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Has Ozone Therapy a Future in Veterinary Medicine?

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ABSTRACT

Ozone gas absorbs harmful ultraviolet radiation from the sun and plays a role in the continuation of the biological balance of the earth. It was used as a disinfectant due to its bactericidal and fungicidal effects. The Germans used in the treatment of gaseous gangrenous soldiers in the First World War and after the success in the treatment, ozone was started to be used in the treatment of diseases as medical ozone. Ozone gas plays a role in strengthening the body's defense mechanism. Nowadays, surgery, internal diseases, neurology, urology, dermatology and gynecology are used in the treatment of diseases as well as in many areas such as cosmetic and disinfection. Ozone treatment has been accepted as a complementary medicine practice with the regulation published in the Official Gazette on 27 October 2014 in our country. In this review, information about the use of medical ozone, the mechanism of action, the routes of administration, the issues to be considered in its use and the use of the treatment of which diseases will be given.

Keywords: *Ozone, Effect, Application route*

INTRODUCTİON

Ozone is a chemical gas which composed of three oxygen atoms, having a characteristic odor, a colorless structure at a room temperature and a liquid blue color (Tanyeli, 2009). Oxygen molecule (O_2) is an unstable molecule in constant state, but ozone is an effective factor in the blue color of the sky. As a result of the breakdown of the oxygen molecules in the stratosphere layer of the atmosphere, two reactive oxygen atoms are released, which are exposed to endothermic reaction with intacting oxygen molecules and three-atom ozone gas is released. (Eyüpoğlu, 2010; Kutlubay et al., 2010). A large part of the ozone in the atmosphere is located in the stratosphere layer, which is 20-50 km high, while the remaining part is in the troposphere layer which is 10-15 km high (Babucçu, 2011; Yiğitarslan et al., 2018).

Ozone, which is a heavier gas than air, plays an important role in the continuation of the biological balance of the earth by absorbing the ultraviolet rays coming from the sun by reacting with the polluted air. (Babucçu, 2011; Onyay et al., 2015).Ozone gas was discovered by German chemist Christian Friedrich Schönbein in 1839 and it was started to be used as a biological disinfectant with bactericidal and fungicidal effects in hospitals in 1856 (Kutlubay et al., 2010; Onyay et al., 2016). In 1995, the US Department of Health accepted the use of ozone therapy as a complementary medical practice, thus increasing the pre-clinical and clinical academic studies and contributing to the widespread implementation of ozone therapy in the medical field all over the world (Aytaçoğlu et al., 2015). In addition to protecting from athmospheric radiation, ozone has long been in the service of humanity in the food, sterilization industry and veterinary fields (Babucçu, 2011).

Medical Ozone Production

Medical ozone is obtained by silent electric discharged generators and it is always mixture of püre ozone and püre oxygen. The concentration of ozone can vary from 1-100 µg / ml depending on the application.(Tanyeli, 2009; Otay et al., 2015) While only 5% of this gas generated from the generator is made of ozone; the remaining part consists of oxygen. It is a mixture of 0.05% O_3, 99.95% O_2 or 5% O_3 to 95% O_2 obtained from 100% pure oxygen. Medical ozone is obtained as a result of passing the high voltage difference of pure oxygen in special generators (Yiğitarslan et al., 2018). The energy in the generators provides the decomposition of the single O_2 molecules into oxygen atoms and the atoms combine with a

free O2 molecule to form the O_3 molecule (Tanyeli, 2009). Use of normal air in ozone production is not recommended. Because it contains high nitrogen, toxic nitrogen dioxide (N_2O_2) occurs (Babuccu, 2011).

It is reported that ozone generators should be used in applications to slow down this transformation (Kutlubay et al., 2010).Medical ozone is always prepared at the site with a special generator and is applied immediately, because at the end of one hour only half of the original ozone remains; the rest re-decomposes to oxygen. While ozone producing parts of ozone devices should be made from unreacted substances (steel, specially anodized aluminum, ceramic, glass or teflon), the parts used to give ozone are recommended to be glass, polyethylene, polypropylene or teflon (Tanyeli, 2009).

