Ozonotherapy as a Method of Alleviating Symptoms of Oral Mucositis and other Selected Oral Diseases– Literature Review

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Abstract

Ozone (O3) is a variety of oxygen, consisting of triatomic molecules. For 150 years now, it has been used in various fields of medicine, including dentistry, due to its anti-inflammatory, analgesic and anti-microbial properties. This paper provides an analysis of the available literature from the last 10 years, aimed at evaluation of the effectiveness of ozonotherapy in alleviating symptoms of oral diseases, particularly oral mucositis – a serious complication of cancer therapy. Symptoms may include erythema and ulcerations accompanied by pain and difficulty eating. The literature review was performed. Several studies have demonstrated a significant effect of ozonotherapy on reduction of pain and improvement of the quality of life of patients undergoing surgical or periodontal treatment. There are few reports in the literature on the effectiveness of ozone therapy in relieving the symptoms of oral mucositis. Scientific studies have confirmed the analgesic, anti-inflammatory and regenerative properties of ozone.

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Introduction

Oral mucositis (OM) is a common complication of chemo- and radiotherapy implemented in the course of treatment against cancer. It also affects patients after stem cell transplantation. Symptoms may include erythema and ulcerations accompanied by pain and difficulty eating. It has a significant impact on patients' quality of life and further oncological treatment. There are various methods of alleviating symptoms of OM gathered, inter alia, in the MASCC/ISOO guidelines.[1] These recommendations are regularly updated and constitute a guide for clinicians in the fight against oral mucositis. Ozone is used in numerous areas of dentistry for its regenerative, analgesic and anti-inflammatory properties. There are few scientific reports on the effectiveness of ozone therapy in relieving oral mucositis symptoms; however, it has been successfully implemented in combating other diseases with accompanying pain and inflammation, e.g., periodontitis, periimplantitis, or lichen planus.

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Materials and methods

The literature review was performed in the databases: PubMed, Wiley, Springer. All English-language works on ozonotherapy for oral mucositis, published in the years 2011–2021, were included in the analysis. The search terms used were: 'Ozone oral mucositis', 'Ozone therapy oral mucositis', 'Ozone AND treatment AND "oral mucositis"'.

Results

The search yielded a total of 602 records. Studies concerning only the oral cavity area were selected for analysis. Articles on hyperbaric oxygen therapy as well as treatment of caries and root canal disinfection were rejected. Conference summaries, book chapters and abstracts were excluded. After disregarding duplicate records, the remaining articles were included in the analysis along with the literature. The articles were evaluated to determine whether they should be included in the literature review. A

total of 70 articles were evaluated for this work.

Oral mucositis

Oral mucositis (OM) is one of the most common side effects of chemo- and radiotherapy performed in the course of most cancer treatments.[2, 3] OM can also be observed after stem cell transplantation.[4] Inflammatory lesions of the oral mucosa are usually local, but in some cases the inflammatory process may also involve the entire gastrointestinal tract.[5] Literature data indicate diversified occurrence of OM. When chemotherapy is implemented, OM may be observed in 40–76% of patients, and in case of radiotherapy – in 60–80%.[2, 3, 4, 6, 7] With chemoradiotherapy, the percentage of OM occurrence is higher than with conventional chemotherapy, and after bone marrow transplant it can affect 70%–90% of patients.[4, 8] Symptoms usually develop 7–10 days after radiotherapy and 3–14 days after the commencement of chemotherapy, and intensify after 7–14 days.[2, 6, 7] In some patients, aggravated symptoms may appear at the end of radiotherapy and persist for 2 to 4 weeks after treatment.[9] Healing normally takes 2–4 weeks; however, recovery time may be longer in more severe course of OM.[2, 6, 7, 9] This condition may develop at an early stage of treatment. After the first cycle of chemotherapy, the incidence of OM can reach 18–40%.[3] In the case of radiotherapy (in cycles of 6–7 weeks), redness of the oral mucosa may appear 2–3 weeks after the commencement of treatment.[9] It is believed that in paediatric patients undergoing chemotherapy, OM may develop even in 80%–90% of cases (depending on the diagnosis and treatment), but then healing is more rapid.[6, 7] This tendency may result from both increased number and more rapid division of cells in the basal layer of the epithelium.[6, 7, 9]

The symptoms of OM are initially limited to erythema accompanied by a feeling of dryness in the mouth and general discomfort.[5,6,10]

