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Review Article

Dentistry Section

Hyperbaric Oxygen Therapy—A Novel Treatment Modality in Oral Submucous Fibrosis: A Review

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ABSTRACT

Oral submucous fibrosis (OSMF) is a chronic, debilitating disease characterized by juxta epithelial fibrosis of the oral cavity and regarded as a potentially malignant disorder. 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. Novel treatment modality such as Hyperbaric oxygen therapy (HBOT) involves inhalation of 100% oxygen at increased atmospheric pressure usually ranging between 2.0 and 2.5 atmospheres for periods between 60 and 120 min. HBOT which can increase oxygen tension and delivery to oxygen-deficient tissue, is a supplementary therapy to improve hypoxic environment of OSMF and also possesses potent anti-inflammatory properties. This article enlightens on possible beneficial effects of HBOT in the management of OSMF at cellular and molecular level.

Keywords: Collagen, Hypoxia, Oxidative stress, Potentially malignant disorder

INTRODUCTION

Oro-pharyngeal cancer is more common in developing countries than the developed ones. Worldwide, oral cancer is one of the most prevalent cancers and is one of the 10 most common causes of death [1]. 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 [2].

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 [3]. Of all the PMD, Leukoplakia, Oral submucus fibrosis, Oral lichen planus are the most common lesions.

Oral submucous fibrosis (OSMF) is a chronic, debilitating disease characterized by juxta epithelial fibrosis of the oral cavity. It is regarded as a precancerous and potentially malignant condition with incidence rates of 0.07–1.22% and malignant rates of 2.3–7.6%. Widely accepted definition of the disease as given by Pindborg and Sirsat (1966) is a chronic disease of insidious onset which can affect any part of the oral mucosa, rarely oropharynx .The disease starts initially with formation of vesicles with stomatitis, leading to fibro-elastic changes in the lamina propria causing fibrosis that leads to trismus, epithelial atrophy leading to burning sensation and inability to eat [4].

HYPERBARIC OXYGEN THERAPY (HBOT)

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. Hyperbaric Oxygen Therapy—"HYPER" means increased and "BARIC" means pressure.

The concept of using respiratory gases at ambient pressures in the treatment of illnesses dates back three centuries. In 1662 hyperbaric air was used by Henshaw for the treatment of "affections of the lung" [5]. In 1834 Junod (France), built a chamber to treat pulmonary conditions at pressures between 2 and 4 atmospheres absolute (ATA). Hyperbaric air was used to treat a wide variety of ailments, including cardio – pulmonary disease, carcinomas, diabetic foots and psychological disorders and was used as an aid to surgery, providing "deeper anaesthesia and less cyanosis". Orval J Cunningham in the early 1900s, successfully treated sufferers of the Spanish flu epidemic with hyperbaric air.

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 [6,7].

When we normally breathe air (with 21% O_2) 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 O_2 combined with hemoglobin and 0.32 ml dissolved in plasma. At the same pressure if 100% O_2 (oxygen) is inspired, O_2 combined with hemoglobin increases to a maximum of 20 ml and that dissolved in plasma to 2.09 ml [Table/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 O_2 dissolved in plasma raises from 4.4 ml/dL to 6.8 ml/dL with increase in 1 ATA. This raised O_2 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.

Few Physiological and biochemical effects of hyperoxia [8]

1. Improved leucocyte killing activity.
2. Promotion of angioneogenesis in problem wounds, flaps and irradiated tissues.

[Table/Fig-1]: Multiplane Hyperbaric chamber

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.

Few Indications for HBOT Approved by the Undersea and Hyperbaric Medical Society [9]

1. Decompression sickness and Air or gas embolism.
2. Carbon monoxide poisoning .
3. Clostridial myositis and myonecrosis (gas gangrene).
4. Intracranial abscess, actinomycosis.
5. Necrotising soft tissue infections.
6. Skin grafts and flaps (compromised).

Contraindications for HBOT [8]

1. Absolute
   a. Untreated tension pneumothorax.
2. Relative
   a. Upper respiratory tract infection.
   b. Asymptomatic pulmonary lesions seen on chest x-ray.
   c. History of thoracic or ear surgery.
   d. Pregnancy.
   e. Claustrophobia.

Adverse Effects [8]

1. Middle ear barotrauma is the most common complication of HBOT therapy, with an incidence of about 2%. Inner ear barotrauma is a very rare occurrence [10].
2. Sinus squeeze is the second most common complication of HBOT therapy.
3. Tooth pain can occur during compression or decompression and this typically follows dental treatment that has created an air space under a dental filling.
4. Pulmonary oxygen toxicity can occur in patients if exposed for prolonged periods.
5. Fire is the most common fatal complication of hyperbaric oxygen therapy.

