# Ozone and Its Usage in General Medicine and Dentistry A Review Article

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**Abstract:** Ozone, an allotropic form of oxygen, is successfully used in the treatment of different diseases for more than a hundred years. It is highly valued for various effects, such as antimicrobial, antihypoxic, analgesic, immunostimulating etc. on biological systems. These mechanisms of action supported with a lot of case reports and scientific studies allow using it in different fields of medicine. This review of literature is another attempt to summarize different modalities of ozone application in dentistry. Further studies are necessary to standardize indications and treatment protocols of this promising medical agent.

## Introduction

Ozone (O3) is a triatomic molecule, consisting of three oxygen atoms. Its molecular weight is 47,98 g/mol [1]. Ozone is thermodynamically highly instable compound that, dependent on system conditions like temperature and pressure, decomposes to pure oxygen with a short half-life [2]. Ground-level ozone is an air pollutant with harmful effects on the respiratory system. Ozone in the upper atmosphere filters potentially damaging ultraviolet light from reaching the Earth's surface. It has many different applications in various fields; one of them is usage of ozone in medicine [3].

Ozone therapy is one of the modern non-medication methods of treatment. It is being used for more than 100 years. Medical reports on successful application of ozone in therapy of different diseases and studies of its effects caused a rapid growing interest in it. Some other factors were responsible for its wide spreading, such as simplicity of performance, good tolerance by patients, absence of side-effects or adverse reactions and high medical-social and economic efficiency. Even though ozone therapy is still being ignored by most of medical establishment because of facts that gaseous ozone is quite toxic and has strong oxidative properties [4].

The word ozone was first used by Schonbein in 1840. He subjected oxygen to electrical discharges and noted "the odour of electrical matter". Schonbein concluded that odour was due to a gas which he named ozone, from the Greek ozein (odorant), and described several of its properties. Numerous researchers since that time have worked to elucidate the nature and actions of ozone. Mariniak and Delarive showed that it is an allotropic form of oxygen, and Mulliken and Dewar clarified its molecular architecture.

The ability of ozone to destroy toxic or noxious industrial impurities (phenols, cyanides, tetraethyl lead among others) and to inactivate bacterial contaminants in sewage has made it an attractive alternative to chlorination. In 1901 Wiesbaden, Germany became the first city to use ozonation for purification of its drinking water, followed by Zurich, Florence, Brussels, Marseille, Singapore and Moscow (the largest installation in the world), among others. The history of ozone's medical applications has nebulous and anecdotal beginnings. The names A. Wolff, Payr and Aubourg will always be linked with pioneering research, especially in the field of locally applied medical ozone [5]. J. Hansler developed one of the first reliable models of medical ozone generators. A. Wolff successfully treated putrescent wounds, suppurating bone fractures, fulminating inflammations (phlegmons) and abscesses during the First World War, publishing his results already in 1915. This field then received a major impulse through the work of the surgeon and ozone therapist Erwin Payr, who presented his epoch-making publication (of 290 pages), entitled "Ozone Treatment in Surgery" (Über Ozonbehandlung in der Chirurgie) at the 59th Meeting of the German Surgical Society (Deutsche Gesellschaft für Chirurgie) in 1935. This can be called the real beginning of ozone therapy.

However, it was much later in the 20th Century, i.e. not before the 1950s, that the use of medical ozone stayed forgotten. In particular, the absence of ozone-resistant materials such as plastics, made it difficult for the practitioner to apply ozone locally in treating wounds or via rectal insufflation, as any noticeable amount of ozone in the ambient air made the effort practically impossible. In 1958 Hänsler presented his first medical ozone generator, which was capable of producing an ozone / oxygen mixture at therapeutically variable dosages (concentrations). Together with H. Wolff, they introduced ozone therapy as we know it today [6].

Following in his research the great number of publications by Payr and Aubourg, it was H. Wolff who subsequently introduced extracorporeal blood treatment into medical practice; Werkmeister developed local treatment methods in the form of "subatmospheric ozone gas application", and Rokitansky – as a surgeon – presented the first comprehensive studies on the topical and systemic treatment of diabetic gangrene. Knoch then introduced rectal ozone insufflation into proctology.

A large number of the indications described by Payr had been abandoned in favour of other, more effective methods; in some indications medical ozone could be applied complementary to a basic therapy. This particularly applied in the case of rheumatism / arthritis and inflammatory diseases of the joints, for which Fahmy has developed a wide therapeutical concept [6].

Although relatively simple as regards application forms and active mechanisms, the use of ozone in dental medicine developed very modestly. As mentor, we must here mention the Swiss therapist A. Fisch, who himself acquainted Payr with ozone, and who presented a doctoral thesis (1952) and first publication on the use of ozone in dental medicine in 1935 [6]. It was not until the end of the 1980s, though, that medical ozone once more became a subject of dental research (Kirschner, Filippi) [6] and dental practice (Lynch) [7].

