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Ozone Therapy in Periodontics - A Review

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ABSTRACT

Introduction

Periodontitis is a complex disease which is marked by microbial and host response interaction. Microorganisms have also been found to be associated with the commencement of disease in the subgingival environment.[1]

Ecological plaque hypothesis suggests that a disease is not only hindered by suppressing the presumptive pathogens alone but also by impeding with the factors responsible for the transition of plaque microflora from the commensal to a pathogenic relationship with the host. The critical event in ecological plaque hypothesis is collapse of microbial hemostasis and shifting the ecological balance of plaque back toward one that is compatible with dental health. Thus, preventing strategies include altering subgingival environment which includes application of oxygenating agents. An alternative approach by the suppression of subgingival bacteria is to inhibit their growth by changing the subgingival environment (anaerobic) to aerobic.[1]

Ozone which is present in atmosphere is an uncoloured gas form of oxygen. It is formed as a result of exposure to ultraviolet (UV) rays on a combination of three atoms of oxygen. It is also formed by the action of lightening discharges and has the capacity to absorb harmful UV rays.[1]

In 1785, Van Marum noticed that the air next to his electrostatic machine acquired a characteristic odor when electric sparks were passed. "Ozone" was named by Schonbein in the year 1840. It is derived from the Greek word "Ozein" meaning odorant. At very low temperature, ozone which is a pale blue gas will be condensed to a deep blue liquid. It is unstable and quickly gives up the nascent oxygen to form oxygen. Hence, the powerful oxidizer, ozone, is routinely used in human medicine to kill bacteria and fungi and to inactivate viruses. The nascent oxygen released by the spontaneous breakdown of ozone combines with water molecules to form hydroxyl group which is a more powerful oxidizer.[1]

Ozone is a powerful oxidant with distinct antimicrobial activity and has the capacity to act as a metabolic and host immune modulator. Ozone has been used for sterilization of cavities, root canals, and periodontal pockets, in the treatment of early carious lesions; to enhance epithelial wound healing, such as that caused by ulceration and herpetic lesions; as a rinse for avulsed teeth; and as a denture cleaner. The routes of administration of ozone for both gaseous and aqueous forms are topical and regional.[2]

It has been documented that aqueous ozone possesses a distinctive biocompatibility to fibroblasts, Cementoblasts, and epithelial cells, suggesting aptness of its use against oral infectious diseases such as periodontal disease, apical periodontitis, and peri-implantitis.[3]

Ozone in periodontitis treatment is used as an adjunctive to scaling and root planing (SRP) as compared to SRP alone.

Ozone has a role to play several actions in the human body such as an immune-stimulating, an analgesic, an anti-hypoxic, a detoxicating, an antimicrobial, a bioenergetic, and a biosynthetic agent.[4]

Ozone therapy as a contemporary non-invasive method of treatment is gaining popularity; it is a strong oxidizing agent with a high antimicrobial power against oral microorganisms, without developing resistance neither for gaseous, nor for aqueous ozone. It is used widely in varying treatment methods in the field of medicine, dentistry, veterinary, food industry, and water treatment.

1. Antimicrobial effect- Ozone works destructively against bacteria, fungi, and viruses. The antimicrobial effect of ozone is a result of its action on cells by damaging its cytoplasmic membrane due to ozonolysis of dual bonds and also ozone-induced modification of intracellular contents (oxidation of proteins loss of organelle function) because of secondary oxidants effects. This action is non-specific and selective to microbial cells; it does not damage human body cells because of their major antioxidative ability. Ozone is very efficient in antibiotics resistant strains. Its antimicrobial activity increases in liquid environment of the acidic pH. In viral infections the ozone action lies in the intolerance of infected cells to peroxides and change of activity of reverse transcriptase, which takes part in synthesis of viral proteins.[6] Being a very strong oxidant it joins with biomolecules containing cysterine, cysteine, methionine, histidine (all being part of bacterial cell membranes. The main targets of their attack are the thiol groups of the amino acid cysteine. As a result of the reaction of ozone with unsaturated fatty acids of a lipid sheath of a virus the lipid sheath of a virus melts. The research shows that a few-second-application of ozone stops all vital functions of bacteria which are incapable of developing any self-immunity to its action. Gram+ (Gram-positive) bacteria are more sensitive to the action of ozone than Gram–

