IJPSR (2021), Volume 12, Issue 2 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 March 2020; received in revised form, 14 May 2020; accepted, 22 May 2020; published 01 February 2021

OZONE THERAPY: A PARADOX OR PANACEA IN VARIOUS AILMENTS

Prachi Pimple * and Gaurav Doshi

SVKM's Dr. Bhanuben Nanavati College of Pharmacy, V. M. Road, Vile Parle (W), Mumbai - 400056, Maharashtra, India.

Keywords:

Oxidative stress, Reactive oxygen species, Inflammation, Radical, Antioxidant

Correspondence to Author:
Dr. Prachi Pimple

Assistant Professor,
Department of Pharmaceutics,
SVKM's Dr. Bhanuben Nanavati College of Pharmacy, V. M. Road,
Vile Parle (W), Mumbai - 400056,
Maharashtra, India.

E-mail: prachi.Pimple@bncp.ac.in

ABSTRACT: Ozone gas (O_3), being an unstable molecule, attracts uncertainty as an alternative to medication, opening avenues for copious research. Ozone therapy (OT) shows its therapeutic efficacy by its reactions with biological components and the production of oxidative stress. It is found useful in various disease conditions like cancer, cardiovascular diseases, pulmonary diseases, wound healing, dental conditions, *etc.* The therapy on contrast also shows side effects depending on the type of treatment includes burns, coughing, cramping, headaches, nausea, vomiting or severe respiratory complications, and also sometimes flu-like symptoms. The investigation for the use of the OT as a technology is still under development to be used in several ways like ozonated water, injections, insufflations, oil, blow the gas into the body, use an ozone sauna, autohemotherapy. The therapy raises many questions to be used as a solution for diseases with self-contradiction due to the adverse effects occurring after the use of therapy or exposure to the ozone.

INTRODUCTION: Ozone (O_3) is found to have some dangerous effects, but O_3 therapy (OT) is studied for years for its application in various segments and minimal plus preventable side effects. O_3 is a colorless, water-soluble unstable molecule explosive in nature. Over 150 years, medical O_3 is used as a disinfectant and ailment for several diseases, especially in wound healing. It is generated by the UV system, cold plasma system or corona discharge system. OT is known to restore oxygen metabolism, avoid stroke or shock damage, eradicate or inactivate pathogens, reduce pain and inflammation, and improve the immune system.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(2).754-59

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(2).754-59

O_3 acts on bacteria by undergoing oxidation and disrupting the cell envelope, whereas cell growth is inhibited in fungi at certain stages, and in viruses, their reproductive cycle is disrupted and damages the capsid by the peroxidation effect. O_3 induces the production of prostacyclin and acts as a vasodilator. It is also effective as inflammation, asthma, chronic pulmonary obstructive disease (COPD), osteoarthritis, lumbar-herniated disc, *etc.* [1]

O_3 is effective against diabetic complications by affecting glycemic levels and increases immunity by producing cytokine. It also acts as a disinfectant against various microbes like *Clostridium*, *Acineto-bacter baumannii,* and *Staphylococcus aureus* [1]. It arises many reactions like peroxidation and free radical generation leading to changes in membrane permeability, the reaction of O_3 with unsaturated fatty acids forming lipid ozonation products causing inflammation or enzyme inactivation.

Lung alveoli are affected during photochemical smog by O_3 and NO_2 combination. On undergoing oxidation, it produces arachidonic acid peroxides causing platelet aggregation. So various mechanisms of actions involved are reaction with reactive oxygen species or polyunsaturated fatty acids and creating lipid ozonation products like hydro-peroxides, isoprostanes, 4-hydroxynonenal, *etc*. [1, 3, 5, 7]

Through stoichiometric calculations, O_3 auto-hemotrafusion was performed using oxygen-ozone (O_2-O_3) infusion. Similar techniques to administer O_3 therapy are ozonation, extracorporeal blood oxygenation, rectal insufflation, and direct injection through intradiscal, intramuscular or paravertebral at the target site of action. Though oral, vaginal, nasal, vesical, tubal and peritoneal cavities are advisable routes [3]. Different methods of applying OT are autohemotherapy, topical ozone, rectal or bladder ozone, prolozone, and hocatt.