Ulcerations of the mucosa appear over time, along with severe pain, spontaneous bleeding, difficulties swallowing food (odynophagia), or speaking.[2,4,5,6,9,10] These changes, if occurring together with neutropenia, may predispose patients to the development of bacterial and fungal infections.[11] Microorganisms present high adhesion to inflamed tissues, which leads to an increase in the number of the former in the oral cavity. In oncological patients, whose immune system is compromised, an infection may lead to numerous serious complications.[12] In the course of OM, malnutrition and weight loss may occur, which entails the necessity of introducing enteral feeding by a nasogastric tube or PEG (percutaneous endoscopic gastrostomy), thus prolonging the time of hospitalization.[1,2,3,4,5]

OM decreases the quality of life of patients and may be the reason for reducing the dose of chemotherapy or delaying oncological treatment. Consequently, the chance of curing the disease is lower and therefore the cost of therapy raises.[3,6,9,11,13] Tsuboi et al.[6] described the case of a 10-year-old female patient diagnosed with acute myeloid leukaemia, who developed mucosal ulcerations with oedema extending to the larynx. This made breathing difficult for the patient and led to the need for intubation. Yeon-Hee Lee et al.[8] assessed OM parameters in adult patients with acute leukaemia. They divided the subjects into a group with acute lymphoblastic leukaemia and those with acute myeloid leukaemia. The evaluation included the location of OM lesions and subjective sensations of patients. Higher levels of discomfort while swallowing, drinking, and sleeping were noted in myeloid leukaemia patients. Difficulties connected with food intake were reported in both groups. The location of oral lesions was also assessed in this study. The lesions most frequently appeared on the ventral part of the tongue, followed by the cheeks, soft palate and gingiva. The available literature suggests that OM lesions most often involve non-keratinised oral tissues: soft palate, laryngeal part of the pharynx, floor of the mouth, cheeks, lateral and ventral part of the tongue, and lips.[2,8,9]

There are several scales to assess the severity of OM. The most commonly used one is the scale according to WHO, which distinguishes the following grades:

0 –no clinical symptoms;
I°–reddening of the mucous membrane, erythema and discomfort;
II°– erythema, ulcerations, the patient can swallow solid food;
III° –the patient tolerates only liquid diet;
IV°– oral food intake is not possible, the patient requires parenteral nutrition.[2, 5, 9]

The National Cancer Institute's Common Terminology Criteria for Adverse Events(CTCAE) is a set of criteria to assess a patient's functioning and oral symptoms.[9] Other widely

implemented instruments include: the Oral Mucositis Assessment Scale (OMAS) and scales evaluating a patient's feelings, e.g., Patient-Reported Oral Mucositis Symptoms (PROMS) scale and Vanderbilt Head and Neck Symptom Survey (VHNSS).

Risk factors connected with OM include the oncological treatment applied and the neutrophil count.[5, 6, 9, 11] The incidence of OM is increased by chemoradiotherapy or bone marrow transplant.[5, 8] Chemotherapeutic agents that boost the development of oral lesions include: anti-metabolites (e.g., 5-fluorouracil, methotrexate, thioguanine, cytarabine), anti-mitotic drugs (vinblastine, vindesine, docetaxel) as well as actinomycin D, bleomycin, doxorubicin, and etoposide.[5, 11, 14] Factors related to radiotherapy include: fraction size, cumulative dose (approximately 15 Gy), size of the irradiated zone, and duration of treatment.[5, 13] According to the literature on the subject, oral lesions occur more frequently in patients with non-Hodgkin's lymphoma, Hodgkin's lymphoma, lymphoblastic leukaemia, or acute myeloid leukaemia.[15] Targeted therapies may exacerbate OM symptoms.[9] Reyes-Gibby et al. demonstrated a correlation between HPV infection and increased OM severity.[16] Among other risk factors, Epstein et al.[5] also mention the periodontal disease, nutritional status, comorbidities such as acquired immunodeficiency syndrome (AIDS), kidney disease, diabetes, as well as tobacco or alcohol use. Murphy et al.[17] indicate that OM develops in 20–30% of patients undergoing radiotherapy, and may reach 60–90% in case of patients subject to chemoradiotherapy. They also state that with accelerated combination treatment schemes, even 100% of patients may develop symptoms of OM. The recommendations of the European Oral Care in Cancer Group (EOCC) specify the following risk groups for oral damage or oral mucositis:[14]

- The low-risk group includes patients with no previous oral problems, with a low number of risk factors, undergoing therapy that is not expected to cause severe oral damage;
- The intermediate-risk group includes patients with previous oral damage, undergoing therapy that may cause moderate degrees of OM, those treated with low-dose radiotherapy targeted to the head and neck region, and people additionally burdened with other factors;
- The high-risk group includes patients with a history of moderate to severe oral complaints, those undergoing radical radiotherapy of the head and neck region, people burdened with additional risk factors, and those undergoing high-dose chemotherapy and/or radiotherapy prior to bone marrow transplant.

