Ozone therapy: A clinical review

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Ozone therapy: A clinical review

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Abstract

Ozone (O_3) gas discovered in the mid-nineteenth century is a molecule consisting of three atoms of oxygen in a dynamically unstable structure due to the presence of mesomeric states. Although O_3 has dangerous effects, yet researchers believe it has many therapeutic effects. Ozone therapy has been utilized and heavily studied for more than a century. Its effects are proven, consistent, safe and with minimal and preventable side effects. Medical O_3 is used to disinfect and treat disease. Mechanism of actions is by inactivation of bacteria, viruses, fungi, yeast and protozoa, stimulation of oxygen metabolism, activation of the immune system. Medication forms in a gaseous state are somewhat unusual, and it is for this reason that special application techniques have had to be developed for the safe use of O_3. In local applications as in the treatment of external wounds, its application in the form of a transcutaneous O_3 gas bath has established itself as being the most practical and useful method, for example at low (sub-atmospheric) pressure in a closed system guaranteeing no escape of O_3 into the surrounding air. Ozonized water, whose use is particularly known in dental medicine, is optimally applied as a spray or compress. Diseases treated are infected wounds, circulatory disorders, geriatric conditions, macular degeneration, viral diseases, rheumatism/arthritis, cancer, SARS and AIDS.

Key words: Allodynia, autohemotherapy, lipid ozonation products, ozone

INTRODUCTION

Ozone (O_3), a gas discovered in the mid-nineteenth century, is a molecule consisting of three atoms of oxygen in a dynamically unstable structure due to the presence of mesomeric states. The gas is colorless, acrid in odour and explosive in liquid or solid form. It has a half-life of 40 min at 20°C and about 140 min at 0°C. Its basic function is to protect humans from harmful effects of UV radiation. Ozone occurs at less than 20 μg/m^3 from the Earth's surface at concentrations that are perfectly compatible with life. Although O_3 has dangerous effects, yet researchers believe it has many therapeutic effects.[1-3] The beginning of precise medical O_3 generators has only recently allowed the mechanisms, action and possible toxicity of O_3 to be evaluated by clinical trials.[2] Ozone has a capacity to oxidize organic compounds,[4] and has well-known toxic effects on the respiratory tract when present in smog.[5-6] In medical use the gas produced from medical grade oxygen is administered in precise therapeutic doses, and never via inhalation, and advocates that it has excellent health benefits in dental caries, decrease blood cholesterol and stimulation of antioxidative responses, modifies oxygenation in resting muscle and is used in complementary treatment of hypoxic and ischemic syndromes.[7-10]

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HISTORY OF OZONE THERAPY

Ozone therapy has been utilized and extensively studied for many decades altogether. Its effects are proven, consistent and with minimal side effects. Medical O_3, used to disinfect and treat disease, has been around for over 150 years. Used to treat infections, wounds and multiple diseases, O_3's effectiveness has been well-documented. It has been used to disinfect drinking water before the turn of the last century. Ozone was known to treat as many as 114 diseases.[11] Ozone therapy has been in use since the 1800s and in 1896 the genius Nikola Tesla patented the first O_3 generator in the US, later forming the 'Tesla Ozone Company."[12] During the first world war (1914-18)

doctors familiar with O_3's antibacterial properties, and with few other medical resources available to them applied it topically to infected wounds and discovered O_3 not only remedied infection, but also had hemodynamic and anti-inflammatory properties.[13] In the late 1980s, reports had emerged that German physicians were successfully treating HIV patients with 03-AHT (Autohemotherapy). There was then no pharmaceutical treatment for HIV and a pandemic was feared, so Canadian authorities authorized the study to test safety and efficacy of 03-AHT in AIDS patients. Ozone had shown promise in *in vitro* testing. Ozone was seen effective at disinfecting extracorporeal blood samples of HIV; unfortunately for AIDS patients, 03-AHT proved to be an *in vivo* ineffective treatment [14-15] [Table 1].

SARS AND OZONE

Ozone is a naturally occurring energy-rich molecule embodying unique physico-chemical and biological properties suggesting a possible role in the therapy of SARS, either as a monotherapy or, more realistically, as an adjunct to standard treatment regimens. Owing to the excess energy contained within the O_3 molecule, it is theoretically likely that O_3, unlike organism-specific antiviral options available today, will show effectiveness across the entire genotype and subtype spectrum of SARS.[25]

