Acta Biomed 2019; Vol. 90, N. 3: 213-217 DOI: 10.23750/abm.v90i3.7265

Review

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

Javad Ameli[1], Abdolali Banki[1], Fariborz Khorvash[2], Vincenzo Simonetti[3], Nematollah Jonaidi Jafari[4], Morteza Izadi[5, 6]

[1]Department of Neurology, Baqiyatallah University of Medical Sciences, Tehran, Iran; [2]Neuroscience Research Center, Isfahan University of medical science; [3]Ozono terapista, Torino, Italy; [4]Health Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran; [5]Molecular Biology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran; [6]Ozone Complementary Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

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 autohemotherapy 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, labroratory 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 autohemotheraphy 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-l 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 (from100 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

References

1. Di Paolo N, Bocci V, Gaggioti E. Ozone therapy editorial review. Int J Artificial Organs 2004; 27: 168-75.
2. Bocci V. Biological and clinical effects of ozone: Has ozone therapy a future in medicine? Br J Biomed Sci 1999; 56: 270-9.
3. Bocci V. Does ozone therapy normalize the cellular redox balance? Implications for the therapy of human immunodeficiency virus infection and several other diseases. Med Hypothesis 1996; 46: 150-4.
4. Braidy N, Izadi M, Sureda A, Jonaidi-Jafari N, Banki A, Nabavi SF, Nabavi SM.Therapeutic relevance of ozone therapy in degenerative diseases: Focus on diabetes and spinal pain. J Cell Physiol 2017 Jun 8. doi: 10.1002/jcp.26044. [Epub ahead of print]
5. Re L, Rowen R, Travagli V. Ozone Therapy and Its Use in Medicine. Cardiology 2016; 134(2): 99-100
6. Elwell CE, Cope M, Edwards AD, et al. Quantifcation of adult cerebral hemodynamics by near-infrared spectroscopy. J Appl Physiol 1994; 77: 2753-2760
7. Lintas G, Molinari F, Simonetti V, et al. Time and timefrequency analysis of near-infrared signals for the assessment of ozone autohemotherapy long-term effects in multiple sclerosis. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc 2013: 6171-6.
8. Molinari F, Acharya UR, Martis RJ, et al. Entropy analysis of muscular near-infrared spectroscopy (NIRS) signals during exercise programme of type 2 diabetic patients: quantitative assessment of muscle metabolic pattern. Comput Methods Programs Biomed 2013; 112: 518-528.
9. Molinari F, Simonetti V, Franzini M, et al. Ozone autohemotherapy induces long-term cerebral metabolic changes in multiple sclerosis patients. Int J Immunopathol Pharmacol 2014; 27: 379-389.
10. Martínez-Sánchez G, Delgado-Roche L, Díaz-Batista A, Pérez-Davison G, Re L. Effects of ozone therapy on haemostatic and oxidative stress index in coronary artery disease. Eur. J. Pharmacol 2012; 691: 156-162.
11. Viebahn R. The Use of Ozone in Medicine. Heidelberg: Karl F. Haug Publisher; 1994.
12. Iliakis E, Valadakis V, Vynios DH, Tisiganos CP, Agapitos E. Rationalization of the activity of medical ozone on intervertebral disc: a histological and biochemical study. Riv Neuroradiol 2001; 14(suppl 1): 23-30.
13. Bocci V. Oxygen-Ozone Therapy, a Critical Evaluation. Doordrecht: Kluwer Academic Publishers; 2002