(Gramnegative) bacteria. Oxygen-free bacteria react to ozone as well. Among cariogenic bacteria Streptococcus mutans and Streptococcus sobrinus are the most sensitive. Ozone easily acts on multi unsaturated fatty acids which occur in virus sheaths. Ozone reacts also with ascorbinians and tocopherols.[7]

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2. Immunostimulating Effect- Ozone influences cellular and humoral immune system. It stimulates proliferation of immunocompetent cells and synthesis of immunoglobulins. It also activates function of macrophages and increases sensitivity of microorganisms to phagocytosis.[6] As a response to this activation through ozone, the body's immune cells produce special messengers called cytokines. These molecules in turn activate other immune cells, setting off a cascade of positive change throughout the immune system, which is stimulated to resist diseases. This means that the application of medical ozone is extremely useful for immune activation in patients with a low immune status and/or immune deficit.[8] Ozone causes the synthesis of biologically active substances such as interleukins, leukotrienes and prostaglandins which isbeneficial in reducing inflammation and wound healing.[6] Ozone in high concentration causes immunodepressive effect whereas in its low concentration immunostimulating effect.[7]
3. Antihypoxic effect- Ozone brings about the rise of pO2 in tissues and improves transportation of oxygen in blood, which results in change of cellular metabolism – activation of aerobic

processes (glycolysis, Krebs cycle, β-oxidation of fatty acids) and use of energetic resources. Repeating low doses of ozone activate enzymes: superoxide dismutases, catalases, dehydrogenase, and glutatione peroxidases. They are part of complex enzymatic systems which protect organisms against the action of oxygen-free radicals. It also prevents formation of erythrocytes aggregates and increases their contact surface for oxygen transportation. Its ability to stimulate the circulation is used in the treatment of circulatory disorders and makes it valuable in the revitalizing organic functions.[6] Ozone improves the metabolism of inflamed tissues by increasing their oxygenation and reducing local inflammatory processes. By changing the cell membrane structure of erythrocytes and causing the increase of its negative charge it influences the structure change as well as blood cell elasticity. This in consequence reduces blood cell rolling and enables blood flow in capillary vessels. By increasing the concentration of 2,3 Diphosphoglycerate (2,3-DPG), ozone changes the configuration of erythrocytes, which enables them to return oxygen in the inflamed tissue.[7]

4. Biosynthetic Effect- It activates mechanisms of protein synthesis, increases number of ribosomes and mitochondria in cells. These changes on the cellular level explain elevation of functional activity and regeneration potential of tissues and organs.[6]
5. Ozone causes secretion of vasodilators such as NO, which is responsible for dilatation of arterioles and venules.[6] It also activates angiogenesis.[7]
6. Ozone, when acting on the organic substance of mineralized tooth tissues intensifies their remineralization potential. At the same time, it is capable of "opening" dentinal tubules, which enables the diffusion of calcium and phosphorus ions to the deeper layers of carious cavities.[9]

OZONE THERAPY IN PERIODONTICS

The main use of ozone in dentistry is relays on its antimicrobial properties. It is proved to be effective against both Gram positive and Gram-negative bacteria, viruses and fungi.[11]

