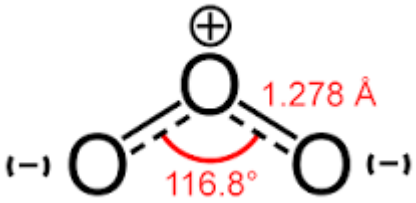
# Clinical Review of Medical Ozone

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## **Introduction**:

Ozone, $O_3$ was discovered in 1839 by German chemist Christian Schönbein[1]. It began to be used in medical applications during World War I to treat gangrene & similar conditions[2]. Although it lacks typical features of a chemical radical, it's the third strongest oxidizing substance known following fluorine & persulphate[3].

Creation of ozone from oxygen requires a significant amount of energy:

$3\ O_2 + 68.4\ Kcal \rightarrow 2\ O_3$[4] that can be applied metabolically.

There are significant differences between ozone and hyperbaric oxygen. These agents are not interchangeable.

Comparison of Indications & Efficacy of Ozone vs. Hyperbaric Oxygen[5]

| | HBO Therapy | Ozone Therapy |
|---|---|---|
| Arterial gas embolism | +++ | --- |
| Decompression sickness | +++ | --- |
| Severe CO poisoning | +++ | --- |
| Severe blood loss-anemia | +++ | --- |
| Clostridial myonecrosis (gas gangrene) | +++ | ++ |
| Compromised skin grafts and flaps | + | +++ |
| Prevention of osteo-radionecrosis | + | +++ |
| Radiation damage | + | +++ |
| Refractory osteomyelitis | + | +++ |
| Necrotizing fasciitis | + | +++ |
| Traumatic ischemic injury | + | +++ |
| Thermal burns | + | +++ |
| Chronic ulcers and failure of wound healing | + | +++ |
| Multiple sclerosis | --- | +? |
| Chronic fatigue syndrome | + | ++ |
| HIV-AIDS | -? | + |
| Senility | + | ++ |

(+ little, ++ modest, +++ good activity, --- no activity)

Ozone has a molecular weight of 48 Daltons with a solubility in water that is ten-fold higher than oxygen at 0 ℃ and in its gaseous form spontaneously decomposes with a half -life of 40 minutes at 20 ℃[6]. $H_2O_2$, one of the decomposition products of ozone has a half-life of 2 minutes in the circulatory system [7] [8] It's so soluble that it can be directly injected intravenously with oxygen at a slow rate without causing embolism as would happen with air due to airs large nitrogen content. It should be noted that while ozone is very damaging to respiratory tissues & airways, it has much more beneficial effects in the aqueous environment of the bloodstream.

**Ozone Generation:**

Commercially available medical ozone generators need to be attached to a pure oxygen source. Ozone can be produced by Ultra-Violet (UV) radiation, electrical discharge/corona spark, using glass, stainless steel, titanium or ceramic containment vessels[9].

UV ozone generators produce ozone via ultraviolet bulbs and ambient air. These are typically inexpensive and least efficient. Can generate ozone in higher humidity levels. Aren't typically used or recommended for ozone therapy.

Corona discharge generators produce ozone via a high voltage of electricity and pure oxygen. Are mid-range in price and produce medical/therapeutic grade ozone. Have difficulty producing ozone in humidity over 60%. Generate excess heat. Are most common type of generator used for ozone therapy.

Cold plasma ozone generators produce ozone via two adjacent electrostatic neon tubes and pure oxygen. Do not produce heat. Are the bulkiest and most expensive type of ozone generator. Are generally suitable for ozone therapy.

Electrolytic ozone generators produce ozone via an electric current and water. Only ozonate water, used for water treatment. Are the least expensive. Not suitable for ozone therapy.

