Indo Global Journal of Pharmaceutical Sciences, 2013; 3(2): 165-171

INDO GLOBAL JOURNAL OF PHARMACEUTICAL SCIENCES
ISSN 2249- 1023

Ozone Therapy: A Milestone in the Treatment of Ailments

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ABSTRACT: Ozone therapy or Ozonated Autohemotherapy (O_3-AHT) has been meticulously used for more than a century to improve cellular function and for quicker healing of diseased tissues. It involves administration of ozone as gas or in liquid form to kill the microorganisms. Furthermore, body provides more energy using oxygen and can eliminate wastes efficiently. Ozone is used by different health organizations for its disinfectant, antiseptic, quick healing properties, circulatory disorders, geriatric conditions, cancer, skin healing, AIDS, rheumatism/arthritis and in water treatment plants etc. It was found to be consistent safe, with minimal and preventable side effects. It should be introduced into the body in large quantities so that the singlet oxygen molecule which is unattached and freely circulating will attack all immature, sick and deformed foreign cells. Availability of ozone in gaseous state further limits its use; hence some special techniques should be designed through strong R&D input which can make this technique widely accepted. Initially ozone was believed to have treacherous effects, yet researchers alleged that it may have therapeutic benefits which directed researchers to study and synchronize its use with the current medical practices.

KEYWORDS: AIDS; Cancer; Ozone Therapy; SARS.

INTRODUCTION

Ozone (O_3) an allotropic form of oxygen gas which is generally found in the uppermost layer of atmosphere i.e. stratosphere, acts as a protective layer to our environment.[1] Oxygen is the most fundamental element required for sustainment of human life and it is the key to good health. The best way to enhance health is to oxygenate every cell in our body. Ozone is an allotrope of oxygen with an extra molecule that is unattached and freely circulating, which will attack all immature, sick and deformed cells foreign to our body, like viruses, bacteria, fungi etc. It also increases the stability of normal good healthy cells. Earlier it was considered as a harmful gas just like NO and CO, but now we all know that both nitrogen oxide (NO)and carbon monoxide (CO) are now regarded as essential gases due to their important physiological actions within the body.[2-4] Similarly, one of the toxic gas hydrogen sulfide is used as a drug in osteoporosis treatment. Dose of the drug is one of the important criterions for evaluation of toxicity. [5] Researchers highlighted the scope of ozone therapy like in health care departments to disinfect operating rooms, sterilize surgical instruments, drinking water containing bacteria and viruses and to disinfect wounds during the First World War Furthermore; ozone therapy found its application in the treatment of tuberculosis and chronic middle ear deafness. Ozone is measured in µmol/mol (ppm), nmol/mol (ppb), and mg/hr or in weight percent.[6]

Synthesis of ozone

Literature revealed, Nikola Tesla in 1896 patented the first ozone generator for commercial production of ozone in the US, which is now known as 'Tesla Ozone Company'. Similarly, Dr. Joachim Hansler patented ozone machine called 'Ozonosan' which led to the expansion of German ozone therapy. [1, 7] Ozone is produced in nature by lightening in atmosphere. It is abundant only in the stratosphere (20,000-30,000 m above the earth's surface) where its concentration is about 16-20 mg/ml. In this layer, it is produced by the action of ultraviolet solar radiation which in turn, protects the earth from ultraviolet solar radiation. However, number of synthetic methods also exists for the synthesis of ozone like: Electric methods (corona discharge method, cold plasma method), ultra violet light (vacuum-ultraviolet (VUV) ozone generators and chemical methods.

Corona discharge method

This is the most common type of ozone generator for both industrial and laboratory use. These types of generators operate by means of a corona discharge tube (Fig 1) with strong electric discharge. [8] This is cost-effective method in comparison to other ozone generators and do not require an oxygen source other than the ambient air to produce ozone concentrations of 3–6%. It has certain limitations that fluctuations in ambient air may arise due to bad weather or other environmental conditions and cause variability in ozone production. Another, drawback of this type of ozone generators is that they also produce nitrogen oxides as a by product and to eliminate this by product formation, air dryers are generally used. Use of an oxygen concentrator can further increase the ozone production and further reduce the risk of nitric acid formation by removing not only the water vapour, but also the bulk of the nitrogen.