Ebensberger et al **[12]** evaluated the effect of irrigation with ozonated water on the proliferation of cells in the periodontal ligament adhering to the root surfaces of 23 freshly extracted completely erupted third molars. The teeth were randomly treated by intensive irrigation with ozonated water for 2 min or irrigation with a sterile isotonic saline solution, serving as a control group. The periodontal cells of these teeth were studied immunohistochemically to mark proliferating cell nuclear antigen (PCNA). It was observed that the labeling index (the number of positive cells compared to the total number of cells suggesting enhancement of metabolism) was higher among the teeth irrigated with ozone (7.8% vs. 6.6%); however, the difference was not statistically significant ($p = 0.24$). They concluded that the 2 min irrigation of the avulsed teeth with non-isotonic ozonated water might lead not only to a mechanical cleansing, but also decontaminate the root surface, with no negative effect on periodontal cells remaining on the tooth surface.

Nagayoshi et al[13] examined the effect of ozonated water on oral microorganisms and dental plaque. Dental plaque samples were treated with 4mL of ozonated water for 10 s. they observed that ozonated water was effective for killing gram-positive and gram-negative oral microorganisms and oral Candida albicans in pure culture as well as bacteria in plaque biofilm and therefore might be useful to control oral infectious microorganisms in dental plaque.

Nagayoshi et al [5] tested the efficacy of three different concentrations of ozone water (0.5, 2, and 4 mg/ml in distilled water) on the time-dependent inactivation of cariogenic, periodontopathogenic and endodontopathogenic microbes (Streptococcus, Porphyromonas gingivalis and endodontalis, Actinomyces actinomycetemcomitans, Candida albicans) in culture and in biofilms. They confirm that ozonated water was highly effective in killing of both gram positive and gram-negative micro-organisms. Depending on the dosage, the oral microbes were inactivated after 10 seconds. Gram negative anaerobes, such as Porphyromonas endodontalis and Porphyromonas gingivalis were substantially more sensitive to ozonated water than gram positive oral streptococci and Candida albicans in pure culture. Furthermore, ozonated water had strong bactericidal activity against bacteria in plaque biofilm. In addition, ozonated water inhibited the accumulation of experimental dental plaque in vitro.Ramzy et al[14] irrigated the periodontal pockets by ozonized water in 22 patients suffering from aggressive periodontitis (age range from 13 to 25 years). Periodontal pockets were irrigated with 150 ml of ozonized water over 5 to 10 minutes once weekly, for a clinical four weeks study, using a blunt tipped sterileplastic syringe. High significant improvement regarding pocket depth, plaque index, gingival index and bacterial count was recorded related to quadrants treated by scaling and root planning together with ozone application. They also reported significant reduction in bacterial count in sites treated with ozonized water.

Huth et al [10] in their study declared that the aqueous form of ozone, as a potential antiseptic agent, showed less cytotoxicity than gaseous ozone or established antimicrobials (chlorhexidine digluconateCHX 2%, 0.2%; sodium hypochlorite-NaOCl 5.25%, 2.25%; hydrogen peroxide-H2O2 3%) under most conditions. Therefore, aqueous ozone fulfils optimal cell biological characteristics in terms of biocompatibility for oral application.

Huth et al[15] in their later paper examined the effect of ozone on the influence on the host immune response. These researchers chose the NF-kappaB system, a paradigm for inflammation-associated signalling/ transcription. Their results showed that that NFkappaB activity in oral cells in periodontal ligament tissue from root surfaces of periodontally damaged teeth was inhibited following incubation with ozonized medium. The Huth 2007 study establishes a condition under which aqueous ozone exerts inhibitory effects on the NF-kappaB system, suggesting that it has an anti-inflammatory capacity.

Muller et al[16] compared the influence of ozone gas with photodynamic therapy (PDT) and known antiseptic agents (2% Chlorhexidine, 0,5 and 5% hypochlorate solutions) on a multispecies oral biofilm in vitro. The following bacteria were studied – Actinomyces naeslundii, Veillonelladispar, Fusobacterium nucleatum, Streptococcus sobrinus, Streptococcus oralis and Candida albicans. Gasiform ozone was produced by vacuum ozone delivery system Kavo Healozone. They concluded that the matrix-embedded microbial populations in biofilm are well protected towards antimicrobial agents. Only 5 % Hypochlorate solution was able to eliminate all bacteria effectively. Usage of gasiform ozone or PDT was not able to reduce significantly or completely eliminate bacteria in the biofilm.

