

Ozone Therapy

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Ozone, or O₃, is a molecule composed of three oxygen atoms. It is highly water-soluble, extremely unstable, and has a characteristic odor that led to its discovery in the mid-1800s. More than a century later, its chemical structure and oxidative action were elucidated.¹ Although it may be best known as an air pollutant that raises oxidative stress levels and causes toxic tissue damage, especially to the eyes and lungs, ozone is also a potent therapeutic agent with a possible role in treatment of conditions ranging from chronic musculoskeletal pain and non-healing wounds to cardiovascular and autoimmune diseases.^{1,2} As is often the case in medicine, the difference between toxin and therapy lies in the dose and form of administration.

Biochemical Actions of Ozone

Ozone exerts its effects by triggering the formation of free radicals and lipid oxidation products, increasing oxidative stress. While excessive or prolonged oxidative stress leads to cell damage and tissue dysfunction, transient moderate exposures to oxidative stress stimulates an adaptive, or hormetic, response, which may be compared to that incurred through exercise. This response includes increased expression of antioxidant and detoxification enzymes, and upregulation of anti-inflammatory cytokines and heat shock proteins.^{2,3} Ozone-derived hydrogen peroxide also has antimicrobial effects, improves oxygen delivery by red blood cells, and may enhance immune defenses.³⁻⁶

Administration of Ozone Therapy

The most common method of ozone therapy administration is called auto-hemotransfusion and involves extracting a small amount of blood, mixing it with an ozone-oxygen gas mixture, and re-infusing it intravenously. Auto-hemotransfusion is used to bring about systemic therapeutic effects. For more localized action, various forms of ozone can be injected intramuscularly, into vertebral disks, or paravertebrally. Ozonated water and oil may be used to treat skin infections and other skin disorders. Alternatively, an ozone-oxygen gas mixture may be administered topically in a sealed chamber or bag. In treating mucosal infectious or inflammatory conditions, such as of the vaginal or gastrointestinal tract, ozone gas is sometimes insufflated (blown) directly over the mucosa, for example, via the vaginal or rectal opening.^{2,5}

Safety

Ozone therapy in recommended doses appears to be nontoxic. Nevertheless, reports of adverse effects attributable to complications of intravenous technique do exist. These include thunderclap headaches, transient blindness, and stroke probably due to air embolism, as well as transmission of blood-borne infection due to non-sterile technique.⁷⁻¹³

Ozone in Treatment of Musculoskeletal Pain

Ozone therapy is widely used to treat musculoskeletal pain and dysfunction, and has been reported to rapidly relieve pain, reduce edema, and improve mobility in osteoarthritic joints.^{14,15} By normalizing redox balance, ozone therapy modulates activities of cytokines, growth factors, and other regulatory proteins involved in tissue repair.¹⁴ In addition, ozone enhances tissue oxygenation through its effects on red blood cells. Lipid oxidation products produced during ozone exposure may even quell pain signaling in the central nervous system.¹⁶

Osteoarthritis

A meta-analysis of research examining the effect of ozone injections into osteoarthritic knee joints included ten studies with a combined total of 319 cases. Ozone injections were given in 5–20 ml amounts, with ozone concentrations of 10–40 mcg/ml. Weekly injections were used in most studies, but frequencies ranged from three times per week to once per 10 days. The meta-analysis revealed a strong positive effect of ozone therapy on pain reduction.¹⁷ Another meta-analysis of eight studies with a total of 718 patients with knee osteoarthritis concluded that intraarticular ozone injections were as effective as treatment with hyaluronic acid or platelet-rich plasma injections but had faster onset of pain relief, with maximum pain reduction after about one month of treatment and waning efficacy after 3–6 months.¹⁸ Combining platelet-rich plasma with ozone therapy may result in less pain at the injection site and faster treatment-related pain reduction compared with platelet-rich plasma injections alone.¹⁹ Ozone therapy has also been found to augment the efficacy of hyaluronic acid injections in osteoarthritic knees, with the combination leading to better pain reduction than either treatment alone.²⁰ When compared with prolotherapy using dextrose, however, ozone prolotherapy (prolozone) showed no advantages.²¹

A study looking at the effects of ozone therapy on surgery outcomes included 80 participants who had undergone arthroscopic surgery for knee osteoarthritis. Forty-two of the participants were given intraarticular ozone injections (20 ml of 20 mcg/ml ozone solution) weekly for four weeks, beginning two weeks after surgery; 38 participants, serving as controls, received no ozone therapy. At a follow-up approximately one year after surgery, those treated with intraarticular ozone injections had less pain and stiffness and better joint function than the control group.²²