Table 1: The chronological use of ozone in medicine

Year	Use/treatment of/with ozone
1987	Abscess, acne, AIDS, allergies, cerebral sclerosis, circulatory disturbances, cirrhosis of the liver, cystitis, bedsores, gangrene, hepatitis, herpes, high cholesterol, colitis, tumors, cancer, osteomyelitis, Parkinson's, rheumatism, Raynaud's disease, scars, inflammation of the vertebrae, stomatitis, joint dystrophy, phlebitis, open sores, urology, vascular surgery, wound healing.[16]
1988	Herpes, AIDS and flu, wounds, burns, Staphylococcus infections, fungal and radiation injuries, and gangrene. Fistulae, hemorrhoids and anal infections. Diabetes and arteriosclerosis. Used in periodontal disease, mixed in water and swallowed for use on gastric cancer, and applied as a wash in intestinal or bladder inflammation. Mixed with olive oil it is used on fungal growths and skin ulcers. Ozone baths are used to irrigate the skin, to disinfect and treat eczema and skin ulcers.[17]
1989	Influence on tumor metabolism was observed, hence subsequently used in treatment of cancer.[18] There was significant increase IgG levels, hence was evaluated for its immunostimulatory activity.[19]
1990	Ozone in combination with 5-fluorouracil was shown to be synergistic *in vitro* against tumor cell suspensions, derived from the breast and the colon.[20] Ozonation of blood was carried out to treat viral diseases. Ozonation of blood was found to increase the release of lymphokines and the stimulation of peripheral blood mononuclear cells.[21]
1991	Ozone was found to have germicidal activity by the virtue of its oxidative destruction of micro-organisms including viruses and bacteria[22]
1992	Ozone therapy was used in rhinoplasty and it was found that there was a significant reduction in the postoperative complications.[23]
1993	Ozonated saline used as irrigating solution and was found to reduce abscess formation in the rats with fecal slurry in the peritoneal cavity.[24]

MECHANISM OF ACTION

Inactivation of bacteria, viruses, fungi, yeast and protozoa: Ozone therapy disrupts the integrity of the bacterial cell envelope through oxidation of the phospholipids and lipoproteins. In fungi, O_3 inhibits cell growth at certain stages. With viruses, the O_3 damages the viral capsid and upsets the reproductive cycle by disrupting the virus-to-cell contact with peroxidation. The weak enzyme coatings on cells which make them vulnerable to invasion by viruses make them susceptible to oxidation and elimination from the body, which then replaces them with healthy cells.[26]

Stimulation of oxygen metabolism: Ozone therapy causes an increase in the red blood cell glycolysis rate. This leads to the stimulation of 2,3-diphosphoglycerate which leads to an increase in the amount of oxygen released to the tissues. Ozone activates the Krebs cycle by enhancing oxidative carboxylation of pyruvate, stimulating production of ATP. It also causes a significant reduction in NADH and helps to oxidize cytochrome C. There is a stimulation of production of enzymes which act as free radical scavengers and cell-wall protectors: glutathione peroxidase, catalase and superoxide dismutase. Production of prostacyline, a vasodilator, is also induced by O_3[Figure 1].[25]

Activation of the immune system: Ozone administered at a concentration of between 30 and 55 μg/cc causes the greatest increase in the production of interferon and the greatest output of tumor necrosis factor and interleukin-2. The production of interleukin-2 launches an entire cascade of subsequent immunological reactions.[27]

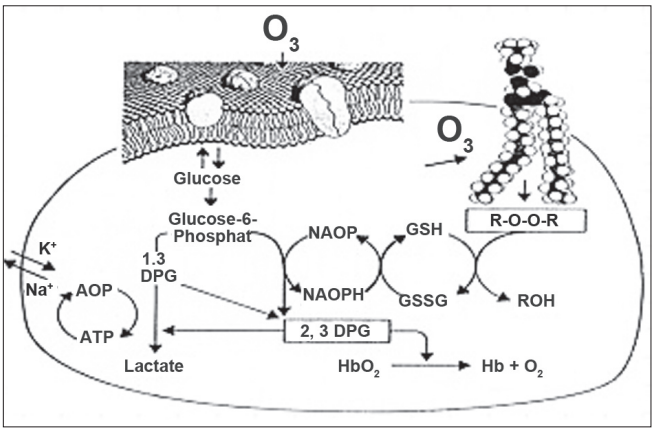

Figure 1: Action of ozone on RBC Metabolism[27]

Mechanism of action of O_3 on the human lung: Ozone exposure induces a significant mean decrement in vital capacity. It significantly increases mean airway resistance and specific airway resistance but does not change dynamic or static pulmonary compliance or viscous or elastic work. It also significantly reduces maximal transpulmonary pressure. And further more significantly increases respiratory rate and decreased tidal volume.[27]

CLINICAL TRIALS

The study to evaluate effect of bimosiamose on O_3-induced sputum neutrophilia: Biomosiamose is an anti-inflammatory glycomimetic and selectin inhibitor.[28] It is found effective against disease states involving inflammatory cells like for example for asthma.[29] This drug, as per last updation, was in phase 2 trials and being evaluated for its efficacy and safety in treating chronic pulmonary obstructive disease (COPD), the study is sponsored by Revotar Biopharmaceuticals AG and was carried out by NCT00962481 (ClinicalTrials.gov Identifier).[30]