Ozone Concentration in µg/ml is expressed as a Gamma (ϒ) value with the residual gas being oxygen; it's essentially a ratio of $O_3$:$O_2$:

| **Ozone Concentration Gamma (ϒ) µg/ml** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Oxygen** | **Ozone Generator Dial Setting** | | | | | | | |
| **(L/min)** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 1 | 2 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 3/4 | 3 | 5 | 7 | 9 | 11 | 13 | 15 | 17 |
| 1/2 | 4 | 7 | 9 | 11 | 14 | 16 | 17 | 19 |
| 1/4 | 9 | 14 | 18 | 22 | 25 | 29 | 31 | 33 |
| 1/8 | 18 | 29 | 33 | 41 | 44 | 46 | 50 | 52 |
| 1/16 | 30 | 37 | 42 | 48 | 54 | 56 | 58 | 63 |
| 1/32 | 36 | 42 | 44 | 51 | 57 | 62 | 66 | 70 |

**Delivery Methods**;

Table; Routes of $O_3$ administration[10]

| Parenteral | Topical or locoregional |
|---|---|
| Intra-arterial (IA)[a] | |
| Intramuscular (IM) | Nasal[b] |
| Subcutaneous (SC) | Tubal[b] |
| Intraperitoneal (Ipe) | Auricular |
| Intrapleural (IPL) | Oral[b] |
| Intra-articular (IPL) | Vaginal |
| (a) Periarticular | Urethral and intrabladder |
| (b) Myofascial | Rectal |
| Intradiscal (ID) | Cutaneous |
| Intraforaminal (IF) | Dental |
| Intralesional (Iles)[c] | |

[a]No longer used for limb ischemia. Hepatic metastasis could be embolized via the hepatic artery.
[b]To be performed during 30–40 sec apnea.
[c]Intratumoral or via a fistula.

Autohemotransfusion procedure involves the extraction of 200 ml venous blood into heparin (25 IU/ml) and $CaCl_2$ (5mM). In a sterile single-use 300 ml container, the blood was mixed with 200 ml of the $O_3/O_2$ gas mixture at a concentration of 60 μg/ml and then slowly reintroduced into the patient. The blood was extra-corporeal for 15–30 min and there were no adverse reactions except hematoma formation in the area of venous injection[11]

Rectal insufflation was employed when the performance status was low, or at the preference of patient. This procedure consisted in rectal insufflation of 300 ml of $O_3/O_2$ gas mixture at a concentration of 60 μg/ml. The main side effects were transient meteorism and constipation in some patients. Due to its high solubility, the ozone rapidly transits across the colonic mucosa into the portal circulation and through the liver to enter systemic circulation.

Ozone can also be insufflated into the vaginal cavity, nasosinus cavities and external ear canals by allowing the ozone generator to fill a low-pressure reservoir that is then attached to a canula which is inserted into the appropriate body cavity of choice for insufflation. Ozone has been safely instilled into the bladder, pleural & peritoneal cavities as well[12].

Ozone can be safely injected into tissues as well[13]. These include areas such as the temporomandibular joint[14].

Ozone can be used to treat intra-thecal tears of the lumbar spinal discs as well as lumbar disc herniations, some of this effect involves modulation of inflammatory cytokines in the area[15]. Cervical disc herniations are also amenable to treatment with ozone[16].

Carpal tunnel syndrome can be improved with injection of 4 cc of ozone and 1 cc of lidocaine directly into the space[17].

Supraspinatus tendon tears < 1.5 cm in length have been shown to heal with ultrasound-guided injection of ozone into the peri-tendon sheath[18].

Rheumatoid arthritis treatment with ozone in rats seems optimal at a concentration of 40 μg/mL when injected intra-articularly into the involved joints[19].

Scleroderma is another systemic connective tissue autoimmune inflammatory disease that shows thermographic improvements after ozone therapy[20].

Fibromyalgia patients also receive relief from ozone therapy via a variety of mechanisms including antioxidant[21], immune modulation[22] and mitochondrial effects[23] [24].

Topically, ozone can be placed directly into an impermeable container such as a bag in which an extremity is encased for topical treatment of wounds and skin. Additionally, it can be bubbled into water (sterilizing it in the process) which can then be topically instilled or applied, or for longer-lasting benefits, into a lipid solution such as olive or other oil and applied directly to the skin or wound.

The benefits listed above are effective in all routes of administration reviewed above. Caution should be used however regarding application to lower respiratory tract as noted in the sections above.

**Ozone Steam-Sauna**;

Ozone breaks down in temperatures higher than mid-90s Fahrenheit[25], and ozone production is reduced when the humidity is more than 60%[26]. In order for a steam sauna (or any sauna) to be effective, it needs to be well over 100° Fahrenheit.