Kronusová[17] used ozone in following cases: prevention of dental caries in fissures of the first permanent molars in children, application of ozone in prepared cavity, after tooth extraction, in case of postextractional complications, in patients with chronic gingivitis, periodontitis and periodontal abscesses, herpes labialis, purulent periodontitis, dentition difficilis, etc. Almost all patients with gingivitis showed subjective and objective improvement of their status, as well as patients with periodontal abscess, where no exsudation was observed. Application of ozone after tooth extraction was found also quite useful – only 10 % of patients suffered from such complication as alveolitis sicca, but even in these cases the clinical course was shorter and more moderate.

The influence of ozonized water on the epithelial wound healing process in the oral cavity was observed by Filippi.[18]

It was found that ozonized water applied on the daily basis can accelerate the healing rate in oral mucosa. This effect can be seen in the first two postoperative days. The comparison with wounds without treatment shows that daily treatment with ozonized water accelerates the physiological healing rate.

In the study by Karapetian et al,[19] periimplantitis treatment with conventional, surgical and ozone therapy methods was investigated, and it was found that the most effective bacteria reduction was in the ozone-treated patient group. The authors concluded that the main challenge seems to be the decontamination of the implant surface, its surrounding tissue and the prevention of recolonization with periodontal pathogenic bacteria.

Kshitish and Laxman[20] conducted a randomized, double-blind, crossover split-mouth study on 16 patients suffering from generalized chronic periodontitis. The study period of 18 days was divided into two time-intervals, i.e. baseline (0 days) to 7th day, with a washout period of 4 days followed by a second time interval of 7 days. Subgingival irrigation of each half of the mouth with either ozone or chlorhexidine was done at different time intervals. They observed a higher percentage of reduction in plaque index (12%), gingival index (29%) and bleeding index (26%) using ozone irrigation as compared to chlorhexidine. The percentile reduction of Aa (25%) using ozone was appreciable as compared to no change in Aa occurrence using chlorhexidine. By using O3 and chlorhexidine, there was no antibacterial effect on Porphyromonas gingivalis (Pg) and Tannerella forsythensis. The antifungal effect of ozone from baseline (37%) to 7th day (12.5%) was pronounced during the study period, unlike CHX, which did not demonstrate any antifungal effect. No antiviral property of ozone was observed. The antiviral efficacy of chlorhexidine was better than that of ozone. They concluded that despite the substantivity of chlorhexidine, the single irrigation of ozone is quite effective to inactivate microorganisms.

How effective is ozone therapy as an adjunct in treating periodontitis?

1. Population: Individuals with chronic periodontitis (CP) and aggressive periodontitis
2. Intervention: Use of ozone therapy as an adjunct to mechanical SRP
3. Comparison: Between ozone therapy group and placebo/no treatment group
4. Outcome: Changes in pocket depth, clinical attachment level (CAL), bleeding on probing (BOP), Plaque Index (PI), and Gingival Index (GI)
5. Selection criteria.

AIM

The aim of the present review article is to evaluate the role of ozone therapy in treating periodontitis.