Evaluate the effects of the drug (SB-656933-AAA) on the body after a single dose in subjects who have inhaled O_3: Drug SB-656933-AAA was developed by GlaxoSmithKline which was found to exhibit good activity in treating COPD as well as cystic fibrosis. This action was found to be enhanced by administration of a single dose of O_3 before administration of the aforementioned drug. This drug until latest updated data was in phase 1 stage, study was carried out by NCT00551811.[31]

Intraarticular O_3 therapy for pain control in osteoarthritis of the knee: Ozone is being currently tested for its effectiveness in relieving the pain in patients suffering from osteoarthritis of the knee. The current status of the study is phase 2 which is sponsored by Ben-Gurion University of the Negev and the study being conducted by NCT00832312.[32]

The Effect of Ozone Therapy for Lumbar-Herniated Disc: Ozone is also being evaluated for its efficacy infiltration and its effectiveness in comparison with microdiscectomy in the treatment of lumbar-herniated disc with criteria for surgery. The study is currently in its phase 2 studies, which is sponsored by Kovacs Foundation and trials being carried out by NCT00566007. The study also evaluates the efficacy of infiltration in presence of corticoids, anesthetics, which is being compared by replacing O_3 by oxygen.[33-35]

ADVANTAGES OF OZONE THERAPY

Diabetic complications are attributed to the oxidative stress in the body, O_3 was found to activate the antioxidant system affecting the level of glycemia. Ozone prevented oxidative stress by normalizing the organic peroxide levels by activating superoxide dismutase.[36-37] Ozone was found to completely inactivate the HIV *in vitro*, this action of O_3 was dose-dependent. Concentration used for inactivation was found to be non-cytotoxic. The inactivation was owing to the reduction of the HIV p24 core protein.[38] Ozone was also found to increase the host immunity by increasing the production of cytokine.[39] In an *in vitro* study, it was observed that O_3 is very effective in reducing the concentrations of *Acinetobacter baumannii*, Clostridium difficile and methicillin-resistant *Staphylococcus aureus* in dry as well as wet samples, hence it can be used as a disinfectant. Oxygen/ O_3 mixture was also found to prolong the appearance of arrhythmia induced by potassium chloride, aconitine, etc., in laboratory animals like rats.[40]

DISADVANTAGES OF OZONE THERAPY

An array of ill-effects are observed owing to the reactivity of O_3 viz oxidation, peroxidation or generation of free radicals and giving rise to cascade of reactions like peroxidation of lipids leading to changes in membrane permeability,[41] lipid ozonation products (LOP) act as signal transducer molecules.[42] The main reason for this being presence of unsaturated fatty acids in both lung lining fluid and pulmonary cell bilayers, O_3 reacts with unsaturated fatty acids to give their specific products i.e., LOP, which activates the lipases triggering the release of endogenous mediators of inflammation.[43] The loss of functional groups in enzymes leading to enzyme inactivation. These reactions further results in cell injury or eventual cell death. Combinations of O_3 and NO_2 occur in photochemical smog, have hazardous effects on lung alveoli and act additively or synergistically. Dietary antioxidants or free radical scavengers like vitamin E, C, etc., can prevent aforementioned effects of O_3.[44-45]

In an *in vitro* study it was observed that arachidonic acid was oxidized in presence to O_3 to give peroxides, viz. arachidonic acid peroxides (AAP), having activity comparable to prostaglandin endoperoxides. These peroxides were fond to show following actions contraction of rabbit aortic strips and rat fundus strips in presence on indomethacin and Vane's mixture of vasoactive hormones at doses comparable to naturally formed prostaglandin peroxides. AAP also caused aggregation of human platelets in platelet-rich plasma, but these effects were not observed in presence of indomethacin and vitamin E, which indicated that these can be used to treat such toxicity of O_3.[46]

RECENT DEVELOPMENT

Ozone was effectively used as an antibacterial agent to treat oral infections caused by *Actinomyces naeslundii, Lactobacilli casei* and *Streptococcus mutans*. Exposure of about 60 s exhibited 99.9% killing efficiency, but exposure for such a long period showed degradation of saliva proteins. So exposure of 10 s to 30 s was proved effective to kill significant number of bacteria.[47]

A single subcutaneous injection of O_3 in mouse with spared nerve injury of the sciatic nerve was found to decrease the neuropathic pain-type behavior. Mechanism of this action is yet unclear but O_3 was observed to regulate the expression of the genes that play vital role in onset and maintenance of allodynia.[48]

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