2. Clinical Effects of Ozone Therapy: The route of administration and concentration of administering ozone is the determining factor of the different effects produced by ozone therapy.

- **Bactericidal, Fungicidal and Virucidal:** Direct oxidative effect on the membrane of microorganism is achieved on the external application high concentration of ozone in the form of a gaseous mixture or ozonated solution. All types of bacteria, fungi, viruses, protozoa are sensitive to oxidation.
- Rectification and stimulation of metabolic processes in the hepatic and renal tissues safeguard neutralization and clearance of the harmful compounds from the organ; this contributes to the detoxification effect of ozone.
- Ozone also synchronizes metabolic reactions of inflamed tissues and settle down the pH.

3. Applications: An OT can benefit biological systems with pharmaceutical science intervention in numerous ways. It is used as an antibacterial against *Actinomyces naeslundii*, *Streptococcus mutans* and *Lactobacilli casei* for oral infection treatment [1].

O_3 damages tumor cells and amplifies radio and chemotherapy in cancer treatment as a complementary therapy. O_3 therapy is beneficial in cancer treatment by modifying tumor hypoxia, loco-regional blood flow, hemoglobin dissociation curve, and 2,3-diphosphoglycerate level 2.

It is also useful in pain management as an analgesic and anti-inflammatory action.

3.1. Wound Healing: OT is used to treat burns by skin healing and reducing uncontrolled bacterial infections and inflammation by activating transforming growth factor-β. It is also proved that epithelial-mesenchymal transition is increased ozone, oil ultimately helps in fibroblasts. OT possesses the disinfectant property with radical scavenging by inactivating bacterial growth [13, 14]. Ozone therapy has been proposed as a treatment for chronic wounds, potentially acting by eliciting mild oxidative stress or disinfection.

3.2 Diabetes: Induction of oxidative stress is a major reason for diabetes pathogenesis, ultimately damaging tissue and producing free radicals. The mechanism involved includes xanthine oxidase pathway obstruction to inhibit ROS production and preconditioning oxidant systems. Insulin effects were found to be potentiated along with ozone therapy integration improves systematic blood pressure and antioxidant capacity resulting in a reduction of glucose and lipid oxidation maintain antioxidant therapy caused by diabetes induction.

People suffering from diabetes mellitus foot ulcers are treated by OT due to the activation of the antioxidant system and superoxide dismutase. However, OT is not yet reliable in the treatment of chronic wounds by intralesional injection. OT is used as a complementary treatment by topically using ozonated water and vegetable oils [8-13].

3.3. Pulmonary Diseases: OT has a dilating effect on smooth muscle by nitric oxide radical, causing blood saturation eliminating hypoxia being useful in asthma and bronchitis treatment. Though, high dose induces gene transcription or inflammatory proteins and cytokine and downregulating to type I interferon protein signal and response to the viral protein [5]. OT improves glucose penetration through cellular membranes by stimulating aerobic glycolysis and the pentose-phosphate pathway promoting hyperglycemia.

3.4. Dental: OT helps to control bleeding, cleansing wounds in soft tissues and bones, improves healing, acts as a disinfectant, especially for hypomineralized teeth therapy, tooth extraction, teeth whitening, gum recession, and root carries management. Ozonated water is sprayed or gargled to rinse the mouth to clean and disinfect the affected area. Tissue or organ regeneration occurs due to the activation of protein synthesis by ozone. O_3 water, oil or gas is applied to oral tissues to prevent dental infections. Though OT emerges as a noninvasive technique to treat dental caries, it may cause adverse effects and is contraindicated in pregnancy, myasthenia, hemorrhage, hyper-thyroidism, and other ozone allergies. The triple ozone treatment system is commercially available as O_3 water for oral infections [16, 17, 18].

