Chapter 13
The Potential Role of Ozone Therapy

Didem Akçalı and Avni Babacan

Introduction

Medical ozone is a complementary treatment modality for various indications in medicine [1, 2]. Oxygen is converted by a generator to an oxygen–ozone mixture and titrated to various concentrations for medical consumption. Ozone treatment is preferred in many diseases such as diabetes mellitus, neurological diseases, osteoarthritis, other pain syndromes, peripheral artery diseases, and infectious diseases. The equipment used is ozone-resistant, such as glass-based and silicone-coated products. Ozone reacts with latex, PVC, and non-ozone-resistant material. The type and concentration of and the schedule for ozone treatment may vary according to the pathology. There are many routes for the administration of ozone treatment and these are mainly classified as local or systemic (parenteral and rectal) administration. In addition, combination of both the local and systemic routes may be useful for complex medical conditions. Ozone treatment does not cause infections when proper technique and sterile equipment are utilized [2].

13.1 Mechanisms of Ozone Treatment in Medicine

Ozone treatment is used to activate the immune system by increasing the body oxygen content to treat infectious diseases with an antibacterial, antiprotozoal, antiviral, and antifungal effect [1, 3]. Ozone reacts with blood plasma and chemical messengers for activating reactive oxygen species and hydrogen peroxide (H_2O_2). Transient oxidative stress stimulates the immune system and increases the oxygen content of

D. Akçalı (✉) · A. Babacan
Gazi University Faculty of Medicine, Anesthesiology and Algology Department, Ankara, Turkey
e-mail: avnibaba@gazi.edu.tr

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the human body. The Madrid Declaration on Ozone Therapy, which is the first extensive reference including recommendations from researchers and physicians performing ozone treatment was released in June 2015 [1, 4].

Mitochondrial energy production decreases in chronic diseases. Ozone treatment stimulates the energy-producing pathways of the cells. Oxygen affinity of the blood cells is increased and this excess oxygen reaches areas where it is needed. Ozone helps the body boost its own healing capacity by its effect on white blood cells. Ozone regulates 2,3-diphosphoglycerate (2,3-DPG) in erythrocytes, and induces the release of nitric oxide (NO) and carbon monoxide (CO), and increases oxygen delivery in ischemic tissues. Ozonated blood leads to a feeling of well-being by the release of endorphins and modifies the biological response [5].

Ozone dissolves in plasma and acts as a pro-drug in a therapeutic window between 10 and 80 μg/ml (0.21–1.68 μmol/ml) in the blood. Important messengers that are produced are H_2O_2 and a mixture of lipid oxygen products (LOPs). The mechanism of effect of rectal ozone is similar; it dissolves immediately in water in the epithelium and reacts with biomolecules to produce H_2O_2 and LOPs. LOPs are absorbed by the lymphatics and venous capillaries and reach the liver and then the whole circulation [6]. During ozonolysis, ozone peroxides are formed and can be considered crucial for the pharmacological effects. Aldehydes are secondary products [5].

Patient responses to mild controlled oxidative stress are variable. The oxidative stress state of patients can be measured by antioxidant activity indicators [4]. Malone dialdehyde (MDA) is a measure for oxidative stress during extracorporeal blood treatment with ozone. Ozone treatment of the blood in the form of major autohemotherapy remarkably increases two cytokines: interferon gamma and tumor necrosis factor alpha [5]. Ozone treatment is beneficial in oxidative-stress-related diseases such as cancer, neurodegenerative diseases, inflammation, and cardiovascular diseases through an antioxidant response. Vitamin C and Vitamin E supplements must be avoided during ozone therapy to ensure a good treatment outcome [6].

Moderate oxidative stress activates nuclear-factor-erythroid 2-related factor 2 (Nrf2), which is essential for antioxidant response elements (ARE) producing many antioxidant enzymes such as superoxide dismutase, glutathione-s-transferase, and catalase. Oxidative stress can be reversed in this way [6]. The analgesic effect is mediated by the induction of IFN-β, activation of superoxide dismutase, and induction of TGF-β. The success rate for medical ozone in pain-related conditions is 50–60% [2].

13.2 Ozone Application Methods

Ozone is effective in low doses but may be toxic in higher doses (principle of hormesis). Major ozone autohemotherapy (MAHT) and rectal ozone insufflation 10–40 μg/ml ozone/oxygen mixture are recommended for systemic application [2].

For systemic diseases, major autohemotherapy (MAHT) is used and is performed by drawing 50–100 ml of venous blood into a sterile single-use pressurized bottle

containing an anticoagulant and infusing it back to the patient after adding an equal volume of an ozone–oxygen gas mixture [7]. Rectal insufflation is used as a systemic method and most of the time preferred for use in intestinal disorders. In the Russian ecole, ozonated saline is used for intravenous infusion [1]. Inhalation of ozone gas is toxic for the respiratory tract. Intraarticular injection, intradiscal injection, etc., are local treatment modalities used in arthritis, sciatica, and vertebral disorders.

During ozone treatment to an individual, oxygen delivery to tissues is improved; the metabolism will be enhanced and the immune system will be activated to release growth factors. This cascade produces a state of wellness by the activation of neuroendocrine mechanisms [6].

Additional effects of ozone therapy are strengthening of the hairs and nails, brightening of the skin, and a healthy appearance. The patients express a happy emotional state with more physical energy and report the ability to fall asleep faster and enjoy a restful sleep [7].

