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LOW-DOSE OZONE THERAPY MODULATES INFLAMMATION AND ACTIVATES ANTIOXIDANT MECHANISMS: EFFECTS ON THE NERVOUS SYSTEM

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ABSTRACT

Ozone therapy (OT) can exert immunomodulatory and anti-inflammatory effects by inducing mild and controlled oxidative stress with the release of reactive oxygen species (ROS), H_2O_2, and the hydroxyl radical. These compounds are harmful at high concentrations but at low doses act as true cell signalling molecules and temporarily increase certain cellular antioxidants. Low-dose ozone (O_3) can increase antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase and modulate inflammation and oxidative stress. It can also lower levels of prostaglandins and pro-inflammatory cytokines by affecting protein synthesis compounds such as NF-kB. High O_3 levels can cause breathing difficulties, irritation, lung problems, and increase the sensitivity of the trigeminal system, promoting vasodilation, neuroinflammation, and headache. Low-dose OT is used for treating neurological disorders such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

KEYWORDS: *Ozone therapy, treatment, inflammation, antioxidant, therapy*

INTRODUCTION

Ozone therapy (OT) is a medical treatment that uses a mixture of oxygen and ozone (O_3) to modulate inflammation, oxygenation, and tissue response (1). Studies are undergoing to elaborate the ways in which OT affects the central nervous system, as many questions still remain open (2). Therapeutic O_3 can exert immunomodulatory and anti-inflammatory effects through mild and controlled oxidative stress (3). Mild and transient oxidative stress can activate the body's protective systems, a phenomenon known as "hormesis" (4). Reactive oxygen species (ROS), such as superoxide anion, hydrogen peroxide (H_2O_2), and hydroxyl radical (•OH) are toxic to cells, but at low concentrations they act as true cell signalling molecules. Small amounts of ROS increase antioxidant enzymes (such as superoxide dismutase, catalase, and glutathione peroxidase), cellular repair systems, and anti-inflammatory and detoxification responses, and activate the body's defence pathways (5). O_3 is a strong oxidant and, when administered in controlled doses, can induce mild and transient oxidative stress (6). A small amount of oxidative stress can activate certain body responses and temporarily increase certain cellular antioxidant systems (7).

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EFFECTS OF OZONE ON THE HUMAN BODY

O_3 can increase antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase (8). It can also modulate inflammatory mediators, the production of ROS, and lipid oxidation products, while excessive oxidative stress can damage lipids, proteins, and DNA (9). These conflicting effects place OT in a controversial position. However, some OT applications are used for vascular disorders, pain, and ulcers, although these therapies are often not supported by international guidelines (10).

O_3 not only acts as a direct anti-inflammatory in small doses, but can also modulate the inflammatory response through mild, controlled oxidative stress, resulting in a reduction of certain pro-inflammatory mediators such as interleukin (IL)-1, tumor necrosis factor (TNF), and IL-6 (11). Pro-inflammatory prostaglandins and certain compounds involved in inflammatory protein synthesis, such as NF-kB, can also be affected (12). Low-dose, controlled treatment with O_3 can activate endogenous antioxidant systems involved in the resolution of inflammation. Moreover, OT can have immunomodulatory and anti-inflammatory effects through mild oxidative stress (7).

The effects of treatment depend strictly on the dose, route of administration, and clinical context. Treatments are often not suitable for all diseases, and high concentrations of O_3 can be highly toxic to human health, as well as to animals and plants (13). The World Health Organization considers O_3 one of the main air pollutants harmful to health (14). High levels of O_3 can cause coughing and difficulty breathing, irritation of the eyes, nose, and throat, lung inflammation, worsening of asthma and bronchitis. O_3 can cause headaches and fatigue through oxidative stress, inflammation, and alterations in respiratory function (15). It is a highly reactive oxidant that, when inhaled, quickly reacts with lipids and proteins in the fluid lining the respiratory organs, producing ROS, oxidizing aldehydes, and lipid peroxidation products. These molecules are mediators of the inflammatory cascade. O_3 increases oxidative stress, which involves superoxide dioxide (O_2), H_2O_2, and hydroxyl radicals (16). In these cases, cellular antioxidant systems such as glutathione, vitamin C, and antioxidant enzymes fail, resulting in mitochondrial damage, a reduction in ATP, and an alteration in cellular energy metabolism (17). These effects cause weakness, fatigue with reduced physical activity, neurogenic inflammation, and headaches (18) (Table I).

Table I. *Low doses of ozone (O_3) can provide therapeutic effects by reducing reactive oxygen species (ROS) and preventing oxidative damage, whereas high doses can induce oxidative stress and become very toxic.*

Ozone Dose	*Possible outcome*	*Biological effects*
Low	Therapeutic effects	Controlled activation of antioxidant system and cellular defenses
High	Toxic effects and potentially life-threatening complications	Oxidative stress, damage vital organs, damage to antioxidant defenses, acute inflammation

Irritation of the airways activates vagal sensory fibers and the irritant receptors transient receptor potential ankyrin 1 (TRPA1) and transient receptor potential cation channel subfamily V member 1 (TRPV1) (19). As a result, chemical mediators such as substance P, calcitonin gene-related peptide (CGRP), and the inflammatory cytokines IL-1, TNF, and IL-6 are released. These mediators can increase the sensitivity of the trigeminal system, promote vasodilation and neuroinflammation, and cause headache (20). The induced lung inflammation reduces oxygen delivery and causes bronchoconstriction, reduced gas exchange, increased work of breathing, and fatigue. In addition to affecting the lungs, the inflammation caused by high O_3 levels causes systemic effects as oxidized molecules enter the circulation, increasing the systemic immune response and altering endothelial function. These effects cause malaise, headache, fatigue, and mental fog (21).

TREATMENTS WITH LOW OZONE CONCENTRATIONS

Treatments with low O_3 concentrations can improve microcirculation and tissue oxygenation (22). Treatment effects can modulate nitric oxide production, reduce blood viscosity, and affect endothelial function, useful in peripheral artery disease, ischemic ulcers, diabetic microcirculation, and venous insufficiency (23). Other positive effects of the treatment include the modulation of neuropathic pain, hernias, venous compression, lumbosciatica, fibromyalgia, certain cerebral vascular conditions, herniated discs, and musculoskeletal syndromes. In neurological therapy, O_3 is used in multiple sclerosis, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (24).

The beneficial effects of OT often depend on the characteristics of the patients treated and OT is contraindicated in hyperthyroidism, pregnancy, coagulation disorders, and favism (G6PD deficiency) (25,26).

CONCLUSIONS

OT acts on the autonomic nervous system, improving tiredness and sleep, reducing muscle tension, and inducing a feeling of increased energy, while at high levels, O_3 damages organs and the body at a systemic level.

Conflict of interest

The authors declare that they have no conflict of interest.

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