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Original Research Paper

Dental Science

OZONE THERAPY IN PERIODONTICS (REVIEW)

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ABSTRACT The usage of ozone in dentistry has been proposed because of its various biological properties like disinfection, antimicrobial activity, biocompatibility and healing properties. In the last few years, various therapeutic protocols with ozone have been developed in various fields of dentistry. Inspite of many advantages, therapeutic ozone's application in dentistry is limited because of its possible side effects. Hence, dentists has to know the appropriate usage of ozone therapy which can provide better patient care and considerably cut down the time and cost of the treatment.

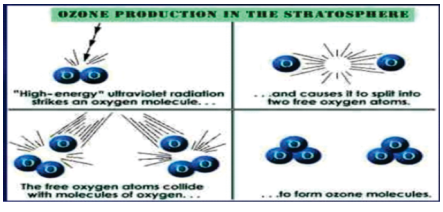
KEYWORDS :

INTRODUCTION

The word ozone comes from the Greek "ozein" meaning odorant. Ozone (also known as triatomic oxygen and trioxygen) is an allotropic form of oxygen occurring naturally in the Earth's atmosphere. It surrounds the Earth at an altitude of between 50,000 and 100,000 feet. [1] It is created, when ultraviolet rays cause oxygen atoms to disassociate and temporarily recombine in groups of three. It is also formed by the action of electrical discharges on oxygen, so it is often created by thunder and lightning.

CHEMISTRY:

Ozone (O_3) concists of three oxygen atoms, with molecular weight is 47, 98 g/mol and thermodynamically highly unstable compound.[11] when compared to oxygen Ozone is 1.6-fold more denser and 10-fold more soluble in water .Ozone is an unstable gas and which gives up nascent Oxygen molecule to form Oxygen gas.As it releases nascent Oxygen, it has been used in medical field to kill bacteria, fungi, to inactivate viruses and to control hemorrhages. [2] Medical grade ozone is made from pure medical oxygen. It is produced commercially in ozone generators, which involves sending an electrical discharge through a specially-built condenser containing oxygen.



History

First discovered in 1840 by the German chemist Christian Frederick Schonbein at the University of Basil in Switzerland, ozone was first used in medicine by Landlerin the year 1870. It was not studied or used until 1932 by the scientific community. Ozonated water was first used as a disinfectant by Dr. E. A. Fisch, a Swiss dentist. By a twist of fate, a surgeon, Dr. E Payr (1871–1946) had to be treated for a gangrenous pulpite and remained astonished by the result achieved with local ozone treatment. He enthusiastically extended its application to general surgery.

At the time, ozone therapy was difficult and limited due to the lack of ozone-resistant materials, such as Nylon, Dacron, and Teflon, until 1950 when ozone-resistant materials were manufactured. At that time Joachim Hänsler, a German physicist and physician, joined another German physician, Hans Wolff, to develop the first ozone generator for medical use. Their design continues to be the basis for modern equipment.

Ozone generators

There are three different systems for generating ozone gas: [4]
Ultraviolet System: produces low concentrations of ozone, used in esthetics, saunas, and for air purification.

Cold Plasma System: used in air and water purification.
Corona Discharge System: produces high concentrations of ozone. It is the most common system used in the medical/ dental field. It is easy to handle and it has a controlled ozone production rate.

Medical grade ozone is a mixture of pure oxygen and pure ozone in the ratio of 0.05% to 5% of $_3$ and 95% to 99.95% of O_2.

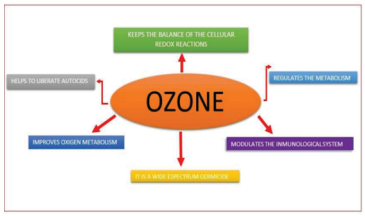
Use of ozone in dentistry

The use of ozone in dentistry is gaining its place in every day's dental practice and is used in almost all dental applications. The undisputed disinfection power of ozone over other antiseptics makes the use of ozone in dentistry a very good alternative and/or an additional disinfectant to standard antiseptics.

Due to safety concerns, $_3$ gas was not recommended for intra-oral use. Only dissolved ozone in water and ozonated oils were and are still commonly used in different fields of dentistry. With the development of a foot pedal-activated dental handpiece with a suction feature, $_3$ gas can now be used safely in situations where diffusion is an important factor, i.e. dental hard tissues.

According to Fritz Kramer, ozone, such as in the form of ozonated water, can be used in the following ways.

1. as a powerful disinfectant
2. in its ability to control bleeding
3. in its ability to cleanse wounds in bones and soft tissues.
4. by increasing the local supply of oxygen to the wound area, ozone can improve healing.
5. ozonated water can increase temperature in the area of the wound, and this increase the metabolic processes related to wound healing.