Risk factors include advanced age, malnutrition, and the use of stimulants.

Pathomechanism

The effect of cytotoxic drugs leads to apoptosis of both cancer cells and healthy tissues. Cells that regenerate rapidly – such as those present in the oral cavity – are particularly susceptible in this respect.[18] This results in decreased cell regeneration and epithelial thinning.[19] The development of oral mucositis involves 5 stages. In the first one, cell damage occurs as a result of oncological treatment through DNA damage or indirectly through reactive oxygen species (ROS). This leads to activation of pro-inflammatory cytokines, such as TNF-α, IL-1β and IL-6, responsible for tissue damage, apoptosis, and increased vascular permeability.[5, 20] Then basal cells of the epithelium are destroyed, which is followed by activation of the cyclooxygenase-2 (COX-2) pathway and increased expression of genes responsible for activation of pro-inflammatory cytokines.[21] The intensified inflammatory process results in the development of ulcers susceptible to bacterial infection. The final stage is healing of the mucosa, an important role in which is played by the extracellular matrix.[20, 21] Submucosal damage (apoptosis of fibroblasts and vascular endothelial cells) may occur even before epithelial damage.[21] The intercellular junctions and the extracellular matrix (ECM) are also disrupted in the course of oral mucositis. During the acute phase of mucositis, the expression of zonula occludens proteins, claudin-1 and occludin is reduced. The mediators TNF-α and IL-1β may affect the permeability of these proteins.[18] Nuclear factor kappa B (NF-κB) plays an important role as it affects the regulation of cyclooxygenase-2, increasing the level of prostaglandins, thus exacerbating the inflammatory process.[18, 22] NF-κB activation may be caused by toll-like receptors (TLR) in response to a bacterial infection.[22] Cytostatic

agents may also lead to the production of considerable amounts of ROS. It is known that ROS affect the NF-κB pathway, increasing gene expression of Il-6 and TNF. They are also responsible for activation of NLRs (nucleotide-binding domain, leucine-rich repeat containing proteins), which leads to the formation of pro-inflammatory cytokines.[3] Mitogen-activated protein kinases (MAPK) may also damage the mucosa. They participate in cell response and regulation of cell division. There are: ERKs (extracellular signal-regulated kinases), JNKs (c-Jun N-terminal kinases), and p38 protein isoforms. The ERK/MAPK pathway is responsible for stimulating cell division. Activation of JNK and MAPK leads to cell apoptosis. Pro-inflammatory cytokines and the bacterial factor, inter alia, are involved in activating the JNK pathway.[22] Sunavala-Dossabhoy et al.[19] described the following grades of oral mucositis based on histopathological assessment: grade 0 – no changes; 1 – a visible basal layer change, cells with atypia present within the nucleus, presence of ≤2 dyskeratotic cells; 2 – epithelial thinning and/or ≥3 dyskeratotic cells in the epithelium; 3a – loss of epithelium without loss of keratinised cell layer; 3b – vesicle under the epithelium; 4 – complete loss of cell layers, ulceration.

Methods of oral mucositis treatment

The Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO) publish and update recommendations regarding the treatment of OM symptoms.[1, 2] The latest guidelines were published in 2020. They are divided into 8 parts: 1) oral hygiene; 2) anti-inflammatory treatment; 3) photobiomodulation – including laser therapy; 4) cryotherapy; 5) anaesthetics, analgesics, and anti-bacterial agents; 6) cytokines and growth factors; 7) agents of natural origin; and 8) methods of gastrointestinal mucositis treatment. The clinical practical guide includes procedures aimed at preventing and alleviating the symptoms as well as treatment of OM. The preparations mentioned include: preventive honey-based preparations, benzydamine rinse in patients receiving moderate-dose radiotherapy in the head and neck region, zinc, keratinocyte growth factor (KGF-1), and palifermin.