Effect Mechanism of Ozone

Ozone is a powerful oxidant which promotes oxidative stress, but may simultaneously limit some factors released by inflammatory cells as well as activating the antioxidant endogenous system (Szponder et al., 2017). Ozone can induce activation of lymphocytes and monocytes to release several cytokines, improve the tissue regeneration mechanism and stimulate the process of granulation and epithelization (Djuricic et al., 2015). Dissolution depends on heat, pressure and concentration. Unlike oxygen, ozone reacts with biomolecules very quicklyin biological fluids. Thus, ozone mixture reacts with polyunsaturated fatty acids, antioxidants and sulfhydryl thiol compounds such as cysteine.Depending on the amount of ozone, carbohydrates and proteins can be affected at different levels from these reactions. All of these compounds can be oxidized against ozone and behave like electron donor. As a result, oxygen derivatives with reactive structure such as superoxide, hydrogen peroxide and hypochlorite are formed. The most important of these reactions is the oxidation of unsaturated fatty acids. In this reaction, two lipid oxidation products are released with hydrogen peroxide (Esterbauer et al.,1991; Bocci, 2006; Rowland, 2009).

It has been reported that hydrogen peroxide acts as a secondary messenger responsible for many of the therapeutic activities of ozone. One of the most important effects of these behaviours is to increase the 2,3-diphosphoglycerate level in erythrocytes, allowing the hemoglobin-oxygen dissociation curve to shift to the right, thus contributing to the faster and easier transport of oxygen to the tissues. Plasma concentration increased hydrogen peroxide is easily revealed in studies of diffuse leukocytes and endothelial cells in various structures with interferon, interleukin and transforming effects and triggering stimuli that increase the growth factor (Halliwell et al., 2000). The half-life of lipid oxidation products can last for long hours, so the effects of reactive oxygen derivatives that have a very short life span on oxidation are considered to be the delayed effect of ozone. Due to their prolonged half-life, lipid oxidation products may exhibit various biological effects in many tissues (Halliwell et al., 2000; Di Paolo et al., 2005). Although exposure to medical ozone leads to an increase in platelet function in a dose-dependent manner, it increases the release of growth factors in their structures by activating passive platelets and thus may have positive effects on recovery in patients with ischemia and ulcers (Aslan et al., 2012).

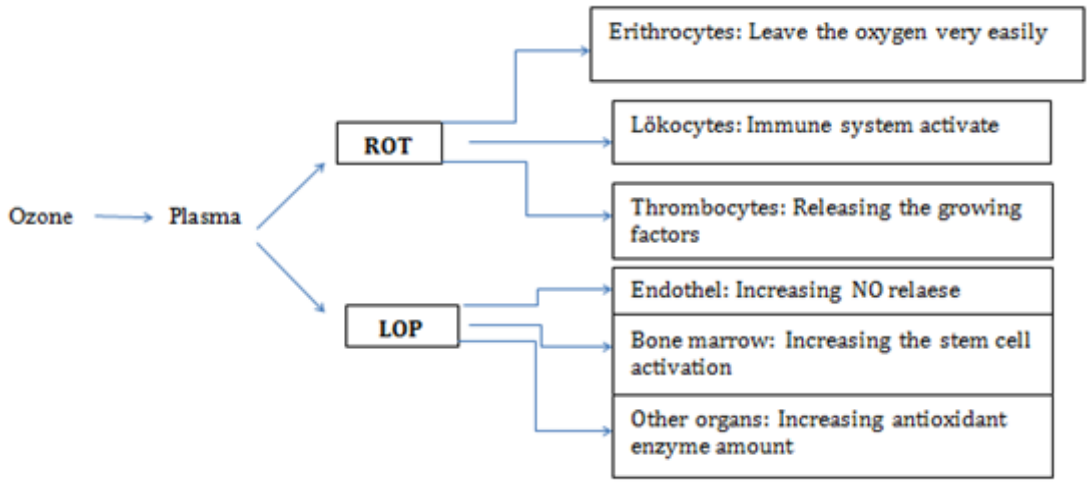

Figure1. *Therapeutic effects in using medical ozone*

ROT: *Reaktive oxygen derivates*, **LOP**: *Lipid oxidation product (Trachootham ve ark., 2008).*