**Mechanisms of Action**;

**Airways & NF-κB;**

Ozone has different effects in the airways than it has in the aqueous circulatory system.

Ozone, in contact with biological water, does not follow Henry's law[27] and, although it is ten-fold more soluble than oxygen, it is not transferred into the alveolar capillaries because it reacts immediately with the biomolecules present in the Alveolar Lining Layer (ALL). It must be emphasized that the average thickness of ALL is only 0.2 micron[28]. As it was hypothesized[29], ozone does not penetrate the cells but oxidizes available antioxidants and reacts instantaneously with surfactant's polyunsaturated fatty acids (PUFA) present at the interface to form Reactive Oxygen Species (ROS), such as hydrogen peroxide and a mixture of heterogenous lipid oxidation products (LOP's) which are toxic to the airways.

In the airways, reactive oxygen species (ROS) such as ozone activate mitogen activated protein kinases (MAPKs). As a result (nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) is released from the complex.

NF-κB is a protein complex that controls [30]transcription of DNA, cytokine production and cell survival. NF-κB is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, heavy metals, ultraviolet irradiation, oxidized LDL, and bacterial or viral antigens [31].

NF-κB plays a key role in regulating the immune response to infection. Incorrect regulation of NF-κB has been linked to cancer, inflammatory and autoimmune diseases, septic shock, viral infection, and improper immune development. NF-κB has also been implicated in processes of synaptic plasticity and memory[32].

This free NFκB enters into nuclei to activate the COX2 gene. COX2 then produces PGE2, which stimulates numerous cytokines, among which TNFα and IL-6. The eicosanoide and cytokines then induce the airway inflammation during the early stage of exposure. These reactions also occur in airway epithelial cells, endothelial cells, and macrophages. This signaling cascade is also supported by the findings of Williams et al[33 34].

**Circulation;**

Ozone improves oxygen delivery by shifting the oxy-hemoglobin curve to the right in acidic conditions, resulting in more unloading of oxygen from the hemoglobin in hypoxemic, ischemic regions where the oxygen is most needed[35].

As an antioxidant it initiates the release of numerous cytokines and other chemical messengers and agents. It does this by creating a transient mild state of oxidative stress by dissolving in the aqueous component of plasma[36]. As it reacts in the plasma, it creates $H_2O_2$ and LOPs[37 38] that act in a variety of ways to cause further biologic effects that can be harnessed for medical application & patient benefit. The LOPs benefit a variety of tissues & organs including; liver, bones, muscle, CNS, gut, skin, spleen, lung, heart, & kidney[39].

**Epigenetics & Nrf2;**

Hormesis, the beneficial effect of a low-level exposure to an agent that is harmful at high levels [40 41]. Nuclear factor erythroid 2-related factor (Nrf2) is part of the antioxidant responsive element (ARE) gene complex [42], is sequestered in the cytoplasm and rapidly degraded allowing for tight control and a half-life of only a few minutes[43]. When certain conditions are present, Nrf2 translocates into the nucleus and transactivates ARE genes[44]. Mild ozonation enhances this process[45], providing insight into the mechanism of its action in tissues with the activation of certain genes to regulate inflammation & other cytokine-driven processes. To date, over 200 genes have been identified that rely on Nrf2 control of their expression including genes involved in protein homeostasis, oxidative stress response, detoxification, DNA repair, proliferation, autophagy, mitochondrial genesis & function, inflammation and the metabolism of amino acids, carbohydrates & lipids[46 47].

**Mitochondrial Restoration;**

$O_3$ stimulates the transmembrane flow of $O_2$. The increase in $O_2$ levels inside the cell due to $O_3$ therapy increases mitochondrial efficiency[48 49].

Nrf2 activation is also involved in mitochondrial restoration & repair after stress insults; impairment of Nrf2 is a hallmark of many mitochondrial-related disorders[50 51 52 53].