Biological actions

The application of ozone in dentistry comes as a result of physico-chemical properties: There are several known actions of ozone on human body, such as immunostimulating and analgesic, antihypoxic and detoxicating, antimicrobial, bioenergetic and biosynthetic (activation of the metabolism of carbohydrates, proteins, lipids) etc.

Antimicrobial (bactericidal, viricidal, and fungicidal)
Damage to cytoplasmic membrane
Oxidation of intracellular contents
Specific to microbial cell
Effective in antibiotic resistive strain
Immuno-stimulating
Activates cellular and humoral immune system
Proliferation of immunocomplement cells
Synthesis of immunoglobulin's
Enhance phagocytosis activity
Activation of biological antioxidants
Analgesic
Anti-hypoxic and detoxicating
Activation of aerobic process (Krebs cycle, glycolysis, oxidation of fatty acids)
Bio-energetic and biosynthetic
Activates protein synthesis
Enhanced cell metabolism (Ribosome, mitochondria)
Biologically active substances
Synthesis of interleukins, leukotrienes and prostaglandins
Synthesis of immunogloblin's

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]

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 micro-organisms 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 is beneficial 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, -oxidation of fatty acids) and use of energetic resources. Repeating low doses of ozone activate enzymes: super-oxide 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]

4. Biosynthetic Effect- It activates mechanisms of protein synthesis, increases amount 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]

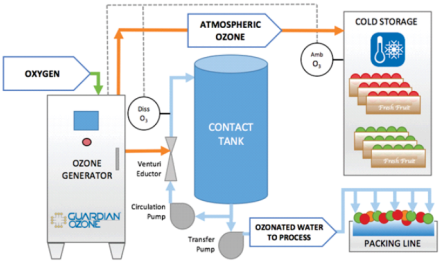
A high concentration of ozone kills bacteria very quickly and is thousand times more powerful than other bacterial killing agents. The average concentration of ozone used in treatments is 25 gm of ozone per milliliter of oxygen/ozone gas mixture that translates into 0.25 parts of ozone to 99.75 parts of oxygen. Evidence-based research has shown that at this concentration, ozone effectively kills bacteria, fungi, viruses and parasites. [10] As an antimicrobial agent, it is a powerful oxidizer at a dramatically lower concentration than chlorine with none of the toxic side effects. [10] Studies have revealed that it only takes 10 sec to kill 99 % of bacteria, fungi and viruses. [11] It can oxidize many organic compounds and it is a powerful germicide. [12] Some of the other effects are circulatory enhancement, disruption of tumor metabolism and stimulation of oxygen metabolism. [13]
According to most authors, a 10-sec-application of ozone causes the destruction of 99% of bacteria, and a 20-sec-application even of 99.9%. In this way, so-called ecological niche appears.

However, it is not conducive to their repeated colonization within 4 to 6 weeks. [14,15] Ozone is not toxic when it is given in the amount of 0.05 ppm for 8 hours. During ozone therapy a maximum concentration of ozone in oral cavity amounts to 0.01 ppm.

Goals of ozone therapy

Setting the standard-of-care and therapeutic goals are based on sound evidence-based science is critical. Therapeutic goals are inclusive and not exclusive of standard of care. The goals of oxygen/ozone therapy are: [10]

1. Elimination of pathogens.
2. Restoration of proper oxygen metabolism.
3. Induction of a friendly ecologic environment.
4. Increased circulation.
5. Immune activation.
6. Simulation of the humoral anti-oxidant system.



Ozone in the Treatment of Periodontal Diseases

Periodontal disease is a multifactorial disease process in the mouth. The role of microorganisms, hostresponse, in the etiology of periodontal disease is well established.

The undisputed disinfection power of ozone over other antiseptics makes the use of ozone in treatment of

periodontitis a very good alternative and/or an additional disinfectant to standard antiseptics.

Ozonated water (4 mg/l) was found 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 as a mouth rinse to control oral infectious microorganisms in dental plaque. In implant dentistry, the use of ozone is currently being investigated for the decontamination of the implant surface in Peri-implant therapy.