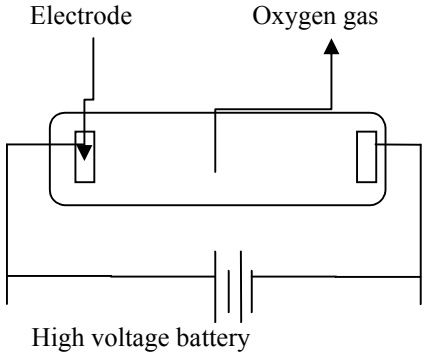

Fig 1: Corona discharge tube for ozone preparation

Ultraviolet method

UV ozone generators, or vacuum-ultraviolet (VUV) ozone generators, utilise a light source which generates a narrow-band ultraviolet light, a subset of that produced by the Sun. The Sun's UV sustains the ozone layer in the stratosphere of Earth.[9] Generally standard UV ozone generators are less expensive but they usually produce ozone with a concentration of about 0.5% or lower. Disadvantage of this method is that it requires the air (oxygen) to be exposed to the UV source for a longer amount of time, and any gas that is not exposed to the UV source will not be treated, Hence, such kind of ozone generators are impractical for use in situations that deal with rapidly moving air or water streams. VUV ozone generators, unlike corona discharge generators, do not produce harmful nitrogen by-products which are advantageous and also work extremely well in humid air environment.

$$O_2 \xrightarrow{\text{U.V light, electricity}} 2O^*$$

$$O_2 + O^* \longrightarrow O_3$$

Fig: 2: Mechanism of production of ozone by UV light.

Cold plasma method

In the cold plasma method, pure oxygen gas is exposed to plasma created by dielectric barrier discharge. The diatomic oxygen splits into single atoms, which then recombine in triplets to form ozone. [10] This method utilizes pure oxygen

gas as the input source and produces a maximum concentration of about 5% ozone. A discharge between two electrodes is manifested which produces a filamentary transfer of electrons and results in ozone generation. Some cold plasma units also have the capability of producing short-lived allotropes of oxygen which include O_4, O_5, O_6, O_7, etc. These species are even more reactive than ordinary O_3 and are used in production of such super oxides. Cold plasma ozone generators are generally very expensive and are less frequently available. Similarly, Electrolytic ozone generation (EOG) splits water molecules into H_2, O_2, and O_3 where hydrogen gas will be removed to leave oxygen and ozone as reaction products.[11] This method of generation can achieve concentrations of 20–30% and is independent of air quality because water is used as the starting substrate.

Laboratory method

In laboratory, ozone can be produced by electrolysis method. [12] The half cell reactions taking place is shown here:

$$3\ H_2O \rightarrow O_3 + 6\ H^+ + 6\ e^- \ (\Delta\ Eo = -1.53\ V)$$

$$6\ H^+ + 6\ e^- \rightarrow 3\ H_2 \ (\Delta\ Eo = 0\ V)$$

$$2\ H_2O \rightarrow O_2 + 4\ H^+ + 4\ e^- \ (\Delta\ Eo = -1.23\ V)$$

In the net reaction, three equivalents of water are converted into one equivalent of ozone and three equivalents of hydrogen.

Methods of administration

In major auto-hemotherapy, anti-coagulated blood is mixed with ozone in the form of liquid or ozone is passed through the anti-coagulated blood as gas and is infused into the blood vessel, which requires larger amount of blood usually 200-250 ml. In minor auto-hemotherapy blood is mixed with ozone and is injected intramuscularly. This type of administration requires only 5-10 ml of blood. Another, direct IV infusion method requires ozone solution in a suitable carrier fluid and which is administered slowly into a major vessel. Furthermore, Ozonated water (ozone is more freely soluble than normal oxygen molecule), ozone in saline has been used topically or given by parental routes. Humidified ozone is administered by the use of catheter tube as rectal/vaginal insufflations. Urinary bladder insufflations are used for chronic inflammatory conditions. Ozone that has been bubbled through olive oil produces oxide radicals (ozonides) which will not irritate respiratory epithelium and thus is applied topically even onto eyes. Intra-articular administration helps in joint healing and prolotherapy. Prolo / Sclerotherapy is another very good alternative for ozone administration as it is less painful than other agents. Even disc shaped protrusions can be injected at interspinous space and around facets in prolotherapy which stabilize joints and accelerate healing. [13]

Mechanism of action

Though many pharmacological investigational studies has been carried out to establish the mechanism by which ozone shows its pharmacological action, but still none of them has explained fully the pharmacological effects of ozone. Some diverse but interlinked steps of mechanisms have been proposed by different scientists as described:

Inactivation of bacteria, fungi, virus, yeast and protozoa

a) In bacteria: damage to cell envelope through oxidation of phospholipids and lipoproteins.
b) In fungi: ozone inhibits cell growth at certain stages.
c) In viruses: ozone damages the viral capsi and renders the reproductive cycle by peroxidation of inner cell contents [14].

