

R E V I E W

Mechanisms of pathophysiology of blood vessels in patients with multiple sclerosis treated with ozone therapy: a systematic review

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Summary. Multiple sclerosis (MS) defines as an intricate disease with numerous pathophysiological processes, including: inflammation, demyelination, oxidative stress, axonal damage, and repair mechanisms that interfere in this disease and highly related to the pathogenesis of MS. In parallel, recent studies have shown that the ozone administration could be very useful in treating neurological disorders and inflammatory and degenerative neurological diseases. In this review, we examine the recent literature on the pathophysiology of blood vessels in patients with multiple sclerosis treated with ozone therapy. (www.actabiomedica.it)

Key words: ozone, multiple sclerosis, pathophysiological, treatment

Introduction

Ozone (O₃) as one of the most significant air pollutants, is a gas or a triatomic molecule that including the three atoms of oxygen, also, O₃ in the mid-nineteenth century was discovered as well as it has a cyclic structure or a dynamically instable structure due to its mesomeric structure or states. In nature, O₃ is created during storms due to the electrical evacuation of the beams that react with atmospheric oxygen to yield ozone. Moreover, it is as a clinical tool to characterization of secure or safe, cheap, and effective with an extensive area of therapeutic applications. Pain management of various diseases is a region where ozone excels, and further studies have been performed to indicate its analgesic attributes (1-5).

In recent years, set of applications on ozone or oxygen-ozone therapy has evident an increasing. O₃-therapy is utilized in medicine to remedy different conditions of diseases and also, currently is one of

the diverse minimally invasive treatments available in medicine science for physicians and researchers, plus, for example, O₃-therapy can be delivered by injection of rectal insufflation, which organizes a simple and minimally invasive pathway, with slight toxicity, automatically replaces to the classical mayor auto-hemotherapy and a large bibliography is based on the exploitation of ozone chemical properties, an unstable allotropic form of oxygen with the symbol O₃ and a molecular weight of 48 kDa. Nevertheless, there are a lot of literatures about the positive effects of the oxygen and ozone therapy on diverse pathophysiological process, tissues, and organs. Furthermore, the biological effects of the rectal insufflation of ozone have been revealed extensively either experimentally or clinically. However, there is requiring of strong materials for the in vivo researches and real-time monitoring of the ozone effects during treatment (6-13).

According to studies and research reports, treatment with O₃ can elevates blood oxygen impregna-

tion, progresses blood circulation, activates erythrocyte metabolism, improves tissue oxygenation and oxygen secure and restores cell function, effectively increasing oxygen metabolism. In addition, O₃ can be provided by major ozone autohemotherapy, which includes in drawing a given amount of venous blood and after in reinfusing it after it has been added to a mix of O₂/O₃. More biologic effects have been ascribed to ozone: elevated glycolysis, effects on red blood cells, rheology; fungicide, bactericidal, and virustatic immunomodulating action, analgesic and anti-inflammatory effects. Furthermore, O₃ can also reportedly improve arterial and venous blood flow, increase the elasticity of erythrocytes, increase the capability of blood to pass through vessels such as the capillaries and consequently increase oxygen supply to whole organ systems. Moreover, also decreases platelet aggregation, and promotes formation of hydrogen peroxide at the site of thrombus, which impairs thrombosis and induces thrombus decomposition as well as O₃ also activates platelets inducing the subsequent liberation to the blood of growth factors that can comfort wound regeneration. In truth, laboratory studies have been suggested that treatment with O₃ is effective in protecting organs from reperfusion losses. Hence, ozone indicates the therapeutic properties of vascular and metabolic treatment. This broad spectrum of practice describes the multitude marks for medical ozone administration (2, 11, 12, 14-25). On the other hand, previous studies demonstrated the ozone capabilities of raising peripheral tissue oxygenation as well as the impact of ozone autohemotherapy on vessels diseases, injuries, macular degeneration and prevention of limb ischemia (15, 17, 26, 27). In a study by Percorelli et al. reported upregulation of the heme oxygenase-1 expression in endothelial cells by ozonated serum (28).

O₃ therapy can be produced a number of messengers that attain to total cells in the body and act to reverse chronic oxidative stress by readjusting the modified cellular redox balance. Plus, these cellular messengers could motivate the emancipation of stem cells from the bone marrow for regenerating distressed or degenerated organs. Nevertheless; this treatment method has been engaged for decades as a supplementary medical approach in a spacious range of pathologies including resistant infections, orthopedic pathologies, degenerative eye disease, various pain syndromes,

ischemic vascular abnormalities and neurodegenerative diseases. However, the use of O₃ treatment on the neurodegeneration related to normal aging remains a rigorous range for investigation (3, 29-32).