Chlorhexidine (CHX) is recommended only in the case of coexisting oral infections. The parameters of photobiomodulation, based on the general treatment applied (haematopoietic cell transplantation, chemoradiotherapy, radiotherapy), have also been determined.[1] The European Organic Certifiers Council (EOCC) does not recommend anti-bacterial rinses for patients with severe OM. However, rinses such as Caphosol, Mugard or those containing benzydamine are suggested for use. Furthermore, such factors as intensification of oral hygiene procedures, administration of analgesics, and increasing the patient's nutritional status should also be considered.[14] Undeniably, the available data suggests an important role of proper oral hygiene in preventing OM.[1, 2, 14] In the literature on the subject, there are also reports regarding Magic Mouthwash which contains, inter alia, diphenhydramine, lidocaine or corticosteroids.[11] Research has also been conducted within the scope of effectiveness of other methods, e.g., melatonin gel, topical application of SIDR honey, traditional Chinese medicine, or ozonotherapy.[3, 12, 23]

Ozonotherapy

Ozone (O_3) is a triatomic molecule that has been used for over 150 years. The first portable ozone generator was patented by Nikola Tesla in 1896 in the United States. The effect of O_3 is of multidirectional nature, including anti-inflammatory, anti-oxidant, anti-microbial, analgesic effect, as well as improvement of blood flow and oxygenation, and boosting the healing processes.[24] According to the literature, ozone is applied in one of three forms: gas, ozonated water and oils.[25,26,27,28,29,30] The reported contraindications for their use are: pregnancy, hyperthyroidism, glucose-6-phosphate dehydrogenase deficiency (G6PDD), acute alcohol intoxication, haemorrhage, history of myocardial infarction, and myasthenia gravis.[29] Toxic effects of ozone include upper respiratory tract irritation, rhinitis, lacrimation, cough, nausea, vomiting, dyspnoea, vascular oedema, or stroke.[31] Complications are very rare (0.0007 per application). In case of ozone poisoning, it is recommended to position the patient on his or her back and implement oxygen therapy as well as treatment with ascorbic acid, vitamin E and n-acetylcysteine.[32] Ozone therapy is used in various fields of dentistry – conservative dentistry, endodontics, periodontics, or dental surgery. Ozone causes the cleavage of alkene double bonds in a reaction called ozonolysis.[33] It has

been demonstrated that O_3 can exert anti-inflammatory effect by blocking the activity of NF-κB, decreasing TNF-α levels, and reducing inflammation and cell apoptosis. It effectively reduces the content of IgE and inflammatory mediators due to its anti-oxidant capacity. Moreover, ozone reduces prostaglandin production by affecting the synthesis of arachidonic acid (responsible for reducing the inflammatory response).[34] Small doses of ozone increase the secretion of macrophages and leukocytes, and increase the phagocytic capacity of granulocytes. They also promote monocyte formation and T cell activation.[24]

Reactive oxygen species (ROS) play an important role in the inflammatory process. Antioxidants act as free radical scavengers, neutralising excess ROS. Antioxidant enzymes such as superoxide dismutase (SOD), catalase or glutathione peroxidase (GPx) are involved in the process of counteracting ROS.[35] Ozone stimulates the flow of oxygen across the cell membrane, activates superoxide dismutase, catalase, or peroxidase, and results in more efficient use of oxygen in the mitochondrial respiratory chain.[36] It also increases tissue oxygenation, improves the overall metabolism, and boosts the activity of antioxidant enzymes in cells.[37] Moreover, ozonotherapy improves blood circulation and enables type I collagen production, thus stimulating the immune system and accelerating wound healing.[34]