Nrf2 prevents oxidative stress through the transcription of numerous antioxidant enzyme systems including:

Glutamate cysteine ligase
Glutathione peroxidases (GPX2, GPX4)
Glutathione reductase
Peroxireductases (PRDX1, PRDX6)
Thioreduxin 1
Thioredoxin reductase (TXN1, TXNRD1),
HMOX1
Biliverdin reductase (BVR)

Mild ozonation modulates genes involved in the cell stress response:
HMOX1
Excision repair cross-complementation group 4 (ERCC4)
Cyclin-dependent kinase inhibitor 1A (CDKN1A)
CTD small phosphatase 1 (CTDSP1)

Clearly, the actions of ozone administration are diverse & complex, starting with the nucleus, progressing to the cytosol & cell, to the organ, tissue & entire organism.

**Metabolic Oxidation Considerations;**

Oxygen equilibrates with the extracellular and intraerythrocytic water before becoming bound to hemoglobin until it is fully oxygenated as shown by the rapid increase of the pO2 from about 40 up to 400 mmHg. Ozone, ten-fold more hydrosoluble than oxygen, readily dissolves in the aqueous environment of plasma and is partly (between 20 and 40%) quenched by extracellular hydrophilic antioxidants such as reduced glutathione, ascorbic and uric acids acting as sacrificial compounds, while the bulk reacts with PUFA transported by the albumin. The "therapeutic window" has been carefully determined and ranges between 10 and 80 μg/ml (0.21-1.68 μmol/ml) ozone per ml of blood. It ensures a small and precise oxidative stress able to elicit medical efficacy, but no toxicity[54 55 56].

**<u>Clinical Considerations of Ozone Therapy-Dosing</u>**;

High-dose ozone induces proinflammatory cytokine gene transcription producing inflammatory proteins, while having a negative regulatory effect of Type 1 Interferon which is responsible for defense against viral infectious pathways[57]. Proper balance is essential.

Oxygen equilibrates with the extracellular and intraerythrocytic water before becoming bound to hemoglobin until it is fully oxygenated as shown by the rapid increase of the $pO_2$ from about 40 up to 400 mmHg. Ozone, ten-fold more hydrosoluble than oxygen, readily dissolves in the aqueous environment of plasma and is partly (between 20 and 40%) quenched by hydrophilic antioxidants such as reduced glutathione, ascorbic and uric acids acting as sacrificial compounds, while the bulk reacts with PUFA & other LOPs transported by the albumin. The "therapeutic window" has been carefully determined and ranges between 10 and 80 μg/ml (0.21-1.68 μmol/ml)[58] ozone per ml of blood. It ensures a small and precise oxidative stress able to elicit medical efficacy, without toxicity.

It must be noted that ozone acts as a pro-drug because, during this fast reactions, ozone disappears but generates two crucial messengers: the first is $H_2O_2$ and the second is a mixture of LOPs finally exemplified by 4-HNE (from omega-6 PUFA) and 4-HHE (trans-4 hydroxy-2-hexenal from omega-3 PUFA).

The behavior and pharmacodynamic of $H_2O_2$ have been ascertained: the initial formation of a gradient between plasma and intracellular water[59] allows its entrance into the erythrocytes, lymphocytes and platelets, but its concentration remains around a few micromoles because it is quickly reduced to $H_2O$ by free GSH, catalase and GSH-Px[60]. Its half-life is less than 60 seconds and yet its intracellular concentration is critical, because in order to activate some biochemical pathways (formation of GSSG with consequent activation of the pentose cycle in the red cell and activation of a tyrosine kinase in lymphocytes), it must reach a critical threshold that, nonetheless, is not cytotoxic.

**Clinical Indications for Ozone Therapy**;

**Pathogen inactivation**[61];

Ozone disrupts the integrity of the cytosolic membrane and infiltrates the microorganisms to oxidize glycoproteins, glycolipids, and block enzymatic function. The combination of these reactions causes inhibition of fungi growth and mortality of bacteria and fungi[62 63 64]. Ozone has also been shown benefit as an adjunct to vancomycin to enhance methicillin-resistant *Staphylococcus aureus* mediastinitis in animal models[65].

Babesiosis is susceptible to increased oxygen concentration. There is evidence that supports a role for ROSs in the intraerythrocytic killing of *B. bovis*[66].