The presence of free radicals is of great importance for the emergence of the biological effects of ozone. Free radicals are reactive substances that contribute to the initiation of a variety of pathological processes, which may react at intermediate steps or occur at the end of pathological processes. These free radicals may occur in various physiological conditions in the organisms that cause mitochondria and phagocytosis during aerobic respiration (Korkmaz et al., 2005). Ozone acts through various mechanisms including the activation of erythrocyte metabolism and immune cells and as a disinfectant especially against the anaerobic bacteria (Zobel et al., 2014). Ozone breaks through the microorganism cell membrane and alse destroys viruses by diffusing through the protein coat in the nucleic acis core, resulting in damage of the viral nucleic acid. To date, hundreds of studies have explained the role of oxidative stress in cell damage and the pathological effects and the increase in the duration of diseases (Powis et al., 1995; Oter et al., 2005;). It is reported that oxidative stress may have side effects. It has been shown that oxidation / reduction reactions are mainly involved in intracellular communication and also play a role in biological mechanisms. It is known that both the reactive molecules and their biological molecules play an important role in the cells with low concentration of oxidation products resulting from the reaction (Powis et al., 1995; Valacchi and Bocci, 1999).In general, medical ozone is used to activate the biological function without any harmful effect. Therefore, the dose of medical ozone applied should be sufficient (not to be below the threshold value) to activate the physiological mechanisms, but it should not be enough to completely reduce intracellular antioxidant systems and cause damage (Halliwell et al., 2000).

The ozone reacts with antioxidants causing changes in the amount of antioxidants and may cause reactive oxygen derivatives to emerge throughout these reactions. In addition, since the half-life of the radicals is very short, it is seen that lipid oxidation products are replaced by their disappearance. Unsaturated fatty acids in the erythrocyte membrane have been reported to be very sensitive to oxidation and oxidation in the membranes of erythrocytes is the majority of the last radical products. In addition, hydrogen peroxide produced during the reactions is considered to be a non-radical oxidizing molecule due to its different molecular structure (Halliwell et al., 2000; Di Paolo et al., 2005; Rowland, 2006).It should be kept in mind that due to the strong oxidizing properties due to the concentration of medical ozone, more than a certain percentage of medical ozone may cause toxic effects to the body.

Indications for Ozone Therapy

Because of current medical treatment has an increasing cost values and antibiotic- resistant infection, ozone therapy needs to be pay attention to. This therapy method is very cheap and does not produce anhtibiotic resistance.Ozone therapy has a wide range of use in medical practice and includes treating variety of diseases such as infected wounds, chronic skin ulcers, early-stage gangrene and advanced ischemic diseases, abcesses, anal fissures, bed sores, gingivitis, peritonitis, vulvovaginitis, sinusitis, stomatitis and periodontitis (Zobel et al., 2012; Szponder et al., 2017).

Table1. *The Indications for Ozone (Viebahn-Haensler, 2005).*

NDICATIONS
External ulcers and skin lesions
Arterial circulatory diseases
Immunodeficiency and immunodys balance eg • Chronic forms of hepatitis B and C • Supportive therapy in cancer patients • Supportive therapy in rheumatoid arthritis
Inflammatory condition such as • Knee arthrosis • Gonarthrosis • Traumatic knee disorders
Dental medicine • Following tooth extraction • Buccal infections (eg candida) • Aphthae • Parodontosis

Ozonation Application Ways

Ozone has different mechanisms of action in systemic (major-minor autohemotherapy, rectal-vaginal insufflation) and local administration (intraarticular injection, intradiscal injection, bagging, subcutaneous injection). While local effects are caused by direct antimicrobial and wound healing properties of ozone; systemic effects occur as a result of activation of various cells such as erythrocyte, leukocytes (Viebahn-Hansler, 2005).