Neurodegenerative disorders have numerous various etiologies and are a group of heterogeneous diseases of the nervous system such as the brain, spinal cord, and peripheral nerves. The outbreak of them increases with extended life hope, illustrating a serious health problem global. In parallel, recent studies have shown that the ozone administration could be very useful in treating neurological disorders and inflammatory and degenerative neurological diseases, via a signed effect on the activity of the cytochrome-c-oxidase. Neuroprotective features of O₃ therapy effects have been predicted in vivo, although, little is known on its clinical and therapeutic impact in neurodegeneration, but O₃ rapidly by generating of two messengers such as H₂O₂ and a mixture of lipid ozonated products acts as pro-medication, which it due to from the response of O₃ with the cell membrane and lipoproteins-bound polyunsaturated fatty acids currently the researchers are distinguishing the clinical efficacy of ozone major autohemotherapy in the treatment of multiple sclerosis (MS). As a perspective, the goal is to apperceive whether MS patients underwent ozone autohemotherapy demonstrate a reduced number of annual relapses or reducing the symptoms of patient, an improvement in the functional scores, and stabilization of the number of white matter lesions. But its effects on brain are remains not clear or unknown (33-36).

Ozone autohemotherapy (OA) as an emerging remedial technique is another procedure of administration for ozone therapy that is achieving increasing in the treatment of neurodegenerative disorders (37-39). OA involves the collection of venous blood from the patient (from 100 to 240 g), and then the blood is blended with an oxygen/ozone (O₂-O₃) mixture, and it via the same vein is reinfused (40, 41). In a study, Molinari et al., 2014 in a long-term monitoring reported that OA had a clear effect on progress of the reduction of chronic oxidative stress and enhance of the mitochondrial functionality of neural cells in MS patients (38). Furthermore, Larini et al., 2003 have revealed that OA can ameliorate blood circulation, activate antioxidant enzymes and scavenge free radicals

(42), as well as in recent years, several studies demonstrated that OA has been already utilized to treat vascular disease (such as peripheral artery disease), advanced ischemic diseases and neurological disease (E.g. spontaneous spinal epidural hematoma, multiple sclerosis), but after OA, no scientific evidence of the oxygen concentration in the brain cortex, which this result is in accordance with published studies (43-47).

MS is a degenerative neurological pathology or a chronic inflammatory autoimmune disease of the central nervous system (CNS) characterized by both vascular and metabolic impairments that leads to demyelination and axonal damage or leads to a deficiency or complete loss in the transmission of nerve impulses for the exact etiology is not yet understood. On the other define, Multiple sclerosis (MS) defines as an intricate disease with numerous pathophysiological processes, including: inflammation, demyelination, oxidative stress, axonal damage, and repair mechanisms that interfere in this disease and highly related to the pathogenesis of MS. In addition, high levels of lipid peroxidation and decreased antioxidants have been found in blood and cerebrospinal fluid of patients at active phases of MS as well as increased oxidative stress levels seen in MS patients has been clearly showed. Moreover, reactive oxygen species (ROS) meliorate transendothelial leukocyte migration and helps to oligodendrocyte injury and axonal degeneration. Since ROS plays an axial role in the primary stage as well as the chronic stage of MS, thus, antioxidant therapy might be an attractive approach to limit disease progression. So, O₃ therapy has a rationale of application as an adjuvant remedy for MS patients. In accordance with past studies, the O₃ therapy elevated the total level of oxygen in the tissue. Increasing oxygen in control is more obvious than MS patients (48-62). Araneda et al. have shown that vascular endothelial growth factor (VEGF)-immunoreactive glial cells are in contact with blood vessel walls during post-ozone improvement showing revascularization and regeneration of the BBB (63). In another study by Broadwater et al., and Molinari et al., have reported that in MS patients the O₃ therapy elevated the overall level of oxygen in the tissue. Findings them suggested that might be explained by increased ozone-induced metabolism. Also it have been shown, the little levels of mitochondrial activity in MS patients probably due to oxidative

damage to DNA. They also observed that the ozone ameliorates mitochondrial activity level, it can be that the enhancement in the neurons metabolic function effected an gain in the level of oxygen expenditure (9,64) as well as Molinari et al., revealed that in a clinical trial study with ozone autohemotherapy on MS patients an increment of cytochrome-coxidase level together with reduction of the chronic oxidative stress level typical of MS cases (9). Other report by Delgado-Roche et al., 2017 have indicated a considerable depletion of oxidative damage on lipids and proteins in patients treated with ozone. Likewise, the pro-inflammatory cytokines levels were lesser after o₃ therapy. Findings can supplies novel insights on the into ozone-induced molecular events, and remonstrate o₃ therapy as a potential therapeutic alternative for MS patients (65). Furthermore, Lu et al., have proposed that ozone autohemotherapy could be useful to treat MS patients, especially because of its raising effect on mitochondria activation (66).

Conclusions

To the best of our knowledge, our findings of this review article suggest that Ozone-therapy is a new therapeutic technique that is achieving elevating importance in treating on MS patient. Therefore, it should be noted that the therapeutic potential of ozone needs to be much attention through its strong capacity with a reduction of toxicity of MS patients undergoing remedy with other drugs and side effects, and it promotes a reduction of cellular oxidative stress, oxidative damage on lipid and proteins, decrease of the pro-inflammatory cytokines levels and an improvement of oxygen blood transportation and delivery. These results will provide many insights to propose the potential neuroprotective mechanism of medical ozone in MS. Finally, O₃ therapy approach could be considered as an affirmative supplement to the actual pharmacological remedies addressed to neurodegenerative disorders such as MS as well as it should also be considered for the clinical efficacy of OA in the treatment of MS.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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