There are several known actions of ozone on human body, such as immunostimulating and analgesic, antihypoxic and detoxicating, antimicrobial (bactericidal, viricidal, and fungicidal), bioenergetic and biosynthetic (activation of the metabolism of carbohydrates, proteins, lipids) etc. [8].

Antimicrobial effect of ozone is the most studied. The main reason for cell death is the local damage of cytoplasmic membrane due to ozonolysis of dual bonds, and also ozone-induced modification of intracellular contents (oxidation of proteins, loss of organel functions) 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. It is necessary to mention studies on the insignificant mutageneous effect of ozone on micro-organisms concerning a limited rising of ozone-resistant microbes. In viral infections the mechanism of 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 [5, 9].

Ozone causes the synthesis of biologically active substances such as interleukins, leukotrienes and prostaglandins. 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.

Ozone brings about the rise of $pO_2$ in tissues and improves transportation of oxygen in blood, which results in change of cellular metabolism – activation of aerobic processes (glycolysis, Krebs cycle, B-oxidation of fatty acids) and use of energetic resources. It also prevents formation of erythrocytes aggregates and increases their contact surface for oxygen transportation. Ozone causes secretion of vasodilators such as NO, which are responsible for dilatation of arterioles and venules. It also activates mechanisms of protein synthesis, increase 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 [9].

**Ozone in medicine – indications and contraindications**

The major indications of ozone treatment were based on multiple case reports from hospitals and practices. Different studies on its mechanisms of action supported those findings from the scientific point of view. The Table 1 presents the basic indications of ozone therapy [6].

As for contraindications of ozone therapy, the following are mentioned in the medical literature: acute alcohol intoxication, recent myocardial infarction, haemorrhage from any organ, pregnancy, hyperthyroidism, thrombocytopenia and ozone allergy [6].

There are also data that repeated exposure to 125 p.p.b. ozone can enhance both lung function and inflammatory airway responses to inhale allergen in subjects with pre-existing allergic airway diseases [10].

The European Cooperation of Medical Ozone Societies warns from direct intravenous injections of ozone/oxygen gas that should not be practiced due to the possible risk of air embolism [3].

Medication forms of $O^3$ in a gaseous form are somewhat unusual, and that is why special application techniques have had to be developed for the safe use of ozone. In local the applications as in the treatment of external wounds, its application in the form of a transcutaneous $O^3$ gas bath has been established as a most practical and useful method, for example at low (subatmospheric) pressure in a closed system guaranteeing no escape of ozone into the ambient air. Ozonized water, whose use is particularly known in dental medicine, is optimally applied as a spray or compress.

Apart from rectal insufflation, principally used in the treatment of intestinal conditions, but also applied systemically, autohaemotherapy [or auto(haemo) transfusion] has established itself as a systemic therapy of choice. A corresponding dosage of ozone gas is passed through or, more correctly, transferred (in the form of microbubbles) to 50 to 100 ml of the patient's blood in a sealed, pressureless system, thus achieving the finest possible distribution to reach the greatest possible number of red and white blood cells with the aim of activating their metabolism. In other words, the organism acquires its own medication, the activated red blood cells and immunocompetent cells then being reintroduced via normal drip infusion. This is a markedly low-risk method when hygiene guidelines are observed, disposable units are used, and the material is ozone-resistant.

In the therapy of pain in the locomotor system, ozone can be applied supportively in the form of intramuscular or intraarticular injections [6].

**The world-wide scale use of ozone therapy**

Ozone therapy is a well established alternative and complementary therapy in most mainland European countries where health authorities have tolerated such practice. The European Cooperation of Medical Ozone Societies, founded in 1972,

**Table 1. The use of ozone in medicine**

| Indications | Mechanisms |
|---|---|
| External ulcers and skin lesions | Disinfection, wound cleansing and improved wound healing |
| Arterial circulatory disorders | Activation of RBC (red blood cell) metabolism with an improvement of oxygen release<br>Activation of ROS (reactive oxygen species) and radical scavengers |
| Immunodeficiency and immunodysbalance:<br>Chronic forms of hepatitis B and C<br>Supportive therapy in cancer patients<br>Supportive therapy in rheumatoid arthritis | Activation of immunocompetent cells with release of cytokins such as interferons and interleukins.<br>Modulation of the immune system<br>Increase of antioxydative capacity by activation of biological antioxidants |
| Inflammatory condition such as:<br>Knee arthrosis<br>Gonarthrosis<br>Traumatic knee disorders | Antiinflammatory effect<br>Activation of antioxidative enzymes as radical scavengers<br>Activation of immunocompetent and cartilage cells with release of TGF-β |