Major Autohemotherapy

Major autohemothreapy is an extracorporeal blood treatment with ozone gas followed by the intravenous reinfusion of the patient's treated blood. This method is used for treatment of

circulatory disorders, infecitons, virüs-caused diseases such as hepatitis B and C, general immune deficiency and diseases caused by insufficiency of the umbilical system and for rheumatic artritis (Nogales et al., 2008; Viebahn et al., 2012; Unal, 2013).

4.2. Minor Otohemotherapy

Minor autohemotherapy is administered to patients by intramuscular injection and its mechansim of action has a non-spesific activation and general stimulation of the immune system. This method is indicated for allergies, acne, frunculosis and adjuvant cancer therapy in the body (Nogales et al., 2008).

Rectal Insufflation

Rectal insufflation is one of the oldest systemic forms of application in ozone threapy. It isalready being viewed as an alternative to major autohemotherapy and it is method of chocie in pediatrics. This method is indicated for local and systemic routes in the body. Local using has ulcerous colitis, proctitis and anal fistulae and systemic using has hepatitis B and C infection and for immunomodulation in poor immune system. Rectal insufflation can be performed with a catheter-dependent ozone-resistant injector or by using an ozone container and a silicone dose bag. (Tanyeli, 2009; Viebahn et al., 2012).

Vaginal Insufflation

The vaginal insufflation is a way that ozone-oxygen gas mixture administered by intravaginal cathether and used for any vaginal, uterine, ovarial or lower abdominal problem including pelvic inflammatory diseases and fibroids. The ozone enters lymph system from this method as well as the blood stream. In this method, humufied ozone is used for insufflation. The ozone-oxygen gas mixture can be given for 5 or 10 minutes at a rate of 0.5-1/min through the intravaginal tip attached to the vaginal speculum and at an concentration of 1500/2500 mcg/l (Altman, 1990; Pressman, 2000; Shoemaker, 2005).

Intraarticular-Periarticular Ozone İnjection

Injections of intraarticular and periarticular ozone / oxygen gas mixtures are known to have positive results in the treatment of various forms of joint damage. The dose and volume of medical ozone to be injected into or around the joint depends on the size of the joint and the clinical appearance of the pathology. It has been reported in studies that it can be used successfully in all arthropathies when combined with medical and physical therapy methods that significantly increase the efficacy of treatment of ozone (Yu et al., 2011).

Intradiscal Ozone Injection

Intradiscal injection of ozone gas was first proposed in the 1980's as a treatment for disc herniation. This method is used for treatment of pain and dysfunction in patients affected by thrombotic and ischemic diseases since the 30s. In this method, ozone is administered in the gas mixture that injected in paravertebral muscles for the treatment of pain and radicular dysfunction. This treatment have shown that produces pain relief in the large extent of patients. The effect mechanism of ozone's intradiscal injection is reactivating immun system response, increasing the efficiency of superoxide dismutase and other enzymes for antioxidant defence (Alexandre et al., 2005; Borelli, 2011; Buric et al., 2019).

Ozone Bagging/ Cupping

Ozone bagging is a technique that ozone is administered to the body surface on a spesific limited area. This procedure is usefull for areas of our body that hard to reach and when limb bagging not possible. Ozone bagging may be effective for human's organ weakness due to age or progressive diseases. This method has a wide variety of use such as gangrene, diabetic foot ulcers, bad sores, tick bites, any wounds that are infected or heal slowly. It uses also for treatment of extremities and local skin lesions. When ozone cupping is administered to area, ozone dosage should be well adjusted. It is applied at higher concentrations initally then the dose is decreased gradually at lower concentrations. Ozone has an oxidative effect on necrotic tissue at higher concentrations and microbicidal and virus-deactivating effect on lower concentrations (Beck et al., 1998; Kutlubay, 2010; Fathi et al., 2012).

