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Ozone Therapy in Dentistry: A Review

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Review Article

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ABSTRACT

Ozone which is a component of upper layer of atmosphere is being used in field of medicine and dentistry over decades and it has gone through many advances since then. Therapeutic use of ozone is successful due to its unique antimicrobial, oxidative and non toxic properties. It renders minimally invasive dental procedures including treatment of incipient carious lesions and sterilization of root canal system. This review article summarizes use of ozone for treatment of various diseases.

INTRODUCTION

Ozone is a chemical compound consisting of three atoms of oxygen with molecular weight of 47,98 g/mol [1]. It is present in upper layer of atmosphere and is highly unstable, giving off nascent oxygen depending on systemic conditions like temperature and pressure [2] . The function of ozone in upper atmosphere is to filter harmful ultraviolet rays from reaching earth's surface. Apart from this, ozone is used in many other fields such as in dentistry and medicine [3]. Ozone is being used successfully in field of medicine for more than a decade due to is properties like simplicity of performance, good tolerance by patients and the absence of side effects. Even though ozone therapy is not accepted by many medical personnel due to its oxidative properties and well known toxic effects on respiratory system [4]. Ozone can enhance the after effects of root canal treatment by utilizing different forms such as ozonated water, ozonated oils directly into infected canals. Direct placement of ozone in infected periodontal pockets is known to seize periodontal disease without any associated side effects.

HISTORY

In 1785 researchers noticed an odor when electric sparks passed in an electrostatic machine. In 1840 Christian Friedrich Schonbein named the substance as ozone, which originated from the Greek word "ozien" –to smell. He is considered as the father of ozone therapy. Due to the known bactericidal and antimicrobial properties of the substance, ozone generator was useful in industrial application and disinfection of water. In 1857 Joachim Hensler, a German physicist and Hans Wolf, German physician developed first Ozone generator for medical use, which was capable of producing a mixture of ozone and oxygen at therapeutically variable dosages [5]. Medically used ozone is a mixture of pure 02 (0.1% - 0.5%) and O_3 (95%-99%) [6,7]. In 1870 evidences show Ozone being used therapeutically to purify blood by C Lenderin Germany [8,9]. It was also used in treating gaseous, post traumatic gangrene in German soldiers during 1st world war [7]. Before 1983, many Swiss dentists have also been known to use ozone in dentistry [8,9].

Mechanism of Action of Ozone

There are several known actions of ozone on human body, such as immunostimulating and analgesic, antimicrobial

(bactericidal, viricidal and fungicidal), bioenergetics and biosynthetic (activation of the metabolism of carbohydrates, proteins and lipids) [10]. Ozone damages bacterial cell wall by ozonolysis and oxidation of intracellular protein [11]. It only affects bacterial cell wall and does not show any adverse effects on human body because of their major anti-oxidative ability. Ozone is very effective in destructing the antibiotic resistant strains in an acidic PH [12]. During viral infections ozone causes intoleranceof infected cells to peroxides and change of activity of reverse transcriptase, whichtakes part in viral protein synthesis [13,14]. As a response to inflammatory process, Ozone stimulates the release of interleukins, leukotrienes and prostaglandins [15], to promote wound healing. Ozone causes secretion of vasodilators, such as Nitrous Oxide, which is responsible for dilation of arterioles, venules and prevents clumping of Red Blood Cells (RBC), thus increasing their surface area for oxygen transportation. It also activates aerobic processes like glycolysis and Krebs cycle at cellular level to stimulate blood circulation [16], hence ozone is also used for treatment of circulatory disorders.

Application of Ozone in Dentistry

The use of ozone has been proposed in dentistry because of its antimicrobial and disinfectant properties. It has been used for treatment of incipient carious lesions, sterilization of cavities, root canals, enhancement of epithelial wound healing.

➢ Treatment of carious lesions-Ozone is delivered to the affected area through a special hand piece equipped with a silicon cup, which is kept in contact with the tooth to form a tight seal. Ozone causes oxidation of bacterial cell wall and bacterial byproduct [17,18]. Pyruvic acid is a byproduct, which is reduced to acetate and Carbon Dioxide by the action of ozone over the tooth surface. This is a conservative procedure for non cavitated carious lesion. Studies demonstrate that 40 seconds application of ozone significantly reduces *S. mutans*, whereas 60 seconds exposure has almost eliminated *S. mutans*, *L. casei* and *A. naeslundi* [19]. Ozone is also effective against microflora associated with root caries lesions [20].