3.5. Cancer: OT is used as a non-conventional form and adjuvant therapy and not used as an alternative therapy to treat cancer as it damages tumor cells directly or stimulating oxidative stress, and affecting blood flow. Administration of systemic OT by autohemotransfusion showed a significant decrease in hypoxia and improved oxygenation. It is also proved as supportive therapy for fatigue and pain in cancer patients using O_2-O_3 therapy [2, 19, 20].

3.6. Aging: Animal models show age-related controlled effects due to prophylactic OT by oxidative stress. OT enhances anti-aging by increasing blood oxygen levels causing an aerobic environment altering skin appearance and healing process. This improves circulation, oxygenated tissues, and sweats out toxins improving metabolism. The treatment is administered by rectal, intra-venous, or sauna with non-interference of the head to avoid respiratory effects. O_2-O_3 therapy is used thermostatically by quasi-total body exposure showing minimal effects acting as a mild stressor [3, 22].

3.7. Orthopedic Diseases: OT was found an alternative for polyarthritis, painful joints, Morton's disease, and osteoarthritis treatment by insufflation of the gaseous mixture by the increase of articular cartilage and matrix synthesis. It inhibits inflammation and ischemia, stimulating an analgesic effect. The Prolozone method is used for joint, muscle pain, sore, and damaged muscles by injecting to the inflamed area. OT is used in various orthopedic conditions like bone infections, rheumatoid arthritis, osteoarthritis, slipped disc, and osteoporosis. O_2-O_3 therapy shows the clinical application as an alternative in musculoskeletal disorders by inactivating viruses and bacteria, promoting tissue hyperoxygenation to treat joints, tendons, and muscles. However, its activity for plantar fasciitis, costochondritis, and myofascial syndrome treatment is under investigation due to its common side effects [7, 23, 24].

3.8. Cardiovascular Diseases: OT activates the immune system and increases endothelial progenitor cells, growth factors, and antioxidant enzymes, ultimately reducing cardiovascular diseases being potential therapy in atherosclerosis and ischemic heart disease. O_2-O_3 therapy has shown the optimal effects of cardiovascular disorders by blocking pathological progress [5, 25, 26].

3.9. Anti-inflammatory and Analgesic: OT is marked safe, economical, and effective in the treatment of pain and inflammation. Compounds like prostaglandins, arachidonic acid is oxidized in a double layer, activates hypoxia-inducible factor-1α, inactivates pain mediators, maintaining inflammation, and acts as an analgesic. However, OT shows the tomato effect and non-patentable technology, which contradicts the treatment. O_2-O_3 therapy, combined with physiotherapy, was found effective in low back pain by paravertebral-intramuscular administration by maintaining cytokines and prostaglandins and increasing superoxide dismutase levels [25, 27, 28, 31].

3.10. AIDS: OT is effective in viral diseases like HIV by injecting ozone-treated blood showing no clinical toxicity or hematologic effects. It also reports the inactivation of human retroviruses in body fluids. Though rectal OT is not approved for AIDS treatment as it possesses life-threatening illness due to oxidation stress transient and super dismutase expression [29, 30].

3.11. Dermatology: OT is used in dermatology as ozone hydrotherapy or ozonated oil with unclear mechanism of action and effects like reducing exudate, epigenetic modifications, *etc*. O_2-O_3 therapy was found useful in different forms of scleroderma, acne, lesions, pigmentation, which could be a replacement to laser therapy [32].