Subcutaneous Ozone İnjection

Subcutaneous ozone injection has a wide range of use such as dermatology, surgery, neurology, pain management, herpes zoster, trigger points and other medical fields. In addition to its local effects, it also has positive results such as increasing in the dynamics of the whole organism, improvement in metabolic processes.Effect mechanism of subcutaneous injections that accelerates lipolysis in the subcutaneous cell tissue due to the interaction between ozone and unsaturated fatty

acids.Ozone concentration can be 2 or 5 µg/ml without local anesthetic or 10/ 15 µg/ml with local anesthetic. Another application way of subcutaneous ozone therapy is ozone acupuncture therapy. The combination of ozone therapy and acupuncture not only creates a new impulse in the energy circulation, but also the continuation of this impulse by providing the use of oxygen in the cells. The treatment includes a 10-12 day session. The combination of acupuncture and ozone therapy can be used in some chronic diseases. With regular and long-term use of this treatment, patients achieve a healthy quality of life (Bocci 1999;Li et al. 2007; Viebahn et al., 2012).

Side Effects and Contraindications of Ozone Therapy

When the ozone is used for medicinal purposes, dosing and dilution should be well adjusted. In some cases, there may be some undesirable problems. In particular, ozone should never be given in pure form. It is recommended to apply with a certain amount of oxygen. Oxygen in this mixture should not be less than 95%. However, normal atmospheric air should be prevented from entering this mixture. Because of the contact with the air of the ozone, the reactive property will be released, thus a toxic gas, nitrogen dioxide (N_2O_2) will be formed. In addition, ozone gas can led to embolism in the vascular system. During all these processes, it has been reported that ozone based materials (stainless steel, neutral glass and teflon) should be used when ozone is administered to patients (Yıldırım, 2011). In the calculation of dose, it can be observed that low doses results in insufficient treatment and ozone may be toxic at high doses. The application occurs successful results at low doses and with no possible acute or chronic toxicity (Onyay et al., 2015). In addition, asepsis and antisepsis rules should be paid attention and appropriate choices should be made in dose and administration routes (Kesikburun and Yasar, 2017).Ozone therapy has side effects when the the application errors occured. Therefore, the side effects of treatment are considered to be almost non-existent. It has been reported that the eye and the lungs are very sensitive to ozone and side effects such as epiphora, upper respiratory irritation, bronchoconstriction, rhinitis, cough, headache and vomiting can occured as a result of long-term exposure. One of the most important complications has been reported to be lung embolization and intravenous direct applications where ozone treatment is performed are prohibited in many countries. There may be inconvenient conditions in the application of ozone therapy, such as glucose 6 phosphate dehydrogenase deficiency (favism), especially early pregnancy, during angiotensin converting enzyme (ACE) inhibitor treatment, hyperthyroidism, bleeding disorder, chronic cardiovascular diseases and asthma patients are known to react with ozone (Tuşat, 2012; Dıraçoğlu, 2016).

Ozone Toxicity

Ozone is extremely reactive oxidant molecule. Its toxicity is complex because of the large number of biological systems that can be affected and the variety of effects that can results from ozone interactions with cellular components (Melhman et al., 1987).A continuous exposure to ozon efor 7 days at 0.5 to 0.8 ppm results in a significant enhancament of collagen synthesis and precursor but a negligible effect is observed when animals exposed to 0.2 ppm (Hussain et al., 1976).

Clinical Applications of Ozone

In a study researchers have found that rheumatoid arthritis with intraarticular 40 µg / mL ozone injection reduces joint swelling effectively. This effect occurs likely by up-regulating tumor necrosis factor (TNF-r1) and by down-regulating synovial TNF-α and TNF-r2 (Chen et al., 2013).Researchers investigated the efficacy of percutaneous ozone injection for secondary back pain in patients with disc herniation and percutaneous ozone administration in patients with chronic low back pain. It was reported to give positive results in decrease of the pain (Magalhaes et al., 2012).