Stimulation of oxygen metabolism

Ozone therapy causes an increase in R.B.C. glycolysis rate which leads to stimulation of 2, 3 diphosphoglycerate as a result of which an increase in amount of oxygen reaching the tissues is observed. Ozone stimulates the Krebs's cycle by enhancing the oxidative carboxylation of pyruvate and stimulating the production of ATP. It also causes a significant reduction in NADH and oxidizes cytochrome C. There is a stimulation of production of enzymes which act as

a free radical scavengers and cell wall protectors: glutathione peroxidase, catalase and superoxide dismutase [14].

S. No.	Dosage form	Route of administration	Dosage	Applications
1.	Ozonated distilled water	Oral	5mg/l (O_3/O_2)	Surgery, gynaecology, esophagitis, gastritis, paradontosis and ulcers
2.	Ozonated vegetable oil	Oral, external administration	100 ml of oil with ozone concentration of 20mg/l (O_3/O_2), for external administration; 24mg/l (O_3/O_2), one teaspoonful, 20-30min before meals 2-4 times a day, gradually increasing the dose to one tablespoonful 2-4 times a day	Disinfectant, antiseptic, mycosis
3.	Ozonated Saline for intravenous infusions	Parentral	400 to 100000 mcg/l of ozone/oxygen mixtures, dose calculated by of 40mcg per kg of body weight	General stimulating metabolic effect
4.	Rectal insufflations	Rectal ,through Janet syringe or poly-chlor-vinil tube	10-60mg/l, the volume ranges from 150ml to 1000ml	Alternative to major autohemotherapy, where intravenous injections are difficult to handle
5.	Vaginal insufflations	vaginal speculum, through special nozzles	2.5mg/l, ozone /oxygen mixtures with the gas rate 5-1l/min for 5-10 minutes	
6.	Ozone aerated plastic bag	Body parts	6-8ml/l of ozone/oxygen mixture	Purulent sluggish wounds, bed sores, painful cicatrices, burns

Activation of immune system

Ozone administered at a very narrow range of concentration of about 30 to 55 µg/cc causes the greatest increase in the production of interferon and greatest output of tumor necrosis factor and interleukin-2. The production of interleukin-2 launches an entire cascade of subsequent immunological responses following this mechanism. Recognition of any foreign particles by T-cell antigen receptor (TCR) leads to cascading effect of reactions and which further leads to production of second messengers, inositol triphosphate (IP_3) and diacylglycerol (DG). IP_3, then releases Ca^{+2} from the ER into the cytosol, thereby increases cytosolic Ca^{+2} levels. In presence of calcium, calmodulin then dephosphorylates nuclear factor activated T-cells (NFAT) and results in transcription of cytokines such as IL-2,TNF-α,IL-6 etc. [15]These products help in proper functioning of our immune system. Maziere et al. [16] concluded through his studies that as nuclear factors are activated by oxidative stress, in the same way ozone therapy may activate NFAT leading to activated immune system. Ozone therapy has shown many positive results in the treatments of various diseases. But the main problem lies with the appropriate concentration of the ozone for curbing the activity of cytotoxic T-cells and increasing the amount and activity of the CD^{4+} T-regulatory cells.

APPLICATIONS OF OZONE THERAPY

Topical applications

O_3 has been widely acclaimed as one of the best bactericidal, antiviral and antifungal agents and has also been used as a clinical therapeutic agent for chronic wounds, such as ulcers, ischemic ulcers and diabetic wounds. The beneficial effects of

O_3 on wound healing may be accounted because of its ability to decrease the frequency of bacterial infection, ameliorated impaired dermal wound healing or increased oxygen tension by O_3 exposure in the wound area. [17-19] Role of O_3 has been reported to activate of transcription factor NF-κB which is important to regulate inflammatory responses and eventually the entire process of wound healing. [20, 21]

Dental application

Periodontitis, a destructive inflammatory disease of the supporting tissues of the teeth occurs due to accumulation of specific microorganism or a group of microorganisms in oral cavity, resulting in progressive destruction of periodontal ligament and alveolar bone with periodontal pocket formation, gingival recession, or both. [22] It has been estimated that more than 500 different bacterial species are capable of colonizing the adult mouth and the lesions of the oral cavity have an immense impact on the quality of life of patient with complex advance diseases. There are three fundamental forms of ozone derived preparations have been used for their treatment like: ozonated water, ozonated olive oil, and oxygen/ozone gas. The former two preparations have the capacity to entrap and release oxygen/ozone and hence are found to be the most suitable for treatment purposes. But excess consumption leads to few other undesirable side effects, so there is a need to develop an ideal delivery system for sustained release of ozone. [23]

