxygen for 4 h daily over three or seven days. So it demonstrated that HBO therapy may be useful for some autoimmune diseases. OLP is a common T-cell-mediated inflammatory autoimmune disease, with the features of disease chronicity, depressed immune suppressor activity and the presence of auto-cytotoxic T-cell clones in lesions.

Overall, HBO appears to be anti-inflammatory and has immunosuppressive effects. Several studies suggested that HBO could be helpful to cure OLP, especially the erosive type. Meanwhile, the increased oxygen content could result in several molecular effects including the inhibition of IFN-c and TNF-a, up-regulation of the IL-2 receptor, as well as inhibition of T-cell proliferation. We could speculate that HBO may decrease T-cell proliferation and/or reduce expression of IFN-c to prevent CD4+ T cells from triggering the activation of CD8+ T cells in OLP.

Enhancement of fibroblast apoptosis and inhibition of fibroblast activation: Notably, Conconi et al. found that exposure to HBO at 2.5 ata for 120 min enhanced apoptosis of mouse fibroblast cell line. In addition, HBO could reduced cell proliferation and promoted cell death when skin fibroblasts were cultured in a high-glucose medium at 2.5 ata for 90 min on three consecutive days. Considering that different levels of pressure and duration of exposure may result in assorted effects, HBO may induce apoptosis of lymphocytes or/and decrease lymphocytic proliferation so as to keep fibroblasts from activating cytokines. For instance, HBO at 1.0 or 2.5 ata for 30 and 60 min enhanced 3T3/J2 fibroblast cell growth while at 2.5 ata for 120 min, it exerted a proapoptotic effect. Furthermore, HBO may potentially contribute to the inhibition of fibroblasts by reducing IL-1b and TNF-a production.

Studies have suggested that arecoline reduces cytokines such as IL-1, TNF-a, and tumor growth factor-beta (TGF-b) from inflammatory cells, and inhibits collagenase enzyme activity and collagen Phagocytosis, thus inducing OSF fibroblasts to elevate collagen synthesis. Overall, HBO may be beneficial for OSF by triggering fibroblast apoptosis and inhibiting fibroblast activation. (fig 3)

Relation of HBO on Orally Potential Malignant Disorders at the molecular level

Reduction of HIF production-

Hypoxia elicits a range of adaptive responses to promote cells' survival and is mainly regulated by hypoxia-inducible factors (HIFs), a family of transcription factors. HIFs orchestrate signaling of angiogenesis, metabolism, growth, and survival . A growing body of experimental and clinical data has validated HIFs as targets for cancer therapy. It has been revealed that HIF-1a is associated with up-regulation of various growth factors: VEGF, TGF-b, and fibroblast growth factor (FGF) . Interestingly, research about colorectal, gall bladder, and prostate carcinogenesis found that up-regulation of HIF-1a was associated with increased expression of VEGF. Recent studies on renal and lung fibroblasts showed that up-regulation of TGF-b by HIF-a resulted in hypoxia. Several reports showed that over expressions of HIF-1a protein were related to the pathogenesis of many inflammatory and autoimmune diseases such as rheumatoid arthritis and osteoarthritis.

Regulation of VEGF expression and angiogenesis:

HBO could promote vascular proliferation in wounds .In an irradiated rabbit model, Marx et al. found that hyperbaric oxygen showed an eight- to nine fold increase in vascular density over norm baric oxygen. Furthermore, VEGF expression was induced by HBO via ERK, JNK, and c-Jun/AP-1 activation. Vessels, as the channel to deliver oxygen and nutrition, and recycle metabolic residues, altered structure and density when inflammation and tumorigenesis occurred. (fig 4)

CONCLUSION

The HBOT is a relatively new treatment, as it has struggled to be supported scientifically over the last 50 years. The use of HBOT as an adjunctive therapy according to the internationally recognized indications has become widely accepted, mainly due to the clarification of the physiological effects of hyperbaric oxygen in various systems and its mechanisms.

In summary, it is possible for us to utilize HBO treatment as a potential supplementary therapy to improve the whole hypoxic microenvironment of OPMDs. It is important to understand that different doses of hyperoxia have different effects. A further investigation is required, in order to ensure the best possible both clinical and therapeutic effect.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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