DISCUSSION

In 2014, Shoukheba and Ali evaluated the effect of subgingival application of ozonated olive oil gel as an adjunct to SRP in aggressive periodontitis patients. The control group which consisted of 15 patients received oral hygiene instructions, SRP of all teeth, in addition to the subgingival application of an ozonated olive oil gel (Oxaktiv® gel). Clinical parameters such as PI, GI, BOP, and CAL were analyzed. The results of ozone irrigation showed improvement in all the clinical parameters in the ozone-treated group, which was maintained up to 6 months except for BOP up to 3 months.[2]

A prospective randomized clinical study was conducted by Gianluca Sacco in 2016 on 113 patients with periodontal disease. Local oxygen–ozone therapy was used in combination with traditional mechanical therapy versus the use of mechanical therapy alone in a group of patients with periodontal disease. After 6 months of root planing, the individuals who received oxygen–ozone therapy as an integral part of the periodontal treatment had significant stabilization of the clinical values. It was observed in particular that in both groups that the deepest pockets (PD > 6 mm) had the greatest decrease.[3]

Kshitish and Laxman developed a randomized, double-blind, crossover, split-mouth design. This split-mouth design was used in this study for subgingival irrigation of each half of the mouth with either ozone or chlorhexidine at different time intervals. The interpretation of clinical and microbial data is from baseline to the 7th day. The higher percentage of PI (12%), GI (29%), and Bleeding Index (26%) reduction was observed using ozone irrigation as compared to chlorhexidine.[4]

A study conducted by Yilmaz *et al*. evaluated the clinical and microbiological results of treatment with Er: yttrium aluminum garnet (YAG) laser and topical gaseous ozone application as adjuncts to initial periodontal therapy in CP patients. Thirty patients with CP were randomly divided into three parallel groups, each composed of ten individuals. Group 1: SRP + Er: YAG laser; Group 2: SRP + topical gaseous ozone; and Group 3: SRP alone. The clinical parameters were monitored at day 0 and day 90. Clinical parameters such as PI, SBI, PD, and relative attachment levels were measured at the end of the observation period; statistically significant improvements in clinical parameters were observed within each group.[5]

Al Habashneh *et al*.[6] determined the clinical and biological effects of the adjunctive use of ozone in nonsurgical periodontal treatment. Forty-one patients with CP were randomized to treatment with either subgingival SRP followed by irrigation with ozonated water for the test group or subgingival SRP followed by irrigation with distilled water irrigation for the control group. The parameters such as PI, GI, BOP, PPD, gingival recession, and clinical attachment loss were evaluated at baseline and at 3 months and statistically significant improvement was observed in the study parameters in both groups at baseline and 3 months, except for GI.

In a randomized study, Sae Hayakamo *et al*. evaluated the clinical and microbiological effects of NBW3 irrigation as an adjunct to subgingival debridement for periodontal treatment. Twenty-two patients were randomly assigned to one of the following two treatment groups: full-mouth mechanical debridement with tap water (WATER) or full-mouth mechanical debridement with NBW3 (NBW3). Full-mouth clinical measurements of PPD, CAL, and the percentage of BOP (%) were recorded at baseline and at 4 and 8 weeks after treatment. There were significant improvements in all the clinical parameters after 4 weeks in both groups. The reduction in the PPD and the clinical attachment gain after 4 and 8 weeks in the NBW3 group was significantly greater than that in the WATER group. BOP (%) was reduced by 15.69 and 8.98 at 4 weeks and 13.47 and 6.97 at 8 weeks in the NBW3 and WATER groups, respectively.[7]

CONCLUSION

Treating patients with ozone therapy reduces the treatment time with a great deal of difference and it eliminates the bacterial count more precisely. The treatment is completely painless and increases the patients' acceptability and compliance with minimal adverse effects. Local ozone application can serve as a potential atraumatic, promising antimicrobial agent to treat periodontal disease nonsurgically, both for home care and professional practice. It may serve as a good tool during supportive periodontal therapy. Ozone may be considered as an alternative management strategy due to its powerful ability to inactivate microorganisms. Thus, subgingival ozone irrigation can be successfully used as an adjunct to periodontal treatment. Although more clinical research has to be done to standardize indications and treatment procedures of ozone therapy, still many different approaches are so promising, or already established, that hopefully the use of ozone therapy becomes a standard treatment for disinfection of an operation sites in dentistry.

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