

Correspondence

The place of ozone therapy in radiotherapy

Oxygen is an element that is heavily present in living things. The use of oxygen in many reactions in the organism results in free oxygen radicals. These free oxygen radicals are undesirable byproducts for the body, and their high levels can be toxic to the organism. The organism develops antioxidant defence systems against these free radicals and protects deoxyribonucleic acid, proteins and lipids from this toxic effect. Additional treatments may be needed when antioxidant systems are weak or inadequate. One of these is ozone treatment. After contact with plasma, ozone acts on various tissues by forming reactive oxygen derivatives and lipid oxidation products. These reactive oxygen derivatives show the effect of erythrocytes to more easily release oxygen to the tissues, activation of leucocytes, release of growth factors in platelets, increase in endothelial nitric oxide release, erythrocyte production in bone marrow and increased stem cell activation and antioxidant enzymes in other organs.¹⁻⁴

Ozone is used in medicine as a complementary treatment due to its (i) anti-inflammatory, (ii) antimicrobial, (iii) antioxidant, (iv) immunostimulant and (v) antihypoxic effects. Ozone shows the antimicrobial effect of hydrocarbons in the cell membrane by reacting with double bonds and damaging the cell membrane. Ozone helps in the synthesis of biologically active substances such as interleukin, leukotriene and prostaglandin, which play a role in the suppression of inflammation. It also stimulates proliferation of cells of the immune system and increases sensitivity of macrophages to phagocytosis. In addition, ozone increases the contact surface of erythrocytes for oxygen transport, preventing erythrocytes from precipitating. This is important in circulatory disorders, stimulation of circulation and revitalization of organ functions. Ozone, which causes the release of vasodilators such as nitrous oxide, causes dilatation of the arterioles and venules. Thus, it has analgesic and detoxification effects. It also stimulates the mitochondria and ribosomes in cells and increases intracellular protein synthesis. These changes increase activation of cell functions and increase regeneration of tissues and organs. Although ozone gas is toxic, it has medical benefits when used in a controlled manner. While low concentrations are ineffective, high doses may have a negative effect (weakness, fatigue, etc.). To date, no serious side-effects of medical ozone therapy have been reported.

Ozone, which has a widespread application,¹⁻⁷ is administered systemically (major and minor auto-haemotherapy and rectal insufflation) or topically (low-pressure ozone gas application, ozonized water application and intra-articular injection) according to the condition of the disease.¹⁻¹⁰

Ozone, an agent previously used for disinfection and sterilization, is currently used in many diseases where medical treatment is insufficient. Medical ozone therapy is used in the treatment of circulatory disorders, cancer, inflammatory diseases (open wounds, colitis and hepatitis), burns, neurological diseases (Parkinsonism, trigeminal neuralgia, Alzheimer disease, headaches and migraine), weakness and chronic fatigue and degenerative joint diseases.¹⁻³

With the discovery that cancer cells have a lower respiratory rate, ozone has been tested in cancer. The basis for the use of ozone is that cancer cells cannot multiply in a high oxygen environment. However, there is no clinical study that suggests that cancer cells disappear in high oxygen environment.² Whether or not ozone therapy is useful in combination with radiotherapy (RT) has been investigated in animal experiments. Scientific evidence has reported that ozone treatment is effective. In a tumour cell model study conducted by Kızıltan *et al.*, ozone therapy administered simultaneously or alone with RT was

shown to prolong survival with anti-oedema and antitumour effects in mice with peritoneal carcinomatosis.³ Gultekin *et al.* investigated the protective effects of ozone therapy on organ damage caused by total body irradiation (TBI) in rats and reported that ozone therapy increased the level of antioxidant enzymes in the blood and inhibited oxidative stress in cells and tissues by reducing lipid peroxidation.⁴ In our previous animal study, we reported that ozone therapy had an inhibitory effect on acute liver injury caused by TBI.⁵ In the literature, there are limited number of clinical studies related to the application of medical ozone with RT, and no published randomized controlled study. Clavo *et al.* used ozone therapy in the treatment of refractory haemorrhagic radiation proctitis that did not respond to conventional therapies, and statistically significant improvement was observed.⁶ In a study from Spain, 12 of 19 patients with advanced head and neck cancer received chemotherapy and RT and 7 patients received ozone therapy and RT. No difference was found between the two groups in terms of overall survival. However, it was reported that ozone treatment was beneficial, and there was no significant difference in the number of patients in the groups.⁷ Another study reported that intravesical ozone therapy is effective and safe in progressive haematuria due to radiation.¹¹ Velikaya *et al.* and Jordan *et al.* found ozone to accelerate wound healing in skin reactions due to RT.^{12,13}

Ozone therapy has been found to be an easy-to-use and cost-effective complementary treatment. There are no serious side-effects with ozone therapy. Today, in oncology, ozone treatment improves the general clinical condition of patients undergoing RT and prevents the development of complications. Although the number of clinical studies related to the potential benefit or damage of RT and medical ozone use is limited, the results are positive. Randomized controlled trials with a well-designed, long follow-up period and a large number of patients are required to include ozone therapy in the treatment protocols.

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