Vertebral Disc Herniation

Ozone therapy involving injections into or around intervertebral discs has been reported to shrink herniated discs and relieve nerve pain in a number of studies.²³⁻²⁹ Its efficacy may be strongest in those under 50 years of age and those with limited disc pathology,^{23,26} and its benefits may persist for as long as ten years.³⁰ Dose comparison studies on the effects of intradiscal ozone injections indicate concentrations of 30–40 mcg/ml may have the best effect, while 60 mcg/ml can increase pain and inflammation, in patients with lumbar disc herniation.^{31,32} An interdiscal ozone injection during spinal fusion surgery in patients with lumbar disc herniation was found in one trial to improve surgical outcomes, with more rapid pain relief and recovery of lumbar function.³³ Findings from a comparison trial suggest ozone injections may be more effective than pain medications in treating low back pain and sciatica due to disc herniation: 80% of patients with treated with ozone therapy were pain-free six months after treatment, compared with 50% of those treated with anti-inflammatory analgesics.³⁴

Plantar Fasciitis

One study in people with chronic plantar fasciitis compared the effects of a single ozone injection to a steroid injection. Both treatments led to reduced pain and enhanced function at two weeks, but ozone therapy had more lasting effects as measured 12 weeks after the injection.³⁵

Ozone Treatment of Skin Disorders

Ozone has been used as an antibacterial treatment for gaseous gangrene since at least the first world war. Recent research suggests ozonated water can work as effectively as alcohol-based hand sanitizers, without causing dryness and irritation, in a health care setting.³⁶ Topical ozone therapies are now used to treat a range of skin infections as well as inflammatory conditions. Ozone hydrotherapy has been reported to reduce edema and inflammation, decrease pruritis and pain, and enhance wound healing. Ozonated plant and fish oils containing unsaturated omega-3, omega-6, and omega-9 fatty acids have a longer shelf life than ozonated water and can be used topically for antimicrobial, moisturizing, and skin barrier-protective effects. Auto-hemotransfusion, at doses of 20–40 mcg/ml, may be the best option for skin conditions related to systemic disorders, such as diabetic ulcers, herpes zoster and postherpetic neuralgia, psoriasis, and atopic dermatitis.⁵

Wound Healing

A review of nine studies with a combined total of 453 participants suffering from chronic non-healing wounds concluded topical ozone therapy improves wound closure and may have a role as an alternative or adjunct to standard care.³⁷ Case reports suggest ozonated oil and ozonated water are both effective for eradicating methicillin-resistant *Staphylococcus aureus* (MRSA) skin infection.³⁸

Fungal Infections

Topical ozone therapy may also be effective in treating cutaneous fungal infections. In a study in 60 participants affected by tinea pedis, daily foot baths using ozonated water followed by application of topical ozone for four weeks was as effective as standard treatment with topical antifungal agents (naftifine plus ketoconazole) and caused no side effects.³⁹ Ozonated sunflower oil alone, twice daily for six weeks, was also as effective as standard topical drug therapy (2% ketoconazole) for clearing tinea pedis.⁴⁰ In a trial with 400 subjects affected by fungal nail infections, more than 90% of those treated with topical ozonated sunflower oil twice daily had resolution of their infection after three months; in addition, 44% remained infection-free after one year.⁴¹ Sanitizing footwear with ozone gas has been proposed as a helpful measure alongside other treatments for fungal skin or nail infections of the feet.⁴²

Atopic Dermatitis

One study included 60 children with atopic dermatitis. Treatment involved showering in ozonated water three to five times per week and using topical ozonated oil twice daily, and was compared with showering in regular water and using a placebo oil twice daily. After two weeks, treatment was effective in almost 90% of children receiving ozone treatment, but only 31% of those not receiving ozone treatment showed effective treatment response.⁴³ Daily showering with ozonated water and twice-daily application of ozonated oil to atopic dermatitis lesions for seven days reduced *S. aureus* colonization and improved symptoms in a pilot trial with 12 participants.⁴⁴

Psoriasis

One trial with 40 participants found treatment of psoriasis with topical ozonated oil twice daily was as effective as standard treatment with topical corticosteroid (flumetasone) after one week.⁴⁵

Ozone Treatment of Vascular Disorders

Heart Failure

One study compared outcomes in 40 ozone-treated heart failure patients with those in 40 similar patients receiving standard therapies. Ozone therapy by autohemotransfusion three times per week and intramuscular injection once per week for five weeks led to increased levels of antioxidant enzymes, improvement in some markers of left ventricular function, and increased six-minute walk distance.⁴⁶

Coronary Artery Disease

Ozone therapy may benefit people with coronary heart disease in part due to its ability to prevent blood clots. A study that included 53 people with coronary artery disease compared treatment with antithrombotic medication to the same medication plus ozone therapy via rectal insufflation (200 ml of 40 mcg/ml ozonated gas for 5 minutes/day). After 20 days, ozone therapy was associated with greater improvements in hemostatic markers and antioxidant status.⁴⁷