In endodontics, files lubricated with ozonated oils and use of ozonated water is recommended instead of sodium hypochloride. A slow insufflation with about 30 ml concentrated ozone should be done for 45-50 seconds before obturating the canal. Ozone is also used for bleaching of endodontically treated teeth.

➢ Periodontal therapy- Progression of periodontal disease is caused by plaque biofilm, use of ozonated water was known to be effective in reducing count of both gram+ve and gram-ve bacteria in dental plaque [21]. Ozonated oil is used as a therapeutic agent in treatment of acute necrotizing ulcerative gingivitis.

➢ Ozone in prosthodontics- Ozone is used in disinfection of dentures, as denture plaque control is essential to avoid denture stomatitis. When dentures are exposed to ozonated water, antimicrobial activity has been observed against candida albicans [22]. Ozone in gaseous form has proved to be a more potent antimicrobial agent when compared with ozonated water. When applied on the surface of removable partial denture alloys ozone had very little impact on quality of alloy in terms of surface roughness and weight.

➢ Ozone in oral surgery-ozone accelerates the healing process [23]. Patients with chronic osteomyelitis when exposed to ozone, more rapid bone and soft tissue healing were observed with minimum complications. Ozone therapy also found to be effective for treatment of refractory osteomyelitis in addition to the treatment with antibiotics, surgery and hyperbaric oxygen.

➢ Ozone in treatment of periimplantitis- Studies has proved that ozone is efficient in reducing adherent bacteria on titanium and zirconia without affecting their adhesion and proliferation of osteoblastic cells. It also promotes wound healing due to increase in tissue circulation.

Contraindications of Ozone Therapy

1. Pregnancy
2. Glucose 6 phosphate dehydrogenase deficiency
3. Hyperthyroidism
4. Severe anemia
5. Severe Myasthenia
6. Acute alcohol intoxication
7. Recent Myocardial Infarction
8. Ozone allergy

DISCUSSION

Minimal invasive dentistry has set a new standard of oral health care. According to new researches and clinical studies ozone therapy is capable of treating the carious lesions at very initial stage. Ozone therapy has been proved to be a new therapeutic modality with great benefits for the patient. The undisputed antimicrobial effect of ozone as compared to other antiseptic agents

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makes it a therapeutic agent of choice. Several studies demonstrated the oxidative effect of ozone on microorganisms. Ozone is known to causes decomposition of bacterial cell wall and bacterial byproduct [17,18], it also accelerate healing of wounds [23]. Many evidence based studies have been done to study in vitro biocompatibility of aqueous ozone with oral epithelial cells and periodontal tissues. Even though ozone therapy is not accepted by many medical personnel due to its oxidative properties and well known toxic effects on respiratory system [4].

In spite of the fact, clinical application of ozone is still a matter of controversy. This is supposed to be because of lack of ample in vivo and in vitro randomized controlled trials. Evidence based studies and clinical trials are still required to rationalize the efficacy of ozone. Cochrane databases suggest the lack of consistency between different outcome measures and absence of evidence that application of ozone reverses the decay [24].

CONCLUSION

Modern dentistry subjects to the minimally invasive dental procedures. When compared with conventional treatment procedures ozone therapy is quite promising as it is less invasive, has potent disinfectant property thus reducing bacterial count more specifically and has minimal adverse effects. It allows us to reduce treatment time and patient discomfort, thus increasing patient compliance. Hence it becomes more acceptable to the patient. Contraindications of this controversial method should not be forgotten. In future emphasis should be done on well controlled clinical trials to determine the precise guidelines about the use of therapy.

The use of topical hyaluronidase has been shown to have quicker improvement in symptoms compared with steroids alone. The combination of steroids and topical hyaluronidase shows better long-term results than either agent used alone (Kakar, 1985) [3].