Over the last 20 years, 52 deaths have been reported, most due to inadequate fire precautions [11].

Indications of HBOT in Dentistry [12]

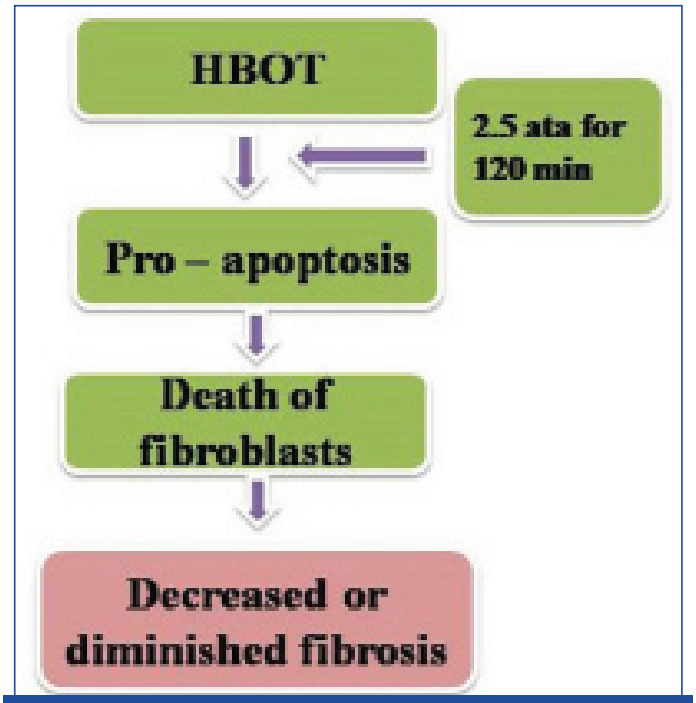
1. Osteoradionecrosis
2. Postradiotherapy cases
3. Mandibular Osteomyelitis, Chronic Refractory Osteomyelitis
4. Periodontal disease
5. Infected Implants

EFFECTS OF HBOTIN OSMF – A MOLECULAR LEVEL APPROACH

1. Collagen Metabolism

In OSF increased fibrosis is due to imbalance between activation of fibroblasts and reduced degradation of collagen leading to increased fibrosis and trismus. Conconi et al., found that exposure to HBOT at 2.5 ATA for 120 min enhanced apoptosis of mouse fibroblast cell line [13]. HBOT also 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 [14].

HBOT may induce apoptosis of lymphocytes or/and decrease lymphocytic proliferation so as to keep fibroblasts from activating cytokines. HBOT 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 pro apoptotic effect. HBOT may potentially contribute to the inhibition of fibroblasts by reducing IL-1b and TNF-α production [13,15,16]. HBOT may be useful in the treatment for OSF by promoting fibroblast apoptosis and inhibiting fibroblast activation [17] [Table/Fig-2].



[Table/Fig-2]: Image showing effect of HBOT on fibroblasts

2. Down Regulation of TGF-β and IFN-γ

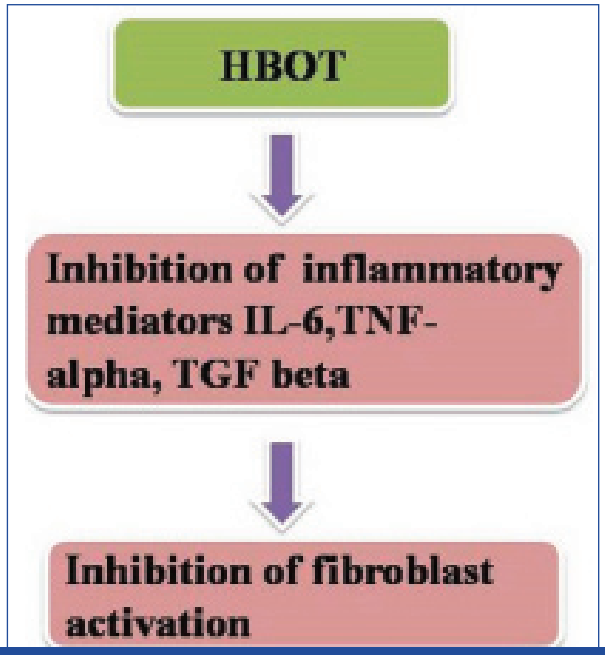
TGF-β expression, IFN secretion and the growth of fibroblasts decreased after chronic exposure to HBOT [18].

