INTRODUCTION
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

HYPERBARIC OXYGEN THERAPY (HBOT)
High pressure HBOT is a non-invasive and safe treatment option that increases local blood oxygenation, stimulates wound healing and reduces the risk of infection. The concept of using respiratory gases at ambient pressures with varying degrees of success reflecting low predictability, requiring further evaluation and standardization. Novel treatment modalities 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.

Mechanisms of action
The clinical benefits of hyperbaric oxygen can be explained by the following principles:

1. **Mechanical effects of pressure:**
   - Increased mechanical pressure of gas is essential to increase the oxygen delivery to tissues.

2. **Physics of gas laws:**
   - The partial pressure of oxygen increases with increased pressure, thus increasing the solubility of oxygen in the blood.

3. **The physiological and biochemical effects of hyperoxia:**
   - Hyperoxia has a direct effect on cell metabolism and increases the oxygen dissociation curve of hemoglobin, leading to increased oxygen delivery to tissues.

4. **Through the reversal of local hypoxia in target tissues:**
   - HBOT can increase 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 increases from 2.09 ml/dL at sea level pressure, 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 hemoglobinopathies such as anaemias, cyanosis, etc.

Few Physiological and biochemical effects of hyperoxia

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

Based on the above mentioned principles, HBOT can be used as an effective treatment modality in OSMF.
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.
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-1β 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].

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...
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, paraaxonase, and heme-oxygenase-1 [21,22].

5. Inflammation
Continous 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 subquent 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-1α 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 degradation. HBOT also increases zinc, decreases copper, and increases ceruloplamin levels [50].

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 ceruloplamin levels [50].

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.

REFERENCES


M. Ashwini Kumar et al., Hyperbaric Oxygen Therapy in the Treatment of Oral Submucous Fibrosis

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