3.12. Gynecology and Obstetrics: OT acts as an adjunct agent in female infertility, especially caused by fallopian tube obstruction; experimented on rats showed better potential when compared to traditional or interventional methods. It is effective in gynecological infections, protects ovarian tissue and endometrium, decreases pelvic adhesions and vaginitis by stimulating blood immunoglobulins, decreasing reactive oxygen species, increasing glutathione peroxidase, and super dismutase activity. The OT may show a positive effect on pelvic inflammatory diseases, tubal occlusion, oocyte loss, *etc*., though clinical trials need constant follow-up to procure the desired results and uncover the unknown effects. On rectal insufflation, OT administration to female Wistar rats showed no teratogenic or embryotoxic effects though controlled clinical trials are recommended, especially towards obstetrics and method of administration [35, 36, 37]. Ozone therapy is proved to be one of the quickest relieving, cost-effective treatments for heart disease like cardiovascular complexities, and fatigue. It has a high success rate in treating heart diseases compared to an invasive procedure such as heart by-pass surgery or angioplasty. This naturopathic course of therapy works by boosting oxygen circulation and the utilization of oxygen by cells in energy production. Oxygen plays a crucial role in energy generation by various human cells. Appropriate energy generation will lead to less or least pain or fatigue. Blood - ozone mixture leads to the maintenance of oxygen use and supply chain.

3.13. Others: The OT show improved oxygen delivery and blood circulation in ischemic tissues by an increase in antioxidative enzymes, increasing erythroblast leading to oxidative preconditioning. It affects vascular and hematological modulation by reduced nicotinamide adenine dinucleotide and cytochrome c oxidation. As OT activates nuclear transcription factor, it is effective in vascular disease and hypoxia. OT was found useful in treating fibromyalgia management by auto-hemotransfusion and rectal insufflations. OT is known to reduce blood pressure with progression prevention. It acts by regulating serum endothelin receptor level reduction in vascular tissue and heart as anti-vasoconstrictor effects being affective in hypertension condition. It strengthens the immune system, cleanses the liver, improves circulation problems, rheumatic illness, allergies, joint stiffness, *etc*. Autohemo OT was found effective in patients with neurological disorders like multiple sclerosis by changing brain metabolism, and circulation OT act as mono or adjuvant therapy in the treatment of SARS by inactivating fungi, bacteria, and viruses by oxidizing cytochrome C and producing prostacyclin. It reduces maximal transpulmonary pressure in the lungs, hence increasing the rate of respiration and reduction in tidal volume [1, 21, 3, 4, 5, 6, 33].

4. Toxicity: Though O_3 possesses various benefits, its toxicity and clinical efficacy depend on the route and concentration of dose administration as lung inhalation is a major concern. O_3 therapy escalates airway resistance without altering lung characteristics, and due to its low antioxidant competencies, direct contact with eyes and lungs is avoided. The production of oxidative stress by OT results in inflammation and tissue injury. Many experiments also show evidence for the respiratory system and pulmonary organ damage by exposure or inhalation of OT. Some contradictions may involve bleeding organs, thrombocytopenia, or apoplectic shock. It may possess some teratogenic or embryotoxic effects; hence clinical trials are required before OT implementation in various diseases or disorders. Intravenous administration of OT showed neurotoxicity involving nausea, headache, confusion, and blurred vision [3, 4, 34].

5. Different Methods of Applying Ozone Therapy:

- **Autohemotherapy:** Major clinical application that involves withdrawing 60-200 ml of blood along with the addition of ozone and finally reinfusing it.
- **Limb Bagging:** An application-based technique in which a plastic bag is placed over the affected limb area and thereby infusing ozone into the bag to cover the ulcer or rash.
- **Prolozone:** An injectable ozone technique that provides therapy for joint as well as muscular pains, repairs the damaged cartilage, tearing of tendons and ligaments.
- **Insufflation:** The technique directly delivers ozone to the rectum, vagina, or urinary bladder.

- **Hocatt:** It is termed as the ability to expose the entire body to the healing effects of ozone. Ozone is drawn toward negatively charged foreign cells such as bacteria, yeast, viruses, and parasites, which neutralizes them further enhances the killing of these active infections.