14. Zaky, S. et al. Preliminary results of ozone therapy as apossible treatment for patients with chronic hepatitis C. J Altern Complement Med 2011; 17: 259-63.
15. Bocci V, Zanardi I, Travagli V. Ozone: a new therapeutic agent in vascular diseases. Am J Cardiovasc Drugs 2011; 73-82.
16. Clavo B, et al. Ozone Therapy for Tumor Oxygenation: a Pilot Study. Evidence-based Complement. Altern Med 2004; 1: 93-98.
17. Shah P, Shyam AK, Shah S. Adjuvant combined ozone therapy for extensive wound over tibia. Indian J Orthop 2011; 45: 376-379.
18. Sagai M, Bocci V. Mechanisms of Action Involved in Ozone Therapy: Is healing induced via a mild oxidative stress? Medical Gas Research 2011; 1: 29.
19. Di Filippo C, et al. Acute oxygen-ozone administration torats protects the heart from ischemia reperfusion infarct. Inflamm Res 2008; 57: 445-449.
20. Chen H, et al. Ozone oxidative preconditioning inhibits inflammation and apoptosis in a rat model of renal ischemia/reperfusion injury. Eur J Pharmacol 2008; 581: 306-14.
21. Bocci V. Autohaemotherapy after treatment of blood with ozone: a reappraisal. J Int Res 1994; 22: 131-144.
22. Coppola L, Verazzo G, Giuta R, et al. Oxygen-ozone therapy and hemorrheological parameters in peripheral chronic arterial occlusive disease. Trombosi e Aterosclerosi 1992; 3: 85-89.
23. Rokitansky O, Rokitansky A, Steiner J, et al. Ozontherapie bei peripheren, arteriellen. Durchblutungsstorungen: klinik, biochemishe und blutgasanalytische untersuchungen. In: Wasser, IOA, ed. Ozon-Weltkongress. Berlin: 1981: 53-75.
24. Wenzel DG, Morgan DL. Interactions of ozone and antineoplastic drugs on rat lung fibroblasts and Walker rat carcinoma cells. Res Commun Chem Pathol Pharmacol 1983; 40: 279-287.
25. Bocci V, Luzzi E, Corradeschi F, et al. Studies on the biological effects of ozone: III, an attempt to define conditions for optimal induction of cytokines. Lymphokine Cytokine Res 1993; 12: 121-126.
26. Borrelli E, Diadori A, Zalaffi A, Bocci V. Effects of major ozonated autohemotherapy in the treatment of dry age related macular degeneration: a randomized controlled clinical study. Int J Ophthalmol 2012; 5(6): 708-13.
27. Tylicki L, Niewglowski T, Biedunkiewicz B, Burakowski S, Rutkowski 8. Beneficial clinical effects of ozonated autohemotherapy in chronically dialysed patients with atherosclerotic ischemia of the lower limbs--pilot study. Int J Artif Organs 2001; 24(2): 79-82.
28. Pecorelli A, Bocci V, Acquaviva A, et al. NRF2 activation is involved in ozonated human serum upregulation ofHO- I in endothelial cells. Toxicol Appl Pharmacol 2013; 267(1): 30-40.
29. Bocci V. Ozone as a bioregulator. Pharmacology and toxicology of ozone therapy today. J Biol Regul Homeost Agents 1196b; 10: 31-53.
30. Bocci V. Ozone: A new medical drug. Springer, Dordrecht, 2005.
31. Bocci V. Scientific and medical aspects of ozone therapy. State of the art. Arch Med Res 2006; 37: 425-435.
32. Di Paolo N, Bocci V, Gaggiotti E. Ozone therapy. Int J Artif Organs 2004; 27: 168e175.
33. Sagai M, Bocci V. Mechanisms of action involved in ozone therapy: is healing induced via a mild oxidative stress? Med Gas Res 2011; 1: 29-45. 10.1186/2045-9912-1-29.
34. Milo R, Miller A. Revised diagnostic criteria of multiple sclerosis. Autoimmun Rev 2014; 13: 518-524.
35. Viebahn-Hänsler R, León OS, Fahmy Z. Ozone in medicine: the low-dose ozone concept-guidelines and treatment strategies. Ozone Sci Eng 2012; 34: 408-424.