Placental extract (PE)

Intralesional injection of aqueous extract of healthy human placenta. The rationale for using placental extract (PE) in patients with OSMF derives from its proposed anti-inflammatory effect (Sur, 2003), hence, preventing or inhibiting mucosal damage. Cessation of areca nut chewing and submucosal administration of aqueous extract of healthy human PE (Placentrex) showed marked improvement of the condition (Anil, 1993) [2,3].

In search of an effective drug without any contraindications and at the same time cheap and safe, local injections of Placentrex were tried in the treatment of Oral submucous fibrosis.

Tissue therapy

Filatov introduced tissue therapy, a new method of treatment of disease in 1933 and later in 1953. This owes its inception to corneal transplantation. His theory was that animal and vegetable tissues when severed from the parent body and exposed to a condition unfavorable, but not mortal to their existence undergo biological readjustment leading to the development of substances in state of their survival to ensure their vitality biogenic stimulators. Such tissues or their extracts when implanted or injected into the body after resistances to pathogenic factor stimulates metabolic or regenerative process thereby favoring recovery [6].

Injection Placentrex is an aqueous extract of human placenta.

Mode of Action

The mode of action is essentially “Biogenic stimulation”. It is also suggested that it stimulates the pituitary, adrenal cortex and regulates the metabolism of tissues. It was proved experimentally to increase the blood circulation by ossicillogram and plethysmogram i.e. it increases the vascularity of tissues. It was observed clinically also by the color changes in the mucosa.

As it contains **(Table 1)** vitamins, ferments and several other substances, it is not possible to postulate the individual action of each constituent. It is imperative to state that each one plays a role in the tissue metabolism and regeneration. It did not produce any untoward effects [6].

Figure 1. Identification of Gingival Biotype.

Technique	Method	Study	Criterion	Advantages	Disadvantages
Direct Technique	Visual inspection	Ochsenbein C, Ross S 1963	Dense,fibrotic-thick biotype	Simple, straightforward, noninvasive,	Subjective and highly variable
		Seibert J, Lindhe J 1969	Thin, friable- thin biotype		
Probe transparency	Calibrated william's periodontal probe	Kan et al 2003	Visibility of probe tip through gingival sulcus	Most accepted, Simple, convenient, and inexpensive	Difficult in identifying in pigmented gingiva
			Visible thin biotype nonvisible thick bioptype		

Radiography	CBCT	Fu JH et al 2010	Thickness of labial plate	Non-invasive, quantitative measurements,	Expensive, requires expertise, higher radiation exposure
			Thick Plate Thick Biotype		
			Thin plate- thin Biotype.		
Ultrasonic Transducer	Ultrasonic Transducer	Kydd et al 1971	< 1.2mm thin biotype	Simple, convenient, and non-invasive	Clinically unfeasible, expensive, difficult in maintaining directionality of transducer, commercially unavailable
			>1.2 mm thick biotype		
Direct Technique	Tension Free Calliper	Kan et al 2010	< 1.5mm thin biotype	Simple, convenient, and non-invasive	Precision of probe, angulations of probe, distortion of tissue during probing, invasive
			>1.5 mm thick biotype		
	Transgingival probing by periodontal probe	Greenberg J 1976	≥ 1.5 mm thick biotype		

Interferons

Naturally produced proteins with antiviral, antitumor and immunomodulatory actions. Alpha, beta and gamma interferons may be given topically, systemically and intralesionally.

Interferon gamma (IFN--ϒ)

Believed to act via ability to counteract cell surface expression of proinflammatory or proadhesion molecules on immune cells, among other effects. More studies needed to fully understand mechanisms of action.

Contraindications: Documented hypersensitivity; Escherichia coli derivatives or components

Interactions: Live vaccines; rotavirus vaccine

Precautions: Caution in preexisting cardiac disease, seizure disorder, or compromised CNS function; myelosuppression

Action

IFN--ϒ plays a role in the treatment of patients with OSMF because of its immunoregulatory effect. IFN--ϒ is a known antifibrotic cytokine. Patients treated with an intralesional injection of IFN--ϒ experienced improvement of symptoms. IFN--ϒ, through its effect of altering collagen synthesis, appears to be a key factor to the treatment of patients with OSMF, and intralesional injections of the cytokine may have a significant therapeutic effect on OSMF (Haque, 2001) [3].