Anti-bacterial effect of ozone

According to in vitro studies, ozone therapy has been proven to offer a beneficial anti-microbial effect. In the study by Eick et al.[38] 23 periopathogen species were treated with ozone (Prozone). The effectiveness was over 90% when applied for 12 s for 10^3 microorganisms, and 18 s for 10^5 microorganisms. *Porphyromonas gingivalis* was sensitive to every ozone treatment. *Aggregatibacter actinomycetemcomitans* was almost completely eliminated after 18 s of exposure to ozone. *Enterobacter cloacae JGr1* was the most resistant – after two 18-second applications of ozone, 51% of the pathogens of this species were inactivated. Hauser-Gerspach et al.[39] studied the in vitro effect of ozone on bacteria involved in the development of periimplantitis. Ozotop (140 ppm) was used for 24 s in the study. Tests were performed on zirconium and titanium surfaces (smooth and rough surfaces, respectively). The level of *Porphyromonas gingivalis* was below the detection level on ozonated surfaces (reduction of >99.94% of microorganisms). There was a significant decrease of the content of *Streptococcus sanguinis* on both surfaces (>90%), but it was lower than in case of CHX implementation. This is attributed by the authors to lower effectiveness of ozone for biofilm-surrounded microorganisms. During the said study, the adhesion of odontoblast-like cells to ozone-treated surfaces was also assessed. It was demonstrated that ozone therapy does not affect the adhesion of these cells to the material. In the study by Güneş et al.[40] cavities in previously extracted molar teeth were treated by 5 disinfectants (benzalkonium chloride, chlorhexidine gluconate, sodium hypochloride, diode laser and ozone gas). Following cavity disinfection primer, bond and composite were applied. Microleakage was assessed using a microscope. The least microleakage was found in the ozone group, however, no results were not statistically significant. In vitro study by Yavuz et al.[41] showed that using ozone gas prior to adhesive systems had no negative effect on dentin shear bond strength.

In vivo studies also showed an increase of the evaluated parameters in ozone-treated patients. Isler et al.[42] conducted a study in 41 patients with periimplantitis symptoms, undergoing guided tissue regeneration of the periodontium. The study group included patients who received ozonotherapy and rinsed their mouth with saline solution to clean the implant surface. A significant increase was observed in the filling of the bone defect assessed on radiographs in the study group. There were no significant differences in plaque index (PI), gingival index (GI), probing depth (PD), and bleeding on probing (BOP) between the groups, but all parameters were improved. Arakawa et al.[43] described the case of a 43-year-old female patient with symptoms of periimplantitis. The researchers assessed bone levels on radiographic images, PD, BOP, and swelling around the implant. Despite indications for surgical treatment, it was decided to introduce non-surgical procedures. Every week, the patient's deposits were removed and irrigation with ozonated water (concentration of approx. 1.5 ppm) was performed. In addition, irrigation was also carried out at home (3 times a day). After 12 weeks, an improvement of the tested parameters

and a significant reduction in the red complex bacteria were observed. The literature also confirms a beneficial effect of ozone in reducing the risk of periimplantitis.[44]

Anti-inflammatory effect of ozone

Reports on the effectiveness of ozone therapy in non-surgical treatment of periodontitis are varied. In a study on chronic periodontitis, Dengizek et al.[45] used scaling and root planing supported by ozone therapy in a group of 20 patients (Ozone DTA, 3 W, on day 3 and 8 after treatment). The second group of subjects also consisted of 20 people and they underwent the same procedures with the exception of ozone therapy which was replaced with placebo. There were no statistically significant differences in the values of total antioxidant status (TAS), total oxidant status (TOS), nitric oxide (NO), PI, GI, PD, clinical attachment loss (CAL), 8-OHdG, myeloperoxidase (MPO), glutathione (GSH), and malondialdehyde (MDA) compared to the control group. TGF-β level was considerably higher in the ozonotherapy group. Rapone et al.[27] studied the effect of periodontal treatment (scaling and root planing) combined with ozonotherapy (in gaseous form) in patients with coexisting diabetes. The study was conducted for 12 months and included evaluation of the levels of BOP, PD, PI, CAL, and glycated haemoglobin (HbA1c). Improvement in the assayed parameters was noted; however, no statistically significant differences were found between the study and control groups. Tasdemir et al.[46] demonstrated no statistically significant changes in PI, GI, PD, BOP, CAL, IL-1β, and high-sensitivity C-reactive protein (hs-CRP) in a group of periodontitis patients undergoing non-surgical treatment combined with ozonotherapy. The parameters improved in all patients subject to non-surgical treatment. Only the level of pentraxin-3 (PTX-3) in gingival crevicular fluid was considerably lower in the group that received additional ozone therapy. The authors report that PTX-3 level reflects the status of inflammation. Al Habashneh et al.[47] also observed no statistically significant differences after ozonated water treatment for chronic periodontitis. Similar findings, based on the available literature, were reported by Moraschini et al.[48]