publishes guidelines on medical indications and contraindications of ozone and hosts training seminars. In the early 1980's a German survey and investigation into ozone therapy was held by the University of Klinikum Griessen and the Institute for Medical Statistics. This study was published in the Empirical Medical Acts. It revealed over 5 million ozone treatments that had been delivered to some 350,000 patients, by more than 1000 therapists, from this number about half were the medical doctors. Although ozone is used in a complementary capacity by a significant number of doctors in Italy, Switzerland, Austria and Germany it has still not gained popular support with the main stream industry policy makers in those countries, it is not covered by health insurance, nor is it part of the curriculum at most esteemed medical schools. Proposal's to include ozone therapy in German health insurance schemes invoked hostile objections from pharmaceutical researchers who question its evidence base. According to the Wikipedia in general, countries with more socialist style health systems seem to have had less difficulty in accepted ozone as a medicine. No prohibition of ozone therapy is evident in Bulgaria, Cuba, Czech Republic, France, Germany, Israel, Italy, Japan, Malaysia, Mexico, Poland, Romania, Russia, Switzerland, and Ukraine. In the USA, recently passed Alternative Therapy Legislation has made ozone therapy an option for patients in some states. In Alaska, Arizona, Colorado, Georgia, Minnesota, New York, North Carolina, Ohio, Oklahoma, Oregon, South Carolina, and Washington Physicians can legally use ozone treatments in their practice without fear of prosecution [3].

**Usage of ozone in dentistry**

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].

Muller et al. [12] 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, Veillonella dispar, 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 [12].

Baysan et al. [13] assessed antimicrobial effect of Kavo Healozone device on primary root caries lesions (PRCL) and evaluated the efficiency of ozone specifically on Streptococcus mutans and Streptococcus sobrinus. As a result, ozone exposure to either 10 or 20 s under experimental conditions reduced the total levels of micro-organisms in the PRCLs to $<$ 1% of the control values.

Application of ozone for a period of 10 s was also capable of reducing the numbers of Streptococcus mutans and Streptococcus sobrinus in vitro [13].

Holmes [14] observed effect of KaVo Healozone device on PRCL followed by professionally-applied remineralising 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 one PRCL had improved. In 62 % of cases the status remained leathery, while in 37 % of PCRL's had worsened from leathery to soft [14].

Polydorou et al. [15] studied antibacterial effect of Kavo Healozone device on Streptococcus mutans in comparison with the already proven activity of two dentin-bonding systems. Their findings show that an 80 s application of ozone is a very promising therapy for elimination of residual micro-organisms in deep cavities and therefore of potentially increasing the clinical success of restorations.
A 40 s application of ozone was found to reduce significantly the numbers of Streptococcus mutans, but not to extend of other treatments. A longer period of ozone activity could be advantageous as a result of its anticariogenic effect [15].

Nagayoshi et al. [16] tested the efficacy of ozonated water on survival and permeability of oral micro-organisms and dental plaque. They confirm that ozonated water (0.5–4 mg/l) was highly effective in killing of both gram positive and gram negative 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 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 [16].

Huth et al. [17] 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 digluconate-CHX 2%, 0.2%; sodium hypochlorite-NaOCl 5.25%, 2.25%; hydrogen peroxide-$H_2O_2$ 3%) under most conditions. Therefore, aqueous ozone fulfils optimal cell biological characteristics in terms of biocompatibility for oral application [17].

Hems et al. [18] evaluated the potential of ozone as an antibacterial agent using Enterococcus faecalis as a test species. Ozone was used both gasiform (produced by Purezone device), and aqueous (optimal concentration 0.68 mg/l). It was concluded that ozone in solution 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 [18].

Estrela et al. [19] studied antimicrobial effects of ozonated water, gaseous ozone and antiseptic agents (2.5 % hypochlorite and 2 % chlorhexidine) in infected human dental root canals. All these substances had no antibacterial effect against Enterococcus faecalis over a 20 minute contact time in the infected root canals [19].

Thanomsub et al. [20] tested the effects of ozone treatment on cell growth and ultrastructural 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 minutes. 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 [20].

Kronusová [21] 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 [21].

The influence of ozonized water on the epithelial wound healing process in the oral cavity was observed by Filippi [22]. 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 [22].

## Conclusions

In comparison with classical medicine modalities such as antibiotics and disinfectants, ozone therapy is quite inexpensive, and according to many case reports and scientific studies it is very promising. Further research is needed to standardise indications and treatment procedures of ozone therapy. Contraindications of this controversial method should not be forgotten.

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