The primary cause leading to trismus in OSMF may be fibrosis and fibrous band formation in the oral mucosa. Fibrogenic cytokines secreted by activated macrophages or T lymphocytes are very important in the development of fibrotic disorders. Activated macrophages can produce at least six fibrogenic cytokines, such as: IL-1, TNF-α, IL-6, FGF, PDGF, and TGF-β.

Activated T lymphocytes secrete fibrogenic cytokines that act directly on mesenchymal cells, and produce other cytokines that in turn activate macrophages to secrete fibrogenic cytokines that modulate the function of mesenchymal cells indirectly [7].

Cytokines and growth factors produced by inflammatory cells within the lesion may promote fibrosis by inducing proliferation of fibroblasts, up regulating collagen synthesis and down regulating collagenase production [8].

Both IL-1 and TNF- α stimulate fibroblast proliferation in vitro [9]. IL-1β and TNF- α have been demonstrated to upregulate mRNA expression of collagen types I and III [10]. Intradermal injecions of TNF- α stimulate the accumulation of fibroblasts and collagen. TNF- α has also shown to inhibit adherence and phagocytosis of collagen. Similarly, both IL- 6 and IL-8 have also been implicated in the development of fibrosis.

IFN--ϒ is an antifibrotic cytokine that can inhibit collagen synthesis. Improvement of keloids and hypertrophic scare by intralesional IFN--ϒ treatment has been reported. Local injections of IFN--ϒ reduce contracture formation and facilitate mouth opening in OSF patients [7].

Immune Milk

A study was done to test whether immune milk may have some beneficial effects on controlling the symptoms and signs in OSMF patients. The milk from cows immunized with human intestinal bacteria (immune milk) contains an antiinflammatory component that may suppress the inflammatory reaction and modulate cytokine production [7].

The chemical composition of the milk from immunized cows produced under normal dairy processing conditions is identical to that of commercial milk. However, the IgG type I antibody concentration in immune milk is on the average 20-40% higher than normal cow milk. The IgG antibody activities against human gut bacterial pathogens in immune milk are also significantly higher than normal cow milk [11].

In addition, the immune milk contains a highly active anti-inflammatory compound that can suppress the experimentally induced inflammation in animal models and can give a beneficial effect in patients with rheumatoid arthritis [12].

Surgical Treatment

Surgical excision of the fibrotic bands can be attempted but it is observed that such surgical intervention aggravate the condition. However surgical intervention is the only treatment available in the extremely advanced cases of oral submucous fibrosis [9]. It is indicated in patients with severe trismus and/or biopsy results revealing dysplastic or neoplastic changes.

Surgical modalities include the following:

1) Simple excision of the fibrous bands: Surgical excision, especially with a disease like OSMF, causes contractures during healing [2].

2) Split-thickness skin grafting following bilateral temporalis myotomy or coronoidectomy: Changes in the tendon of temporalis muscle secondary to OSMF results in the trismus. Thus, Canniff et al have recommended temporal myotomy or coronoidectomy and skin grafting which seem to be a better palliative treatment in cases where there is severe trismus. A high rate failure with skin grafts is observed [2].

3) Nasolabial flaps and lingual pedicle flaps: Bilateral full thickness nasolabial flaps for severe trismus cases. Surgery to create flaps is performed only in patients with OSMF in whom the tongue is not involved (Kavarana, 1987; Hosein, 1994) [2,3].

If lingual pedicle flap grafting is done after excision of a limited amount of diseased tissue in the retromolar area, it will certainly relieve trismus for a short period. The tongue, which serves as the donor site, is also involved in OSMF. It is therefore, hazardous to graft a part surrounded by the disease with a graft equally prone to develop the disease. The donor site is also compromised and the gain from surgery is short lived [2].

4) Submucosal placement of placental grafts:

These treatments are strictly palliative and they only help in relieving trismus temporarily. Relapse is a common complication that occurs after surgical release of the oral trismus caused by OSMF [4].