On the other hand, Hayakumo et al.[49] evaluated the effect of ozonated water on periodontitis treatment. Ozonated water (with ozone concentration of 1.5 mg/l) was used in the study group while performing periodontal debridement, and the control group was treated with water. Pocket depth, loss of connective tissue attachment, and bleeding on probing were assessed 4 and 8 weeks after the treatment. After 4 weeks, statistically significant differences were found between the study group and the control group. The values of pocket depth and the loss of connective tissue attachment were decreased. The number of bacteria in the subgingival plaque was also lower in the study group. Talmaç et al.[50] demonstrated the efficacy of ozone in its gaseous form in gingivitis patients (divided into smokers and non-smokers). All patients underwent scaling. In the study group, gaseous ozone (Ozonytron) was additionally applied for 60 seconds (every 2 days for a week). A significant improvement in the parameters of PI, GI and gingival bleeding time index (GBTI) was observed in the study group. Another study revealed a significant decrease in MMP-8 in saliva after periodontal treatment with ozonated oil as a rinse.[28]

Analgesic and healing-promoting effect of ozone

Several studies have demonstrated a significant effect of ozonotherapy on reduction of pain and improvement of the quality of life of patients undergoing surgical or periodontal treatment. Glória et al.[25] conducted a study on 20 patients. They underwent extraction of lower wisdom teeth by means of drills with a coolant of distilled water or ozonated water (at a concentration of 8.0 µg / mL). After 24 h, more pain was reported by patients who had been treated with ozonated water, but after 48 h and 72 h the severity of pain was significantly decreased compared to the other group. In a rat model study, Erdemci et al.[51] demonstrated the systemic effect of ozone in promoting bone healing after tooth extraction. The local effect of ozone therapy was not confirmed. Kazancioglu et al.[52] compared the influence of ozone and laser therapy on swelling and trismus after surgical removal of third molars. Pain levels and quality of life were also assessed. It was shown that both ozone and laser action significantly improved the assayed parameters, but ozonotherapy had no effect on swelling and trismus. Ozone therapy was demonstrated to effectively alleviate pain (assessed according to the VAS scale) in patients with temporomandibular joint disorders, compared to pharmacological treatment.[53] This

was probably due to the reactivity of ozone, which stimulates fibroblasts and growth cartilage. An anti-inflammatory effect and reduced risk of infection of the temporomandibular joint have also been cited as possible reasons.

Ozone therapy may be effective in healing wounds resulting from viral or fungal infections such as oral herpes.[54, 55] Therapy accelerates this process, and 25% of lesions may no longer recur.[56] After radiotherapy, mandible changes may occur due to obliteration of vessels within the bone. This affects the degree of tissue oxygenation and may result in slower bone healing after surgery. Ozone therapy may have a beneficial effect by improving the degree of tissue oxygenation and accelerating the healing process.[32] Arozal et al.[30] demonstrated the efficacy of topical ozonated olive oil (Dalethyne) in wound healing process. The researchers observed an increase of healing rate in a rat model of bacteria-infected skin wounds. Wound closure rate was significantly higher on skin injury infected by *Pseudomonas aeruginosa*. For incisions infected by *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Escherichia coli*, Dalethyne increased wound closure rate however results were not statistically significant. Batinjan et al.[57] described the case of a patient 7 months after radiotherapy, who underwent multiple extractions in the mandible. Before surgery, ozone therapy was performed to prevent osteoradionecrosis, and repeated after extraction and placement of sutures. The patient reported for follow-up after the procedure and ozone was demonstrated to contribute to preventing bone necrosis and accelerating wound healing after extraction of teeth. Akdeniz et al.[58] collected fibroblasts from the gingiva of patients. In vitro, these cells were treated with bisphosphonates which may cause bone osteonecrosis and development of wounds that are difficult to heal. Ozone-containing plasma at a concentration of 60 µg/µl was applied for 30 seconds every 24 hours. Decreased genotoxic effect among bisphosphonate- and ozone-treated cells as well as increased wound healing rates were observed. This may be due to improved blood circulation in tissues and their oxygenation, boosted metabolism of calcium, iron, or phosphorus, and effect on phagocytosis and diapedesis, which play an important role in the inflammatory process. Rowen et al.[59] described the case of a patient who developed symptoms of dermatomyositis such as muscle weakness, rash, and face shaped like a full moon. They were caused by inflammation within several teeth. Dental treatment supported by topical ozonotherapy were applied and the symptoms resolved. The authors emphasise the anti-infective effect of ozone and its role in stimulating the immune system. In a study by Veneri et al.[26] patients with oral lichen planus symptoms rinsed their mouth with ozonated or distilled water for 4 weeks. Corticosteroid therapy was also included in both groups. The researchers observed decreased pain level and lesion size, and higher EI (treatment efficacy index) in patients who had received ozonated water.