CONCLUSION: The OT raises many questions for several treatment options requiring preclinical and clinical studies. A protocol needs to be developed for dose variations and response relationships, providing compelling evidence. It releases growth factors and activates immune and neuroprotective systems proving wellness in some conditions. Some reports show the effects of OT as safe and consistent, but O_3 possesses hazardous effects, especially affecting an individual lung during smog leading to death from respiratory ailment. Some reported side effects include poor circulation, heart problems, blood vessel swelling, inactivation of enzymes, pulmonary embolism, etc. OT is still under research where new facts throw light as OT usage for a safe alternative to conventional medications. OT still lies under orthodox medicine will poor regulation due to non-patentable therapy or gas. It may break paths as an innovative therapy by controlled trials with demonstrated validity and toxicity for the suitable disease condition.

ACKNOWLEDGEMENT: We wish to acknowledge Ved Hemen Sanjay (Department of Pharmacology) for his help and support in the compilation of the article.

CONFLICTS OF INTEREST: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

REFERENCES:

1. Elvis AM and Ekta JS: Ozone therapy a clinical review. Journal of Nature Science, Biology and Medicine 2011; 2(1): 66-70.
2. Clavo E: Ozone therapy as adjuvant for cancer treatment: Is further research warranted? Evidence-Based Complementary and Alternative Medicine 2018; 1-11.
3. Smith NL and Wilson AL: Ozone therapy: an overview of pharmacodynamics, current research, and clinical utility. Med Gas Res 2017; 7(3): 212-19.
4. Sagai M and Bocci V: Mechanisms of action involved in ozone therapy: Is healing induced *via* a mild oxidative stress? Medical Gas Research 2011; 1: 29.
5. Di Mauro R: The biochemical and pharmacological properties of ozone: The smell of protection in acute and chronic disease. Int J Mol Sci 2019; 20: 634.
6. Tirelli U: Ozone therapy in 65 patients with fibromyalgia: an effective therapy. Eur Rev Med Pharmacol Sci 2019; 23: 1786-88.
7. Bocci V: The usefulness of ozone treatment in spinal pain. 2015; 9: 2677-85.
8. Saleh S: Additive effect of ozone therapy to insulin in the treatment of diabetic rats. Menoufia Medical Journal 2014; 27(1): 85-92.
9. Bocci V: It is time to integrate conventional therapy by ozone therapy in type-2 diabetes patients. Ann Transl Med 2014; 2(12): 117.
10. Teuvov AA, Baziev AM, Lovpache ZN, Teunikova IS, Chudopal SM: Ozone therapy in the comprehensive treatment of diabetic foot syndrome. Biomed Pharmacol J 2017; 10(4): 1871-78.
11. Liu J: Ozone therapy for treating foot ulcers in people with diabetes. Cochrane Library 2015.
12. Kushmakov R: Ozone therapy for diabetic foot. Medical Gas Research 2018; 8(3): 111-15.
13. Izadi M: Therapeutic effects of ozone in patients with diabetic foot ulcers: review of the literature. Biomedical Research 2017; 28(18): 7846-50.
14. Xiao W: Ozone oil promotes wound healing by increasing the migration of fibroblasts *via* P13K/Akt/mTOR signaling pathway. Biosci Rep 2017; 37(6): 1-11.
15. Agosti ID: Effectiveness of a short-term treatment of oxygen-ozone therapy into healing in a posttraumatic wound. Case Rep Med 2016.
16. Gupta S and Deepa D: Applications of ozone therapy in dentistry. J Osral Res and Rev 2016; 8(2): 86-91.
17. Saini R: Ozone therapy in dentistry: A strategic review. J. Nat Sci Biol Med 2011; 2(2): 151-53.
18. Tiwari S: Dental applications of ozone therapy: A review of literature. The Saudi Journal for Dental Research 2017; 8(1-2): 105-11.
19. Clavo B: Ozone therapy for tumor oxygenation: a pilot study. Evid Based Complement Alternat Med 2004; 1(1): 93-98.
20. Tirelli U: Oxygen-ozone therapy as support and palliative therapy in 50 cancer patients with fatigue – A short report. Eur Rev Med Pharmacol Sci 2018; 22(22): 8030-33.
21. Akcilar R: The effect of ozone on blood pressure in DOCA-salt-induced hypertensive rats. Int J Clin Exp Med 2015; 8(8): 12783-91.
22. Velio B, Iacopo Z and Valter T: Potentiality of oxygen-ozonetherapy to improve the health of aging people. Current aging Science 2010; 3(3): 177-87.
23. Seyam O, Smith NL, Reid I, Gandhi J, Jiang W and Sardar Ali Khan. Clinical utility of ozone therapy for musculoskeletal disorders. Med Gas Res 2018; 8(3); 103-10.
24. Manoto SL, Maepa MJ and Motaung SK: Medical ozone therapy as a potential treatment modality for regeneration of damaged articular cartilage in osteoarthritis. Saudi Journal of Biological Sciences 2018; 25(4): 672-79.
25. Dardes N, Covi V and Tabaracci G: Ozone therapy as a complementary treatment in cardiovascular diseases. Integrative Cardiology 2017; 165-72.
26. Bocci V, Travagli V and Zanardi I: May oxygen-ozone therapy improves cardiovascular disorders? Cardiovasc. Hematol. Disorder Drug Targets 2019; 9(2): 78-85.
27. Rowen RJ and Robins H: Ozone therapy for complex regional pain syndrome: Review and case report. Current Pain and Headache Reports 2019; 23: 41.

