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Editorial

O_3 in Oro-Dental Medicine and Surgery: Innovative Ozone-based Therapies

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Graphical Abstract

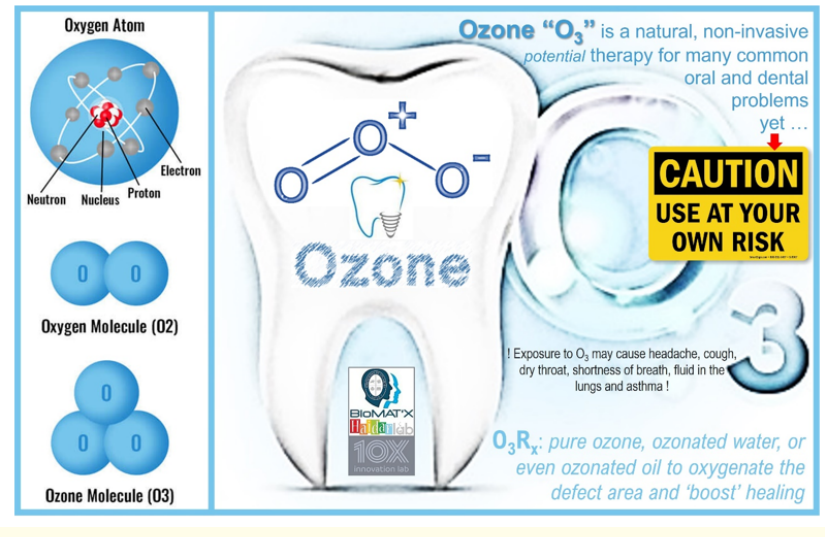

Figure: *Each oxygen atom, of the three oxygen atoms, forms a single bond with the other oxygen atom (equal oxygen - oxygen bonds bound them together at an obtuse angle of 116°) resulting in a negative charge throughout the formed tri-atomic ozone molecule, O_3. O_3 has a short half-life that varies with temperature changes (~140 min at 0°C and ~40 min at 20°C) and is detectable at concentrations as low as 0.025 ppm.*

Keywords: *O_3; Ozone; Dentistry; Surgery; Anti-Microbial; Dental Caries; Dental Pain; Periodontal Diseases*

Precis

Dentistry is ever-evolving. Our patients seek more choices and expect us to have the latest clinical advancements and technological innovations, in treatment. Increasingly, ozone, a super-charged or excited form of oxygen (inorganic oxygen with an extra atom; tri-oxygen where $O + O_2 + \text{energy} = O_3$), is showing its therapeutic potentiality in almost every sub-field of dentistry, including disinfection, tooth decay/dental caries, tooth sensitivity and dental pain, gingival and periodontal diseases as well as in dental implantology and oral surgery. E.A. Fisch, a German dentist in Switzerland used ozone in the 1930s, after its discovery and use in medicine in/since 1885. Whilst the first mention of ozone is often attributed to Dutch physicist Martin van Marun in 178, the German chemist Christian Friedrich Schönbein is widely regarded as the father of ozone therapy. Nikola Tesla patented an ozone-generating system, in 1896, followed by the more modern and innovative "Ozonosan" system patented by Joachim Hansler, in 1959.