Taşdemir et al.[60] evaluated the effect of ozone therapy on healing processes after deepithelialized connective tissue grafts (DGG – Deepithelialized Gingival Grafts) surgery. The study was participated by 30 patients. The study group included patients who received additional ozonotherapy applied with an ozone generator immediately after as well as 1 and 3 days after the procedure. Blood flow (using a laser Doppler flowmeter), pain level according to the VAS scale, and Oral Health Impact Profile (OHIP) index of life quality were assessed. Statistically significant differences were found in the study: increased blood flow, lower level of pain, and higher OHIP in the study group, which could have led to faster healing of lesions after the surgery. Uslu et al.[61] described the study participated by 36 patients who underwent gingivectomy and gingivoplasty. They were divided into 3 groups: one had ozonotherapy performed, one had laser therapy, and the third one was the control group. A GaAlAs diode laser of wavelength length of 810 nm, power of 0.3 W, energy density of 4 J/cm^2 was used for 1 minute. Ozone therapy was performed by means of Ozone DTA- level 9 ozone generator for 1 minute for every 5 mm^2. Treatment was applied immediately, 3 days, and 7 days after the procedure. The assessed parameters included pain levels according to the VAS scale and quality of life based on the OHIP-14 questionnaire. Both forms of alleviating the symptoms were confirmed to have the expected effect: reduced pain, improved quality of life, and faster healing in the study groups. Isler et al.[62] also demonstrated the effectiveness of ozone in healing wounds formed on the palate after collection of free gingival graft (FGG). Reduced wound size was observed after ozonotherapy

compared to laser light irradiation. It was also demonstrated that both methods significantly reduced postoperative pain. Al-omiri et al.[63] conducted a study in 138 patients with recurrent aphthous stomatitis (RAS). The researchers applied ozonotherapy to 69 subjects using a HealOzone X4 ozone generator for 60 seconds. There was a decrease in size of lesions and reduction in pain level according to the VAS scale, which occurred faster than in the control group. Muric et al.[64] described the case of a patient with three ulcer-like lesions in the oral cavity, resulting from traumatizing effect of an implant-supported overdenture. Ozone therapy was applied by means of OzonytronX (10–100 μg/ml of ozone). After three applications, faster healing of the lesion and reduced pain were noted. There was also a study on 16 rabbits with induced recurrent aphthous stomatitis.[65] 8 of which received ozonotherapy applied with Ozonimed (for 40 seconds, level 9). The study group demonstrated fewer necrotic lesions, reduced amounts of eosinophils and neutrophils, and higher numbers of fibroblast and histiocytes. Epithelial recovery was also observed.

Ozonotherapy in the treatment of oral mucositis

There are few reports in the literature on the effectiveness of ozone therapy in relieving the symptoms of oral mucositis. Scientific reports have confirmed the analgesic, anti-inflammatory and regenerative properties of ozone. Ozonotherapy significantly improves blood supply to tissues and has a bactericidal effect, which promotes healing.[13, 66] It also regulates the level of cytokines.[54, 55] Ozone can be effective both in the gaseous form and as ozonated water.[66] Some reports suggest that the water used as oral rinse is more recommended due to the lower risk of entering the lungs.[67] There are available studies on the efficacy of ozonated sunflower oil (Oleozon) in relieving oral mucositis symptoms, compared to nystatin and CHX therapy, in children undergoing chemotherapy.[68] The effect of ozonotherapy in treating OM symptoms has been confirmed in studies on animal models.