Treatment of cancer

When cancer cells get exposed to ozone gas therapy, they die very rapidly. Ozone find its application in fighting against cancer by variety of mechanisms, such as destruction of cancer producing pathogens, oxidative destruction of xenoestrogens and other carcinogens, increasing levels of cancer fighting cytokines, increasing levels of superoxide dismutase (SOD), increasing WBC activity, decreasing lactic acid levels by preventing its conversion into glucose through gluconeogenesis and direct destruction of cancer cells through an overload of peroxide within the cancerous cells. [24]

Treatment of AIDS

It has been reported that ozone may overcome the AIDS virus by a fundamentally different processes than usually attempted by other drugs. It simply oxidizes the molecules of HIV virus and thus decreases the burden on liver and immune system [25].

Treatment of SARS

Ozone is a naturally occurring energy-rich molecule with unique physicochemical and biological properties indicating a promising role in the therapy of SARS (severe acute respiratory syndrome), either as a monotherapy or, as an adjunct to standard treatment schedules. Owing to the excess energy contained within the O_3 molecule, it shows effectiveness across the entire genotype and subtype spectrum of SARS in comparison to the available organism-specific antiviral drugs. [14]

In neurodegenerative diseases

Oxidative stress is one of the reasons for the progression of the neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) which are related to the action of reactive oxygen species (ROS) in the body. Sagai and Bocci [26] found that the Nrf2/ARE {Nuclear factor (erythroid-derived 2) antioxidant response element (ARE)} pathway provide protection against neuro degeneration. The ROS leads to mitochondrial dysfunction and neuro-inflammation while Nrf2 counter acts this action by activating the antioxidant response element (ARE) pathway [27].

Other potential Applications

It kills viruses, improves the delivery of oxygen from the blood stream to the tissues of the body, speeds up the breakdown of petrochemicals etc. It also increases the production of interferon and tumour necrosis factor, thereby helping the body to fight infections and cancers. Furthermore, it increases the efficiency of antioxidant enzymes and

increases the flexibility and efficiency of the membranes of red blood cells.

Demerits of ozone therapy

A series of ill-effects have been observed with ozone therapy due to its reactivity which give rise to per-oxidation of lipids and other biological molecules resulting in alteration of membrane permeability and generation of lipid ozonation products (LOP) which activates the lipases triggering the release of endogenous mediators of inflammation. Furthermore, combinations of O_3 and NO_2 which occurs in photochemical smog have hazardous effects on lung alveoli and act additively or synergistically. Adverse reactions of ozone that were revealed from the human studies are erythrocyte damage, hemolysis reduced glutathione concentration, reduced leukocyte viability, cytokine production and pancytopenia. Dietary antioxidants or free radical scavenger like Vitamin E, C, etc. can prevent above mentioned effects of ozone. [28-31]

Paradox in ozone utilization

There has always been a paradox over the toxic effects of ozone. Lung toxicity was observed due to the reaction of ozone with polyunsaturated fatty acids (PUFA) resulting in production of ozone-specific products like lipid ozonation products (LOPs). LOPs acts as signal transduction molecule by activating lipases, such as phospholipase A_2 or phospholipase C, thereby releasing arachidonic acid (AA) which gets converted into chemical mediators like PGs, COXs, LOXs etc. leading to inflammatory response. Furthermore, number of experiments and clinical studies indicated the damages caused to respiratory system and pulmonary organs after prolonged inhalation to tropospheric ozone. Number of parameters to be considered for investigating effects of ozone in the human body like topography, anatomical characteristics, biochemical characteristics of organs etc. [32-36].

CONCLUSION

Despite the existence of a paradox situation in the use of ozone in medical treatment, the medical data from different findings revealed its applications in different physiological and pathological conditions like diabetes, AIDS, cancer, SARS etc. It also improves blood circulation, oxygenates haemoglobin, possesses anti-microbial activity, corrects dizziness, neutralizes acid and overcomes weakness, acts as cell energizer, vitality booster, immune enhancer, skin purifier, liver cleanser and blood purifier. Ozone therapy has been successfully used but further research in this area is still needed so that it can become a vital medical friendly utility in the near future.

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