Multivitamin Therapy

Vitamins, iron and mineral rich diet should be advised to patients with OSMF. Intake of red tomatoes, fresh fruits and green leafy vegetables should be included in the regular diet. Intake of green tea should be included in the diet chart. Various studies have implicated deficiency of iron both as a cause and effect in etiopathogenesis of OSMF. Thus routine hemoglobin levels followed by iron supplements should be included in treatment plan [13].

Physiotherapy

Muscle stretching exercises for the mouth may be helpful to prevent further limitation of the mouth. This includes forceful mouth opening with the help of sticks, ballooning of mouth, hot water gargling. This is thought to put pressure on fibrous bands. Forceful mouth opening have been tried with mouth gag and acrylic surgical screw.

Role of microwave diathermy

Microwave diathermy has been used in many clinical conditions. Rae and Co-workers found microwave diathermy especially valuable in the treatment of fibrosis and trismus following dental extraction and other musculo-skeletal conditions. It was therefore thought to use microwave therapy in treatment of submucous fibrosis.

Role of Ultrasound

Ultrasound used for therapeutic purpose has a frequency of about 0.8-1 MHz and an intensity of 0.5-3 w/cm^2. Ultrasound selectively raises the temperature in some well circumscribed areas. Though skin of cheek, subcutaneous fat, muscle, connective tissue and buccal mucosa all have different acoustic impedances, the difference is not vast and hence less amount of energy is reflected at the interfaces between any two tissues and maximum energy reaches the lamina propria of the buccal mucosa. Ultrasound thus proves to be an efficient deep heating modality. Most of the heat generated by ultrasound in the buccal tissue is due to volume heating rather than structural heating. Volume heating occurs due to absorption of ultrasound by tissue proteins and its conversion to heat. Structural heating occurs at interfaces between two tissues of different acoustic impedance [14].

Others

a. Vinegar

Dilute organic acid solvent e.g. 0.5 M acetic at an adjusted pH exhibits an increased capacity to induce swelling of most tissues. Dilute acid solvents (pH 2.5) are capable of solubilizing non-cross linked molecules and fibres in which cross links are prevalent owing to the labiality of this type of cross link at acid pH 5. In practical terms, however, this effect of dilute acid solvents is limited to a portion of the collagen in the dermis and some tendons of relatively young organisms, since the more stable form of cross-link is prevalent in the fibres of virtually all other tissues. This observation recorded from animal experimental models.

A form of dilute organic acid (4% acetic acid at pH 6.5) which is commonly used for human consumption as a culinary ingredient (Vinegar) was used. This rather safe and solely noninvasive procedure embodies periodic swabbing of the affected oral mucosa with the active ingredient. using a cotton applicator. It is speculated that atrophied oral mucosa in SF augments the permeability of the mucosa to acetic acid thereby causing swelling and breakage of the collagen cross linkages, which renders it less stable. Given the nature of Submucous Fibrosis collagen, being mature (Type I & III) and normal when it meets dilute acid at a lower pH it was speculated to behave in a pre-determined manner eliciting swelling and partial degeneration. This altered collagen, in principle attracts a macrophage affected scavanging action, thereby inducing progressive collagenolysis [3].

b. Injection of Gold, Vitamin A and Collagenase, and Vasodilator injection can be used in the management of OSMF. Chemotherapeutic agents like topical application of Bleomycin can also be used in severe cases.

c. Turmeric:

Administration of turmeric powder offers protection against benzopyrene induced increase in micronuclei in circulating lymphocytes and it is an excellent scavenger of free radical in vitro. Turmeric oil and turmeric oleoresin both act synergistically in vivo to offer protection against DNA damage [15].

Further outpatient care

Regular physical examinations, biopsy specimen analysis, and cytologic smear testing should be scheduled to detect oral dysplasia or carcinoma, especially in patients with severe OSMF. Patients with surface leukoplakias require close follow-up monitoring and repeat biopsies. Patients with dysplasias and carcinomas should receive routine treatment for these entities [3].

CONCLUSION

Treatments proposed for OSMF are aimed at improving the patient's ability to open the mouth, which becomes restricted when more scar tissue is formed as the disease progresses, but none have proved curative or have reduced the morbidity significantly.

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