Borrelia burgdorferi, the causative agent of Lyme disease is microaerophilic-it grows best in an environment with reduced oxygen availability[67].

Plasmodia species are also microaerophilic and thus may have an increased sensitivity to the oxidizing effect of ozone[68].

Ozone therapy can be used alone with great effect against microaerophilic, facultative anaerobic, and other pathogens. It can also be used to augment antibiotic therapy against infections. Ozone can be given locally or systemically as described above. This is a very versatile and potentially useful agent.

**Diabetes & metabolic dysfunction**;

Diabetes causes metabolic disruptions along 4 major mechanisms[69];

1. Increased formation of intra- & extra- cellular advanced glycation end-products (AGE's) known to activate AGE receptors (RAGES).
2. Increased flux through the polyol pathway enhancing the catabolism of glucose-generating sorbitol leading to an equivalent reduction of NADPH & NO synthesis essential for production of glutathione, an essential endogenous antioxidant.

3. Protein kinase-C activation facilitating accumulation of diacylglycerol, a lipid intermediate in vascular tissues that can severely compromise normal cellular function, inducing lipotoxicity.
4. Increased anabolism of plasminogen activator inhibitor-1 (PAI-1) and transforming growth factor β1 (TGFβ1) through up-regulation of the hexosamine pathway leading to activation of the harmful NF-κB signaling cascade.

Additionally, interaction of AGE's & erythrocyte membranes can induce generation of lipid peroxides & cell adhesion to the endothelium promoting transendothelial migration of activated monocytes capable of increasing oxidative damage to cells & tissues[70] [71].

Ozone reduces hyperglycemia & hyperglycemic markers[72] [73] in rat studies.

Dentistry is another area in which ozone has been used for decades[74].

**Cardiovascular & Vasculopathies**;

Ozone has been shown to help with nitric oxide generation[75], chronic ischemia in type-2 diabetic rats[76] [77] as well as partially prevented diabetic neuropathy in other rats[78]. Age-related vasculopathies and neuropathies can benefit from ozone treatment.

Peripheral arterial occlusive disease, congestive heart failure, stroke, dry age-related macular degeneration all benefit from ozone treatment[79].

**Immune System Activation;**

Ozone causes increases in $H_2O_2$ levels which also have a variety of immune system effects. $H_2O_2$ increases activity of Interferon, Tumor Necrosis Factor, Interleukin (IL)-2[80], NFκB[81] [82], Transforming Growth Factor β-1 (TGF β-1) which then increases cytokine release and upregulate tissue remodeling as well as nitric oxide (NO). $H_2O_2$ & NO can then stimulate increased Interleukin-8 activity allowing production of reactive oxygen species scavengers[83]. Ozone also modulates endotoxin activity in the renal system with *E. coli* [84] which has implications for it's benefit in treating septic shock. Ozone is useful in a variety of chronic infectious diseases including[85] HIV, Hepatitis C, Herpes Simplex and others.

In an experimental mouse model, implanted rheumatoid arthritis synovial fibroblast cells that were then infused in vivo with 3% and 5% $O_3$ application significantly decreased the proinflammatory cytokines IL-1β, IL-6, and TNF-α without any toxicity or severe side effects[86].

Ozone therapy increases mitochondrial oxygen utilization, possibly through re-engagement of the oxidative phosphorylation chain of respiration[87] which is impaired in diseases such as fibromyalgia.

**Central nervous system, pain states, mood, stroke, neurodegenerative conditions**[88] [89];

Ozone can be directly injected into tissues subcutaneously or given via autohemotransfusion to treat neuropathic pain, allodynia and hyperalgesia (increased sensitivity and pain from stimuli that are normally not painful)[90] [91] [92].

The pathogenesis of neurodegenerative diseases is significantly associated with oxidative stress. Increased oxidative stress is also associated with neuronal cell death during the pathogenesis of multiple chronic neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). It was found that the Nrf2/ARE pathway protects against neurodegeneration[93 94 95].

Ozone has also been widely reported to produce a euphoric effect while improving cognitive functions and overall mood status[96] during autohemotransfusion, this effect is also found with stroke patients while reducing neuronal injury and radical formation. Multiple sclerosis patients have been noted to improve after rectal insufflation with an efficacy similar to infusion of methylprednisolone[97]. Parkinson's disease patients also benefit[98 99 100 101 102].