Thanomsub *et al*. 2002 tested the effects of ozone treatment on cell growth and ultra-structural changes in bacteria (*Escherichia coli, Salmonella sp., Staphylococcus aureus and Bacillus subtilis*). It was discovered that ozone at 0.167 mg/min/l can be used to sterilize water, which is contaminated with up to 105 cfu/ml bacteria within 30 min. Destroying of bacterial cell membrane was observed, subsequently producing intercellular leakage and eventually causing cell lysis. Nevertheless, these ozone concentrations have no significant effect on the cell viability in bacterial cultures at higher concentrations of 106 and 107 cfu/ml.[18]

Ebensberger *et al*. in 2002 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 b 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. 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.[19]

Holmes in 2003, observed effect of Kavo healozone device on Primary root carious lesions (PRCL) followed-by professionally-applied remineralizing solution containing xylitol, fluoride, calcium, phosphate and zinc. This treatment modality was applied to 89 patients, aged from 60 to 82 years. After 18 months, 100% of ozone-treated PRCL s had improved. In control group, where lesions were left without treatment, only 1 PRCL had improved. In 62% of cases the status remained leathery, while in 37% of PRCL s had worsened from leathery to soft.[5]

Nagayoshi *et al*. 2004 tested the efficacy of ozonated water on survival and permeability of oral micro-organisms. Gram negative bacteria, such as Porphyromonas endodontalis and Porphyromonas gingivalis were substantially more sensitive to ozonated water than gram positive oral streptococci and *c. 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*.[20]

Hems and Gulabivala, 2005 evaluated the potential of ozone as an anti-bacterial agent using Enterococcus faecalis as a test species. Ozone was used both gasiform (produced by Purezone device), and aqueous (optimal concentrations 0.68 mg/l). It was concluded that ozone in solutions was antibacterial against planctonic Enterococcus faecalis after 240 s treatment. However it was not effective against Enterococcus faecalis cells in a biofilm unless they were displaced into the surrounding medium by agitation. Gaseous ozone was not effective on the Enterococcus faecalis biofilm.[21]

Ramzy *et al*. in 2005 irrigated the periodontal pockets by ozonized water in 22 patients suffering from aggressive periodontitis. Periodontal pockets were irrigated with 150 ml of ozonized water over 5-10 min once weekly for a clinical 4 weeks study using a blunt tipped sterile plastic syringe. High significant improvement regarding pocket depth plaque index gingival index and bacterial count was recorded related to quadrants treated by scaling and rootplaning together with ozone application. They also reported significant reduction in bacterial count in sites treated with ozonized water.[22]

Huth *et al*. in 2006, in their study declared that the aqueous form of ozone, as a potential antiseptic agent, showed less cytotoxicity than gaseous ozone or established anti microbials (chlorhexidine digluconate [CHX]: 2%, 0.2%; sodium hypochlorite 5.25%, 2.25%; hydrogen peroxide-H_2O_2 3%) under most conditions. Therefore, aqueous ozone fulfills optimal cell biological characteristics in terms of biocompatibility for oral application.[23]

Muller *et al*. in 2007 compared the influence of ozone gas with photodynamic therapy (PDT) and known antiseptic agents (2% chlorhexidine, 0.5 and 5% hypocholrate solutions) on a multispecies oral biofilm *in vitro*. *Actinomyces naeslundii, Veillonella dispar, Fusobacterium nucleatum, Streptococcus sobrinus, Streptococcus oralis and c. albicans* were studied. 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 bacteria in the biofilm.[24]

Kronusova 2007 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 post extractional 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 exudation 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.[25]

Karapetian *et al*. in a study of peri-implantitis, treatment with conventional, surgical and ozone therapy methods was investigate and it was found that the most effective bacteria reduction was in the ozone-treated group.[26]

Kshitish and Laxman in 2010 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 the 7th day, with a wash out 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 O_3 and chlorhexidine, there was no anti-bacterial effect on Porphyromonas gingivalis (Pg) and Tannerella

forsythensis. The anti-fungal effect of ozone from baseline (37%) to 7th day (12.5%) was pronounced during the study period, unlike CHX, which did not demonstrate any anti-fungal effect. No anti-viral property of ozone was observed. The anti-viral 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.[27]

Fillippi. A observed the influence of ozonized water on the epithelial wound healing process in the oral cavity. It was found that ozonized water applied on daily basis can accelerate the healing rate in oral mucosa.[28]

CONCLUSION

Since its introduction in 1840, ozone therapy is proving to be a new therapeutic modality with great benefits to the patients. Ozone with its potent antimicrobial power and competency to stimulate the circulatory system and modulate the immune response, accomplish a therapeutic agent of choice in the treatment of medical pathologies and infectious oral diseases.There is good evidence of *in vitro* biocompatibility of aqueous ozone with human oral epithelial cells, gingival fibroblast cells and periodontal cells. Further, the use of ozone is an easy and painless treatment modality.

The clinical application of ozone has not achieved strong level of efficacy and cost effectiveness. This divergence of the study outcomes may be related to the methodological differences linked to the lack of *in vitro* and *in vivo*, long term randomized controlled trials and double blind studies. There is still a need for the highest level of evidence, i.e., well designed; double-blind randomized clinical trials to justify the routine use of ozone as a treatment modality in dentistry.

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