36. Molinari F, Rimini D, Liboni W, et al. Cerebrovascular pattern improved by ozone autohemotherapy: an entropy-based study on multiple sclerosis patients. Med Biol Eng Comput 2017; 55(8): 1163-1175.
37. Rimini D, Molinari F, Liboni W, Simonetti V, Franzini M. The speed of reinfusion affects the vascular system during ozone major autohemotherapy. Ozone Therapy 2017; 1 (3): 56-60.
38. Molinari F, Simonetti V, Franzini M, et al. Ozone autohemotherapy induces long-term cerebral metabolic changes in multiple sclerosis patients. Int J Immunopathol Pharmacol 2014; 27(3): 379-89.
39. Han X, Molinari F, Rossati S. Assessment of Ozone Autohemotherapy on Patients with Multiple Sclerosis by Time-frequency Analysis of Near-infrared Spectroscopy Signals. International Journal of Bioelectromagnetism 2016: 18(1); 32-37.
40. Bocci V, Brito GS. Ozone therapy in critical patients. Rationale ofthe therapy and proposed guidelines. Riv Ital Ossigeno Ozonoterapia 2006; 5: 7-11.
41. Viebahn-Hänsler R, León Fernández OS, Fahmy Z. Ozone in medicine: the low-dose ozone concept-guidelines and treatment strategies. Ozone Sci Eng 2012; 34: 408-24.
42. Larini A, Bianchi L, Bocci V. The ozone tolerance: I) enhancement of antioxidant enzymes is ozone dose-dependent in jurkat cells. Free Radical Research 2003; 37(11): 1163-1168.
43. Bocci V, Zanardi I, Travagli V. Ozone: a new therapeutic agent in vascular diseases, American Journal of Cardiovascular drugs 2011; 11(2): 73-82.
44. Lintas G, Molinari F, Simonetti V, Franzini M, Liboni W. Time and time-frequency analysis of near-infrared signals for the assessment of ozone autohemotherapy long-term effect in multiple sclerosis, Conference Proceedings of the IEEE Engineering in Medicine & Biology Society 2013; 6171-6174.
45. Yu L, Lu XJ, Shi HC, Wang Q. Does ozone autohemotherapy have positive effect on neurologic recovery in spontaneous spinal epidural hematoma? American Journal of Emergence Medicine 2014; 32(8): 949.e1-949.e2.
46. De Monte A, van der Zee H, Bocci V. Major ozonated autohaemotherapy in chronic limb ischemia with ulcerations, Journal of Alternative and Complementary Medicine 2005; 11(2): 363-367.
47. Di Paolo N, Bocci V, Salvo DP, et al. Extracorporeal blood oxygenation and ozonation (EBOO): a controlled trial in patients with peripheral artery disease. The international journal of Artificial organs 2005; 28(10): 1039-1050.
48. Sospedra M, Martin R. Immunology of multiple sclerosis. Annual Reviews in Immunolology 2005; 23: 683-747.
49. Milo R, Kahana E. Multiple sclerosis: geoepidemiology, genetics and the environment. Autoimmunity Reviews. 2010; 9: A387-94.
50. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part II: Noninfectious factors. Annals of Neurolology 2007; 61: 504-13.
51. Simon KC, Munger KL, Ascherio A. XVI European Charcot Foundation lecture: Nutrition and environment, can MS be prevented? Journal of the Neurological Sciences 2011; 311: 1-8.
52. Van der Mei IA, Simpson Jr. S, Stankovich J, Taylor BV. Individual and joint action of environmental factors and risk of MS. Neurologic Clinics 2011; 29: 233-55.
53. Kurtzke JF. Geography in multiple sclerosis. Journal of Neurology 1977; 215: 1-26.
54. Kurtzke JF. Geographic distribution of multiple sclerosis: An update with special reference to Europe and the Mediterranean region. Acta Neurologica Scandinavica 1980; 62: 65-80.
55. Morovic S, Zamboni P. CCSVI is associated with multiple sclerosis. Neurological Research 2012; 34: 770-779.
56. Dake MD. Chronic Cerebrospinal Venous Insufficiency and Multiple Sclerosis: History and Background. Tech Vasc Interv Radiol 2012; 15: 94-100.
57. Lu F, et al. Oxidative damage to mitochondrial DNA and activity of mitochondrial enzymes in chronic active lesions of multiple sclerosis. J Neurol Sci 2000; 177: 95-103.
58. Gonsette RE. Neurodegeneration in multiple sclerosis: the role of oxidative stress and excitotoxicity. J Neurol Sci 2008; 274: 48-53.
59. Lisak RP. Neurodegeneration in multiple sclerosis: defining the problem.Neurology 2007; 68: S5-S12.
60. Greco A, Minghetti L, Sette G, Fieschi C, Levi G. Cerebrospinal fluid isoprostane shows oxidative stress in patients with multiple sclerosis. Neurology 1999; 53: 1876-1879.
61. Ferretti G, Bacchetti T, Principi F, et al. Increased levels of lipid hydroperoxides in plasma of patientswith multiple sclerosis: a relationship with paraoxonase activity. Mult Scler 2005; 11: 677-682.
62. Hafler DA. Multiple sclerosis. J Clin Invest 2004; 113: 788-794.
63. Araneda S, Commin L, Atlagich M, et al. VEGF overexpression in the astroglial cells of rat brainstem following ozone exposure. Neurotoxicology 2008; 29: 920-927.
64. Broadwater L, et al. Analysis of the mitochondrial proteome in multiple sclerosis cortex. Biochim Biophys Acta - Mol Basis Dis 2011; 1812: 630-641.
65. Delgado-Roche L, Riera-Romo M, Mesta F, et al. Medical ozone promotes Nrf2 phosphorylation reducing oxidative stress and pro-inflammatory cytokines in multiple sclerosis patients. Eur J Pharmacol 2017; 811: 148-154.
66. Lu F, Selak M, O'Connor J, et al. Oxidative damage to mitochondrial DNA and activity of mitochondrial enzymes in chronic active lesions of multiple sclerosis. J Neurol Sci 2000; 177(2): 95-103.

Received: 15 April 2018
Accepted: 14 June 2018
Correspondence:
Morteza Izadi
Professor of Molecular Biology Research Center,
Baqiyatallah University of Medical Sciences,
Tehran, Iran, P. O. Box: 1435916471
Tel. 021-82483250;
Fax 021-88040106
E-mail: Mortezaizadimd@yahoo.com