3. Suppression of TNF-α Secretion

TNF-α could up-regulate mRNA expression of collagen types I and III in cultured lung fibroblasts [19]. This suggests that HBO may have the potential to treat OSF by inhibiting TNF-α and influencing the synthesis of collagenase [17] [Table/Fig-3].

4. *Oxidative Stress [19]*

Oxidative stress occurs when the formation of oxygen free radicals exceeds the antioxidant defense capabilities [20]. It is established



[Table/Fig-3]: Image showing effect of HBOT on inflammatory mediators

that the lipid peroxidation increases with severity of the disease which is reflected in increase in the plasma malondialdehyde levels (marker of oxidative stress and lipid peroxidation) when compared to healthy controls.

HBOT treatment provides extra oxygenation of the tissues of the whole body, decrease in the production of reactive oxygen species, lipid peroxidation and increasing the antioxidant activity of enzymes such as Superoxide dismutase, glutathione peroxidase, catalase, paraoxonase, and heme-oxygenase-1 [21,22].

5. Inflammation

Continuous contact between the quid and oral mucosa resulting in absorption and metabolism of the alkaloids in the quid resulting in the chronic inflammation causing activation of macrophages and T cells and an increase in the level of cytokines such as IL6, TNF, IF-α and TGF- β [23].

HBOT has potent anti-inflammatory tissue effects. It has been shown to attenuate the production of pro-inflammatory cytokines including TNF-α, IL-1, IL-1b, and IL-6 and increase the production of anti-inflammatory IL-10 [15,24].

6. Hypoxia

Extensive fibrosis of the connective tissue causes reduction of vascularity, resulting in subsequent hypoxia in both fibroblasts and surface epithelia. Hypoxia causes atrophy and ulceration of the epithelium by inducing apoptosis. In addition, the over expression of hypoxia-induced factor-1a is seen in OSMF, which indicates changes in cell proliferation, maturation, and metabolic adaptation increasing the possibility of malignant transformation [25].

OSMF is now considered as a collagen metabolism disorder, OSMF fibroblasts show 1.5 times increased activity of collagen production, when compared to their healthy counterparts. However, as the disease progresses Type III collagen is almost completely replaced by Type I collagen, and subsequent collagen is considered to be more resistant to regular collagen degradation process [25]. Increased fibrosis leads to relative ischemia and subsequent hypoxia of superficial layers causing epithelial atrophy and ulceration suggesting over expression of Hypoxia-induced factor-1a (HIF-1a). Hypoxia-induced factor-1a plays key role in explaining the possibility of malignant transformation in OSMF [26].

HIF-1a was up-regulated at both the protein and mRNA levels in OSF, which suggested that it may contribute to the progression of fibrosis. Early stages of OSF showed increased vascular density and obviously decreased in the middle and late stages, blocking capillary angiogenesis [17].

HBOT increases oxygen tension, enhances the amount of dissolved oxygen in the plasma, and raises oxygen delivery to the hypoxic areas. HBOT improved ischemia via decreasing expression of HIF-1a [27]. The anti-inflammatory effect of HBOT might occur through the relief of hypoxia and the down-regulation of HIF-1a [28]. HBOT may have the potential to improve the vascular situation.

Role of micro nutrients

Copper is present in high quantities of areca-nut causing it to increase in the blood picture of a chronic gutkha chewer (OSF) The enzyme lysyl oxidase is found to be upregulated in OSF [29] which is a copper dependent enzyme and plays a key role in collagen synthesis and its cross linkage making it resistant to collagen degradation. HBOT also increases zinc, decreases copper, and increases ceruloplasmin levels [30].

CONCLUSION

OSMF is having highest malignant potential than any other oral potentially malignant disorders, in which etio-pathogenesis is poorly understood despite the recent advances. Novel treatment modality such as HBOT in the management of OSMF has been studied. HBOT not only has a cellular-regulation effect, but also plays a role in the management of various cytokines and transcription factors for angiogenesis and anti-inflammatory at cellular and molecular level .

HBOT may be considered as a potential supplementary therapy to improve the localized hypoxic microenvironment of pre cancers such as OSMF, Erosive lichen planus etc. Therefore, more evidence-based, randomized, and controlled studies need to be conducted with HBOT on larger samples to find out the most suitable doses and efficacy of it in treating OSMF.

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