28. Alyan S, Zaghlol R and Mustafa SA: Efficacy of combined paravertebral ozone (O_2-O_3) therapy with physiotherapy in patients with chronic mechanical low back pain. Egyptian Rheumatology & Rehabilitation 2018; 45(3): 106-11.
29. Garber GE, Cameron DW, Hawley-Foss N, Greenway D and Shannon ME: The use of ozone-treated blood in the therapy of HIV infection and immune disease: a pilot study of safety and efficacy. AIDS 1991; 5(8): 981-84.
30. Bocci V, Venturi G, Catucci M, Valensin PE and Zazzi M: Lack of efficacy of ozone therapy in HIV infection. Clinical Microbiology and Infection 2008; 4(11).
31. Braidy N: Therapeutic relevance of ozone therapy in degenerative diseases: Focus on diabetes and spinal pain. J Cell Physiol 2018; 233(4): 2705-14.
32. Zeng J and Lu J: Mechanisms of action involved in ozone-therapy in skin diseases. Int. Immuno Pharmacol 2018; 56: 235-41.
33. Molinari F: Ozone autohemotherapy induces long-term cerebral metabolic changes in multiple sclerosis patients. Int J Immunopathol. Pharmacol 2014; 27(3): 379-89.
34. Tong O and Robbins M: Headache, visual loss, and encephalopathy associated with intravenous ozone administration. Neurology 2019; 59(9): 1643-44.
35. He C and Ma X: Distal fallopian tube recanalization using ozone treatment: a clinical study in two hundred tubal obstruction Chinese patients. Int J Clin Exp Med 2015; 8(2): 2958-61.
36. Menendez-Cepero S: Teratogenic study of ozone. Possible indications in obstetrics and gynecology. J Ozone Ther 2018; 2(2).
37. Merhi Z: Ozone therapy: a potential therapeutic adjunct for improving female reproductive health. Medical Gas Research 2019; 9(2): 101-05.

How to cite this article:
Pimple P and Doshi G: Ozone therapy: a paradox or panacea in various ailments. Int J Pharm Sci & Res 2021; 12(2): 754-59. doi: 10.13040/IJPSR.0975-8232.12(2).754-59.