Regular ozone therapy is needed to treat pathological conditions and must be continued by adopting maintenance therapy (8–10 sessions) [6]. Two to three cycles of ozone treatment per year increase the quality of life and decrease disability [2].

13.3 Medical Ozone Experiences in the Algology Department

Medical ozone treatment modalities have been in use at the Gazi University Algology Department as major and minor autohemotherapy, intraarticular injection, transforaminal/intradiscal injection, and myofascial trigger point injection since 2005.

Ozone treatment is preferred as an additional option in patients with headache and fibromyalgia who are unresponsive to medical treatment and lifestyle modifications. Eight to ten sessions of major ozone hemotherapy are performed and can be repeated every 6 months when needed. For patients with resistant neuropathic pain, and especially in those that suffer drug side effects, add-on systemic ozone treatment is used with surprising results. In our study on knee osteoarthritis patients, we used five sessions of intraarticular ozone injections and this treatment provided reduction in pain intensity and increased the functional capacity [8].

13.4 Ozone Treatment in Headache

Ozone treatment is a valuable complementary treatment for incapacitating headaches resistant to treatment [1]. Safe treatment with ozone involves three principles:

1. Give no harm!
2. Increase the dose step by step.
3. Administer within the range of the relevant concentration.

Migraine and primary headaches are treated with major autohemotherapy (MAHT) and rectal insufflation [7]. Lipid peroxidation plays a significant role in migraine pathogenesis [9]. During major ozone autohemotherapy, endothelial nitric oxide synthase (eNOS) is activated and is important to increase NO causing vasodilation and enhanced tissue oxygenation, enhancing the release of oxygen to tissues by shifting the Hb dissociation curve [5]. This mechanism may be crucial for ozone treatment for headache [4, 5, 7]. Enhanced release of NO and CO causes possibly prostacyclin (PGI_2) COX-2 dependent vasodilation [1].

Ozone can be used successfully for immune modulation at doses of 15–20 μg/ml 300 ml twice a week as major autohemotherapy or 15–25 μg/ml max. 300 ml rectal for rectal ozone insufflation [10].

13.5 Scientific Evidence

The literature on ozone treatment for headache is limited. In Table 13.1, prominent studies in headache patients treated with ozone are summarized (Table 13.1) [7, 11, 12]. Among these, only Kotov's study is a controlled study. Randomized placebo-controlled studies are needed to confirm the therapeutic effect of ozone for headaches.

Scientific evidence for ozone treatment is available for knee osteoarthritis and herniated lumbar discolysis. Knee osteoarthrosis can be effectively treated by para-articular ozone treatment, resulting in pain reduction and increased function.

Table 13.1 Studies for treatment of headache with ozone (reorganized according to Refs. [7, 11, 12])

Patients	Dose, Sessions	Results	Author, Year
Randomized trial 40 patients—ozone 28 patients—control 64% migraine without aura 36% migraine with aura	1200 μg/l, 8–9 sessions, intravenous ozonated saline	25% improvement in headache attack and severity 58% no attack for 5 months	Kotov, 2000
Five patients, refractory migraine	Twice a week, then weekly	Pain relief for at least 6 months	Clavo, 2013
10Y, frontal, daily temporal headache	25 μg/ml 120 ml, rectal, twice a week, 10 sessions	2 attacks/month	Apuzzo, 2016
51Y, apical headache, attacks lasting 3 days	Twice a week, 200 ml MAHT, 8 sessions	Complete pain relief	

Evidence is not clear for intraarticular ozone treatment for knee osteoarthrosis [13]. Ozone treatment is used as paravertebral lower-back injections or intradiscal treatments for lower-back pain. After ozone treatment, the analgesic effect of ozone increases and is sustained for a period of time. Ozone was not found to be superior to hyaluronic acid for osteoarthritis [14]. Intradiscal ozone treatment has II-3 level of evidence (strength of recommendation 1C) and paravertebral or paraforaminal ozone injection has been declared to have II-1 level of evidence (strength of recommendation 1B) [15].

13.6 Ozone Therapy Side Effects

- Accidental inhalation may cause burning of eyes, coughing, nausea or vomiting, or mild headache.
- Rectal ozone may cause mild discomfort, a feeling of passing gas, gurgling, or mild cramps.
- Herxheimer (healing) reaction may be seen as the sign of detoxification and healing. Flu-like symptoms or temporarily feeling worse is an indication to continue the therapy. This is actually the natural healing process.
- Hot sensation in the lower abdomen.
- Increased appetite and sleepiness [2].

13.7 Ozone Therapy Contraindications

Medical ozone treatment is contraindicated in severe coagulation abnormalities, uncontrolled hyperthyroidism, Glucose-6-Phosphate Dehydrogenase deficiency, chronic relapsing pancreatitis, and acute or subacute myocardial infarction. It is also not performed during the first trimester of pregnancy, in ozone allergy and acute alcohol intoxication, and following recent myocardial infarction [9, 14].

Conclusion

Severity of oxidative stress is the distinguishing factor between effective therapy with ozone and toxic reactions. The efficiency of ozone therapy in the treatment of headache needs to be evaluated in further randomized controlled clinical studies with more patients. Headache, and especially migraine, treatment with ozone therapy is a long-lasting, safe, effective, and inexpensive add-on treatment option when treating pain, at least for intractable headache patients. Ozone treatment can be a valuable option before other treatments, especially in intractable headache patients.

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