In patients with hip osteoarthritis, it has been found that the combination of ozone and hyaluronic acid has a 30% increase in functionality and a significant reduction in pain levels in all patients at the first month after treatment (Cardelli et al., 2008).In addition, medical ozone has been found very useful to treat arthritis, arthrosis, lumbar disc herniation and in patients with rheumatic diseases by researchers (Uchiyama and Mihara, 1978). In another study medical ozone is effective when administered to the rats with experimental ovarian torsion and provides positive changes in the histopathological and biochemical markers of ischemia-reperfusion injury in ovarian tissue (Özler, 2009).It was evaluated the antibacterial activity of ozone in the blood and the treatment time was shortened in patients treated with

ozone (Belianin and Schmelev, 2009).It has been observed that ozone applied to patients with tracheal ulcer and erosive tracheobronchitis has complete epithelization in tracheal ulcers and tracheobronchial clearance (Chernekhovskaia et al., 2001). In another study, researchers reported that oxygen / ozone mixture containing 10mg/L ozone, ozone solution with furaciline (1: 5000) and chlorhexidine ozone solution (0.05%) were used in 55 patients with pleural empyema and that ozone treatment provided sanitation in 15 days and accelerated the repair process (Dobkin et al., 2001). It has been reported that medical ozone administered to rats intraperitoneally with necrotizing enterocolitis and caustic esophageal burns decreases the oxidative stress marker MDA, increases the amount of antioxidant enzymes and positively affects the healing process (Bocci et al., 1999; Guven et al., 2008).In an experimental study, rectal ozone insufflation was applied to the rats undergoing subtotal nephrectomy and it was shown that the compensation mechanism in the kidney was more active than the groups who did not receive ozone therapy. The result of the study showed that ozone treatment is thought to prevent vascular damage in subjects by increasing angiogenesis and reversing oxidative damage (Calunga et al., 2005).Patients treated with ozone for the healing of foot wounds in diabetic patients and patients receiving antibiotic treatment were compared. They reported that wound healing was accelerated, hospitalization was shortened, blood glucose levels were controlled faster and antioxidant enzyme levels were increased in patients receiving ozone therapy (Leon et al., 1998).In another study conducted with rats researchers investigated ozone's effect on intra-abdominal incetion in these rats. They find beneficial improvement in inflammatory response from intra-abdominal infection in rats (Souza et al., 2010).

Researchers have observed that topical ozonated oil makes a significant difference in acute cutaneous wound healing in pigs compared to control groups. In addition, they found significant increases in the levels of transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) (Kim et al., 2009). Increased activity of growth factors (TGF), which are extremely important in wound healing in chronic or acute wound areas exposed to ozone, has been shown to be increased and angiogenesis, fibroblast activity and collagen synthesis have been shown to increase (Valacchi and Bocci, 1999; Bocci, 2006; Bocci, 2006a; Kim et al., 2009; Travalgi et al., 2010).Since it is known that ozone alone does not have the ability to penetrate into the skin cell, they have reported that oxidative reaction with substances such as sesame oil or olive oil containing unsaturated fatty acids is required to penetrate the skin. It has been reported that the healing of wounds are accelerated when applied to the wounds created experimentally on the skin. In the light of these studies, it is used in the treatment of chronic wound healing, especially non-healing wounds such as atrophic and ischemic ulcers, and diabetes-induced wounds (Bocci 2006a; Kim et al. 2009; Travalgi et al. 2010).

In another study, 108 patients with different types and prevalence of eczema underwent ozone treatment, and 90% of patients recovered completely after treatment and all symptoms disappeared. In addition, 67% of cases reported that clinical remission continued at 6 months after treatment (Kutlubay et al., 2010).In a study that evaluating ozone's effect on periodontal treatment of patiens with diabetes mellitus has showed enchancing bone regeneration and accelerating xenograft resorption. Researchers concluded that gaseos ozone administration has a beneficial effect on periodontitis in Diabete Mellitus (Alpan et al., 2016).Ozone reacts directly with biomolecules, does not penetrate cells, therefore ozone often reacts with the stratum corneum. This hypothesis was supported by an increasing in lipid peroxidation products, an indicator of increased oxidative stress and decreased antioxidant capacity of the stratum corneum (Valacchi et al., 2005).