Ischemia

Although ozone does not appear to impact vascular tone,⁴⁸ ozone therapy has nonetheless been found to improve blood flow and oxygenation in tissues affected by ischemia. A number of studies have shown ozone therapy through auto-hemotransfusion can improve oxygenation of lower extremities and promote healing of atherosclerotic ulcers in people with peripheral vascular disease,⁴⁹⁻⁵⁵ and in one study ozone therapy improved cerebrovascular blood flow in patients with evidence of brain ischemia.⁵⁶ Ozone's ability to decrease blood viscosity may be the mechanism behind its benefits in ischemic conditions.⁵⁷

Ozone Treatment of Viral Infections

Ozone therapy has been reported to be beneficial for improving markers of liver function and reducing viral load in people with viral hepatitis.⁵⁸ One study found ozone therapy by auto-hemotransfusion every two days for 20 days protected renal function in patients receiving standard treatments for severe chronic hepatitis (not otherwise specified).⁵⁹ In a controlled trial, 40 participants with hepatitis C virus (HCV) received ozone therapy by intramuscular injection and rectal insufflation during a single session at the beginning of the trial, followed by ozone auto-hemotransfusion three times per week for 30 or 60 sessions. Compared with 12 HCV-affected participants not treated with ozone therapy, treatment was associated with higher rates of improvement in clinical and lab parameters. Ten participants in the ozone-treated group were HCV-negative after 30 sessions, and an additional eight of 18 who went on to have 60 sessions were HCV-negative at the end of the trial, while only one participant in the control group became HCV-negative during the trial.⁶⁰ It was also reported that eight weeks of ozone therapy led to improved liver function in 20 people with hepatitis B virus (HBV).⁶¹

In a controlled trial with 60 subjects suffering from herpes zoster, treatment with oral antiviral medication (valacyclovir) plus ozone therapy consisting of ozonated water baths and topical ozonated oil improved healing of lesions and relieved pain better than antiviral medication plus laser therapy and a topical antibiotic (mupirocin).⁶² Findings from a study in mice suggest ozone has the potential to prevent dysplasia induced by human papilloma virus 16 (HPV16).⁶³

Ozone Treatment of Dental Disorders

Ozone therapy has a range of possible applications in dentistry. Ozone appears to have antimicrobial action against biofilms associated with tooth decay and cavities. Ozone therapy for dental purposes may involve tooth and gingival irrigation with ozonated water, insufflation of periodontal pockets with ozone gas, and the use of topical ozonated oil in the mouth. It has even been reported that ozone therapy via ear insufflation may help patients with sinus infections and temporomandibular joint dysfunction.⁶⁴ According to a review of the research, the majority of evidence indicates ozone may be beneficial in cavity prevention and treatment of mild decay.⁶⁵

Ozone and ozonated olive oil have demonstrated antimicrobial action (qualified as strong and modest, respectively) against bacteria associated with periodontal disease.^{66,67} In a pilot trial, ozonated water was more effective than saline but less effective than chlorhexidine when used as an irrigant in people with periodontal disease,⁶⁸ however a pilot study suggests ozone may have other positive effects on gingival health compared with chlorhexidine.⁶⁹ Its potential use as a decontaminant for preventing or treating peri-implantitis is being explored.⁷⁰ However, ozone therapy has not been shown to add to the benefits of non-surgical treatment of periodontal disease (scaling and root planing) in otherwise healthy adults.⁷¹⁻⁷³

Ozone Treatment of Neurological Disorders

A pilot trial included five participants with severe and persistent headaches that were unresponsive to other treatments. Treatment with ozone therapy via auto-hemotransfusion led to decreased severity and frequency of headaches during one year of follow-up.⁷⁴

Ozone therapy via auto-hemotransfusion appears to be helpful in people with idiopathic sudden sensorineural hearing loss, a condition for which standard treatment with steroid medications has low efficacy.^{75,76} Ozone injections in the region of the cervical spine have also been reported to reduce symptoms of vestibulocochlear syndrome such as tinnitus, hearing loss, and vertigo.⁷⁷

Two studies in people with multiple sclerosis (MS) suggest ozone therapy may influence the course of MS by improving cerebral metabolism.^{78,79}

Preliminary clinical trials have found that ozone therapy may slow progression and improve vision in individuals with the dry form of age-related macular degeneration.⁸⁰⁻⁸²

Other Uses of Ozone

Inflammatory Bowel Disease

Ozone administered via rectal insufflation is used by some practitioners to treat inflammatory bowel disease. Although there do not appear to be published reports supporting its efficacy in IBD, a pilot study found ozone therapy appeared to induce regeneration of the colonic epithelium.⁸³

Cystitis

Preliminary research and data from animal studies suggest ozone therapy may also have a role in treatment of cystitis.⁸⁴⁻⁸⁶

Cancer

A growing body of research, which so far includes only preclinical and case studies, indicates ozone has potential as an adjunct cancer therapy.⁸⁷

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