Hayashi et al.[12] conducted a study on 21 rats treated with 5-fluorouracil for 6 days. On day 7 of the experiment, the rodents had 100% acetic acid (50 μl) injected onto the dorsal part of the tongue under anaesthesia. The animals were divided into 3 groups: 7 rats were not treated at all (control group), another 7 individuals – were treated with saline solution, and the remaining 7 animals had treatment with water ozone bubble applied. After the development of oral mucositis, the animals had their mouth rinsed 4 times a day with appropriate solutions, depending on the group. The quantity of bacteria, the weight of the rats, and the severity of oral mucositis according to the NCI-CTCAE scale were evaluated. Measurements were made 3, 5, and 10 days after acetic acid administration. The study revealed differences in the severity of symptoms. In the study group treated with ozone, a lower degree of oral mucositis was observed compared to the other groups. Furthermore, improvement was more rapid in these rats (day 11 of the study, day 16 in the other study group, no improvement in the control group). Bacterial counts decreased over time in all animals, but the decrease was the most significant in the ozone-treated group. A decrease in weight was initially observed in all the rodents, which may have been related to pain and difficulty in food intake. On day 16 of the study, a considerable increase in weight was observed in the ozone-treated group. This may have been caused by less pain felt by this group as well as lower severity of OM symptoms. No side effects were reported during the ozone treatment.

There was also no development of bacterial resistance. Bayer et al.[69] conducted a study on 24 rats treated with 5-fluorouracil. The cytotoxic agent was administered on days 1 and 3 of the experiment. On days 3 and 5, scratches of the buccal mucosa were made with a needle, resulting in the development of ulcerative lesions of OM nature. The rats were divided into 3 groups: the controls, those with laser therapy included, and a group with ozone therapy applied. The animals were weighed and fed daily. Four rats from the control group died due to aggravated oral mucositis. Laser therapy was performed with a diode laser (Epic, BioLase, wavelength of 940 nm) for 20 s per spot, = 7.14 J/cm^2 for 5 days. Ozone therapy was performed with an ozone generator (BiozonixGMbH) for 120 s, for 5 days. After treatment, the rats were subjected to general anaesthesia, and had a specimen collected for examination from the lesion area. The concentration of basic fibroblast growth factor (bFGF), transforming growth factor β (TGF-β), and platelet-derived growth factor (PDGF) – anti-inflammatory factors that play an

important role in wound healing – were evaluated. No statistically significant differences in TGF-β levels were observed between the groups. There was a notable increase in PDGF in the laser-treated group. The level of bFGF was elevated in both study groups, and higher in the laser-therapy group. The authors demonstrated the effectiveness of ozone and laser therapy in the treatment of oral mucositis, suggesting higher efficacy of laser.

There have been few clinical evaluations offering hope for successful use of ozone therapy in relieving OM symptoms. Oldoini et al.[70] described the case of an adult patient with acute lymphoblastic leukaemia, receiving ozone treatment. In the second cycle of blinatumomab treatment (after 7 days), an ulcerative lesion appeared on the palate, which did not respond to therapy for 25 days (with anti-mycotic medications, antibiotics, or analgesics).

Therefore, anti-tumour therapy was suspended. The patient reported severe pain, problems with food and fluid intake and, consequently, a feeling of dry mouth. Fungal lesions also developed in the oral cavity. Ozone therapy was then implemented by means of the OZONE DTA generator every 2 days. In addition, anti-fungal and analgesic treatment was administered. The first ozone treatment consisted of 5 applications of 2 minutes each, with power gradually increased from 5 to 9 (ozone concentration 10 – 100 μg/ml). The patient experienced a reduction of pain already after the first application, and was able to swallow water. After two days, there was visible improvement in the local oral condition: reduction in swelling as well as size of the lesion. After the second treatment, an increase in saliva secretion was observed, and the patient stopped taking opioid analgesics. The fungal lesions also decreased. After 15 days, anti-fungal therapy was restored due to the improvement of the oral condition. After 22 days, ozonotherapy was discontinued as the lesion healed. Yildirim et al.[67] described the case of a 7-year-old patient diagnosed with Burkitt lymphoma, treated systemically with methotrexate, vincristine, adriamycin, prednisolone, and cyclophosphamide. He developed symptoms of oral mucositis, resulting in weight loss and deterioration of blood parameters. The use of ozonated water was introduced, and the patient reported a decreased level of pain after just one day. On day 3 of the treatment, the patient began eating solid foods. The therapy was continued for 7 days (until complete healing of the lesions and improvement in blood parameters).

Conclusions

Ozone therapy undoubtedly aids treatment due to its anti-inflammatory and analgesic properties as well as the fact that it stimulates healing. These benefits can be used in the treatment of oral mucositis; however, the currently available data is insufficient and further studies are required on the subject.

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Declaration of Interest

The authors report no conflict of interest.

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