Recent findings in another study that platelets in heparinised plasma release huge amounts of platelet-derived growth factor and transforming growth factor β_1 after ozonation explains, at least in part, the enhanced healing of torpid ulcers in patients with limb ischaemia following O_3AHT (Bocci, 1999).In a study it was found that ozone has a bactericidal, immune-stimulating and anti-inflammatory effect on endometritis. Ozone was found to be an effective treatment for colpitis in people (Zobel and Tkalcic, 2013).

Ozone Therapy in Veterinary Medicine and Clinical Usage

As ozone has a wide variety of use in human medicine and dentistry due to its effective antimicrobial activity, veterinary medicine has also many treatment areas in several cases and

this treatment method has dated back to more than 30 years in veterinary using. Ozone treatment involves many disorders and diseases of small animals and buiatrics such as mastitis, metritis, endometritis, fetal membrane retention, vaginitis, urovagina, enteritis and laminitis as well as local treatment of various lesions and neuromuscular diseases in veterinary medicine (Teixeria et al., 2013; Duricic et al., 2015; Szponder et al., 2017). The rise of using these alternative methods in veterinary medicine has many advantages to prevent antibiotic resistance and misuse of chemical drugs. Ozone is a very safe treatment method that there is no withdrawal period from milk, meat and other tissues (Djuricic et al., 2015).

In a study conducted with rabbits, it was formed the squamosa cell carcinoma in their ears and they were divided into three groups for treatment. It was only given O_2 to one of the group, O_3 / O_2 mixed was given to other group by intraperitoneal method and the other group was determined as a control group. In a conclusion, it was found that the group treated with O_2 had the23.1% of survival rate of and the another group treated with O_3/O_2 had the 50 % of survival rate. Control group had the 7.1 of survival rate (Schulz et al., 2008).Studies have shown that ozone, especially in intervertebral disc herniated and lumbar pain animals, has been shown to be in parallel with similar studies in humans. This minimally invasive method has been found to be both cost effective as well as effective. It has been proved by studies that an improvement has been achieved. Thus, it is observed that invasive methods, which are frequently preferred in disc hernia patients, are not the first treatment method and minimally invasive methods are preferred more in the treatment (Yiğitarslan et al., 2018). In another study conducted with 60 cows with acute interdigital phlegmon, researchersfound that medical ozone gave better results than ceftiofur and oxytetracycline treatmentand that ozone therapy could be an alternative to antibiotics (Scrollavezza et al.,2002). A study carried out that *O. cynotis* infestation in cats, ozonated olive oil and some essential oils of marjoram (O. majorana L.) oil and garlic (A. sativum L.) oil was dropped 5 times (0.3 ml) in each ear for 10 days. It is concluded that it can be used ozone and the other treatment methods as an easy, inexpensive way. In this treatment researchers conclude that no side effect was observed and they were found to be quite reliable because of their natural origin, and they can be an effective treatment option without leaving residues (Yipel, 2014). In an another study it has been shown that intra-mammary ozone gas application is also effective on bacteriological and clinical improvement in the treatment of acute clinical mastitis caused by coagulase negative staphylococci and it may be an alternative to antibiotics and ozone has an inducing effect on release of endotoxins (Shinozuka et al., 2008; Sertkol, 2016). Treatment of urovaginitis, endometritis and retained placenta with ozone has been found that very effective. The cows ozone treated with showed increased conception rates this is likely due to its disinfecting effect coupled with an immunodulative capacity of the ozone at the level of contact with vaginal and cervical mucosa (Zobel et al., 2012; Zobel et al., 2014). In a study that conducted with dogs undergoing overiohysterectomy, they searched for ozone's analgesic effect. They administered the ozone by intrarectally and into acupoints and researchers find that ozone has an analgesic and no adverse effect (Duricic et al., 2015).

CONCLUSİON

With the current increase in medical costs and antibiotic resistant infections, O_3 therapy deserves more attention because it does not produce resistance and is extremely cheap. Since ozone therapy as a new approach, involves certain problems, including high level of tissue toxicity resulting from oxidation and lipid peroxidation leading to changes in membrane permeability as well as enzyme inactivation, it should be carefully evaluated before being introduced as a broad clinical application.

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