Briefly, O_3 acts as a super-oxygenator, bringing oxygen to the tissues (and increasing the partial pressure of oxygen; bio-oxidative) and assisting body in its natural healing process. This is also mainly due to the capacity of applying ozone (can be colorless or pale blue) in liquid (dissolved in water) or gas or even dissolved in oil base form, with attractive anti-bacterial, -viral, -microbial, and -fungal properties and de-toxication effectiveness. Ozone, a peculiarly piquant-smelling (ozone is derived from the Greek word 'OZEIN' which means odor) allotrope of oxygen, at room temperature, can be useful also to promote clot, reduce inflammation, speed wound healing, and enhance *de novo* bone formation, in fresh extraction sockets, for example, thereby preventing alveolar osteitis (dry socket) on-set. Following third molar surgery, the effects of O_3 therapy on pain, swelling, and trismus were studied by Kazancioglu., *et al.* [1] concluding an effective reduction in post-operative pain; only, with no effect on swelling and/or trismus. It has been demonstrated, nonetheless, that O_3 therapy activates the Krebs cycle via enhancing oxidative carboxylation of pyruvate (pyruvic acid produced by the cariogenic bacteria - dental caries/tooth decay - is oxidized by ozone to acetate and carbon dioxide) and stimulating ATP production. Also, sets off an increase in the glycolysis rate in red blood cells, resulting in the stimulation of 2,3-diphosphoglycerate and thereby, an increase in the amount of oxygen released to the tissues (vaso-dilation). The applicability of ozone has also recently expanded to orthopaedics given its potential capability to also promote implant osseointegration. In an *in vivo* pre-clinical study in a rabbit tibial model, El Hadary., *et al*. [2] demonstrated the impact of short-term administration of immuno-suppressive Cyclosporine A or CsA when combined with topical ozonated oil (0.55 mL) on bone density and quality of dental implant osseointegration. O_3, natural and biocompatible (safe and non-toxic - within the proper indications, dosage and concentration, and administration), can help stimulate oxygen metabolism (boost oxygenation) and prevent oxidative stress, and so, on contact, kills most types of bacteria and viruses, thereby helping patients to augment natural immune responses (immuno-stimulant), *in situ*, with minimal (yet possible) side-effect(s) reporting in the available accruing (yet limited) literature. For example, Nagayoshi., *et al.* in 2004 [3], explored the use of ozone as a sub-gingival irrigation solution in patients with acute necrotizing ulcerative gingivitis. They reported that the anti-microbial and bactericidal property of O_3 was deemed effective in reducing the number of cariogenic bacteria, and further, resulted in a significant reduction in the micro-organisms present, in the plaque biofilm and root canal, for both gram +ve and gram -ve such as *Porphyromonas endodontalis* and *Porphyromonas gingivalis*. O_3 was also reported to be effective for disinfecting root canals and dentinal tubules via its activity against endodontic pathogenic micro-organisms, such as *E. faecalis*, *Candida albicans*, *Peptostreptococcus micros* and *Pseudomonas aeruginosa*. On the other hand, ozone has been suggested to be potentially successful in the treatment of oral mucositis secondary to chemotherapy and radiotherapy, amongst other wound healing impairments or complications, and in various oral mucosal lesions such as herpes, aphthous ulcers, candidiasis, and denture stomatitis. In a trial, Matsamura K., *et al.* [4] used O_3 in extraction sockets (~40 seconds application) before placing the dental titanium implants, and concluded that ozone therapy prevented infections and peri-implantitis, enhanced *de novo* osseo-regeneration and the regeneration of periodontal cells. Using 150 mL of ozonized water to irrigate (for 5 - 10 min, 1x/week for 4 weeks) the periodontal pockets of aggressive periodontitis patients, Ramzy., *et al.* [5] significantly improved pocket depth, plaque and gingival indices, and bacterial count. Noteworthy herein, the ozone concentration commonly used and reported in the literature varies, greatly, depending on the medical/dental indication and the condition of the patient, and can range between 1 gm/mL and 100 gm/mL (0.05 - 5%). Ozone carries a negative charge, hence, can neutralize (destroy the bacterial cellular membrane/envelope; via oxidation of phospholipids and lipoproteins) the positively-charged bacteria, viruses, protozoa and other abnormal cells, whilst normal healthy cells remain un-affected (in theory). O_3, at a low concentration of 0.1 ppm, has been reported sufficient to inactivate bacterial cells including their spores, and interrupt the reproductive cycle in viruses via peroxidation thereby

damaging the viral capsid and virus-to-cell contact. Indeed, in a recent clinical study incorporating 60 patients with herpes zoster, topical ozone (oil) therapy (x2/day) was found to be particularly helpful in relieving pain, shortening the course as well as improving clinical efficacy (to 100%, compared to ~87% in controls receiving oral valacyclovir), without any obvious adverse reactions. Given its short half-life, medical and dental O_3 typically lasts less than 30 minutes, and what is not used or consumed will revert back to oxygen without leaving residual ozone in the environment (clinical setting). Also, given that it can be considered atraumatic, painless, analgesic yet anti-hypnotic, and non-invasive, relative to the absence of discomfort, an increase in patient acceptability and compliance has been reported, with the suggestion that ozone therapy might be an ideal treatment choice, especially for pediatric patients, in a recent literature review by Tiwari., *et al* [6]. The difficult-to-clean deep pits and fissures (and problematic smear layer) is perhaps a fine example of the versatility, feasibility, malleability, and applicability potential of an innovative ozone-based therapy utility. For instance, in another example, Ghobashy., *et al.* [7] concluded that during orthodontic treatment, using an ozonized olive oil significantly reduced enamel demineralization around orthodontic brackets and decalcification of teeth (when the patients combined with the standardized routine oral hygiene regimen). Also, Agrillo., *et al.* [8] documented the successful use of O_3 in cases of BRONJ (bisphosphonate-related osteonecrosis of jaw). Nonetheless, and to the best of knowledge, the US-FDA (Food and Drug Administration of the United States) does not yet approve the use of bio-energetic and -synthetic O_3 in the treatment of disease, in general, and has further noted that ozone has no known useful medical application, mainly due to the reason that there are not large enough long-term studies to understand all the potential adverse effects of its use (a possible competitive and contentious role for pharmaceutical companies, one can wonder?). In the event of an ozone intoxication, the patient must be placed in the supine position, inhale humid oxygen, and take ascorbic acid, vitamin E, and n-acetylcysteine. Overall, today, O_3 can be, therefore, still (or only) be considered as a promising and optional adjunct tool and therapeutic modality to other conventional or traditional treatments in contemporary and future dentistry. It should be used with high caution. Ongoing and future R&D&I (research, development, and innovation) studies are deemed essential to better establish and determine the specific associated clinical indications and guidelines to entirely take advantage of medical and dental O_3 therapy and satisfy/fulfill the ongoing controversies [9-12].

Conflict of Interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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