Ozone can even improve sleep[103] performance.

**Lung Disease**;

Despite the adverse effect of ozone on the airways, using ozone autohemotransfusion therapy, the anti-inflammatory effects of ozone have been found to be beneficial for elderly sufferers of COPD[104] as well as for patients with asthma[105].

Age-Related Macular Degeneration also benefits from Ozone therapy autohemotransfusion in the protocol used for vasculopathies[106]. Retinitis pigmentosa has been successfully treated with ozone autotransfusion since 1986 The best results were achieved when ozone treatment is repeated, at least, twice a year, along all these years, with improvement of 70 % in the visual field and 42 % in the visual acuity. The rest of the patients maintained their visual field or visual acuity the same as the initial value, without worsen the disease[107].

**Musculoskeletal**;

Gangrenous wounds, suppurating fractures, inflammations & abscesses[108].

Disc disease, facet disorders[109], carpal tunnel syndrome[110], generalized & localized osteoarthritic[111] & augments methotrexate in rheumatic[112] arthritic disorders also benefit from ozone therapy including injection directly into the involved area of pathology.

**Skin & mucosal diseases**[113];

Ozone can be mixed into water or other aqueous solutions, oils & creams for topical application, it can be used in occlusive bags or other techniques to treat skin lesions directly in the gaseous form and of course, as with so many other delivery systems, autohemotransfusion and rectal insufflation.

Regarding both cutaneous and mucosal infections and lesions, both ozonated water and different gradation of standardized ozonated vegetable oils will be used twice daily until complete healing. Both ozonated water and oils have been already proved to be excellent disinfectants and healing stimulators, more effective than topical antibiotics, growth factors, only oxygenation, maggot and negative pressure wound therapies[114] .

Any wound or lesions must firstly be cleaned possibly with ozonated water or diluted $H_2O_2$ solution, because the removal of purulent material or fibrin or necrotic cells markedly reduces the effect of ozonated oil because of the residual presence of biological substances[115 116].

Ozone preparations are of possible clinical interest since they are stable for 2 years at 4 ◦C and may be used in the treatment of various infections of cutaneous and mucosal areas. Ozonated oil is currently used topically for wounds repair, anaerobic and herpetic infections, trophic ulcers, burns, cellulitis, abscesses, anal fissures, fistulae, gingivitis, and vulvovaginitis[117]. Consistently with these observations, Matsumoto et al. showed that ozonated oil is effective in almost all enrolled patients in treatment for fistulae and chronic surgical wounds without side effects[118]. Similarly, exposure to ozone significantly reduced the severity of radiodermatitis lesions in patients with cancer[119]. Furthermore, Kim et al. [120] suggested that ozonated oil promotes acceleration in acute cutaneous wound repairs by the increased expression of PDGF, TGF-β1, and VEGF

Ozone is useful in a variety of problems including skin loss in non-healing wounds, ulcers, pressure sores, fistulae, etc. [121 122].

Patients suffering from heavy, chronic, antibiotic-resistant septic complications after trauma, surgical procedures, and secondary skin infections, showing that in the wounds of the all experienced patients, the inhibition of septic processes and wound healing was much faster than normal. A secondary result which should be taken into due account is that this method also lowers the cost of antibiotic therapy[123].

**Cancer & neoplastic states**[124];

Nrf2 helps prevent & repair DNA damage. In theory then, it may be helpful in preventing neoplasms. Hyperactivation of Nrf2 however, has been shown to support tumor progression by multiple ways[125 126]. It may help early tumor cells overcome oxidative stress which is normally a barrier to neoplastic transformation & the start of cancer[127]. Nrf2 hyperactivation supports abnormal cell proliferation by allowing them to overcome the barrier that oxidative stress places against neoplastic transformation[128]. Nrf2 hyperactivation also supports abnormal cell proliferation by encouraging anabolism[129], modulating mRNA translation[130] & promoting angiogenesis[131], and providing drug resistance to cancer cells[132]. These are areas of concern, as O3 can also provide relief from adverse reactions to cancer treatment[133 134].

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