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Use and Applicability of Ozone Therapy in Clinical Practice in Dentistry: An Integrative Review

Uso y Aplicabilidad de la Ozonoterapia en la Práctica Clínica en Odontología: Una Revisión Integradora

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ABSTRACT: Ozone is a colorless gas with a characteristic odor present in nature in the form of trivalent oxygen. In 2015, the Federal Council of Dentistry (CFO/Brazil) approved the use of ozone therapy and in 2018 the Ministry of Health (MS/Brazil) approved the application of Ozone Therapy as a Complementary Integrative Practice in the Unified Health System. Therefore, the objective of this study was to verify the applicability of ozone therapy in dental practice. This is an integrative literature review whose search was performed in the Medline/Pubmed, LILACS, SciElo, and Google Scholar databases. Studies published in the last 5 years in English, Portuguese or Spanish were eligible. After the search, 312 titles were found and after exclusion of duplicates and analysis of abstracts and full text, 13 articles were included in this review. The literature reports the application of ozone therapy in several areas in the treatment of acute and chronic diseases. As a mechanism of action, ozone has a direct antimicrobial effect, immunoregulation, antioxidant defenses, analgesic, and vasodilator effects. In dentistry, its applicability is mainly in preventive dentistry and as a complement in surgical procedures, endodontic, and periodontal treatments.

KEY WORDS: ozone, dentistry, therapeutics.

INTRODUCTION

Ozone is a powerful oxidizing agent that exists in nature as trivalent oxygen (O3). It is a colorless gas with a pungent odor with a high disinfecting power capable of effectively destroying bacteria, viruses, and spores in a few seconds. After the first experiments, the use of ozone was abandoned because of toxicity, since no way to concentrate the gas without residues was found (Saini, 2011).

According to resolution 166/2015 of the Federal Council of Dentistry (Conselho Federal de Odontologia, 2015) Art. 1st. ozone, produced from pure oxygen in precise concentrations according to the therapeutic window, can be used in Dentistry, entitled Ozone Therapy (Conselho Federal de Odontologia, 2015). Ozone therapy was also included by the Ministry of Health in the National Policy on Integrative and Complementary Practices (NPICP) and covers several areas of health, including Dentistry, thus being offered in the Unified Health System (Ministério da Saúde, 2017).

Ozone is a biostimulatory agent, which recruits important cells of the immune system through a complex biochemical oxireduction reaction. Thus, ozone therapy can act by modulating the inflammatory response, enhancing repair processes, and stimulating or even suppressing the immune system (Beretta & Federici, 2017). Medicated ozone therapy has also been shown to increase the number of inflammatory

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mediators, have an analgesic action promoted by modulating inflammation, promote excellent microcirculation, and increase the number of osteoblasts and osteoclasts (Faccini *et al*., 2021). Thus, this study aimed to conduct a literature review on the applicability of ozone therapy in dentistry.

MATERIAL AND METHOD

This is an integrative literature review whose search was carried out through the Virtual Health Library (VHL/BIREME) in the following databases: Medline/PubMed, Latin American and Caribbean Literature on Health Sciences (LILACS), Scientific Electronic Libary Online (Scielo), and Google Scholar. A set of MeSH terms and synonyms that could encompass the largest number of studies related to the reviewed topic was used. The search terms were: Ozone therapy; Ozone; Dentistry; Treatment.

Studies published in Portuguese, Spanish, or English in the last five years that reported the therapeutic and/or aesthetic applicability of ozone therapy in Dentistry and related areas were included. The selection of studies was carried out in two stages. In step one, titles and abstracts of studies potentially relevant to the inclusion criteria were examined. In step two, the full text of all selected articles was accessed and studies that did not meet the inclusion criteria were removed. The level of evidence of the selected and included studies was classified according to the methodology of Souza *et al*. (2010) (Table I).

The general combination of data from the included studies was carried out through descriptive synthesis.

RESULTS AND DISCUSSION

After applying the search strategy, 312 citations were identified in three electronic databases. After removing duplicate articles, 234 citations remained. After an exhaustive review of titles and abstracts, 178 references were excluded. Manual searching from the reference lists of identified studies provided only one additional study. Therefore, 44 articles were kept for full-text analysis. This process led to the exclusion of 31 studies (Fig. 1). In total, 13 articles were selected for data extraction and qualitative synthesis. The flowchart (Fig. 1) details the process of identification, inclusion, and exclusion of studies.

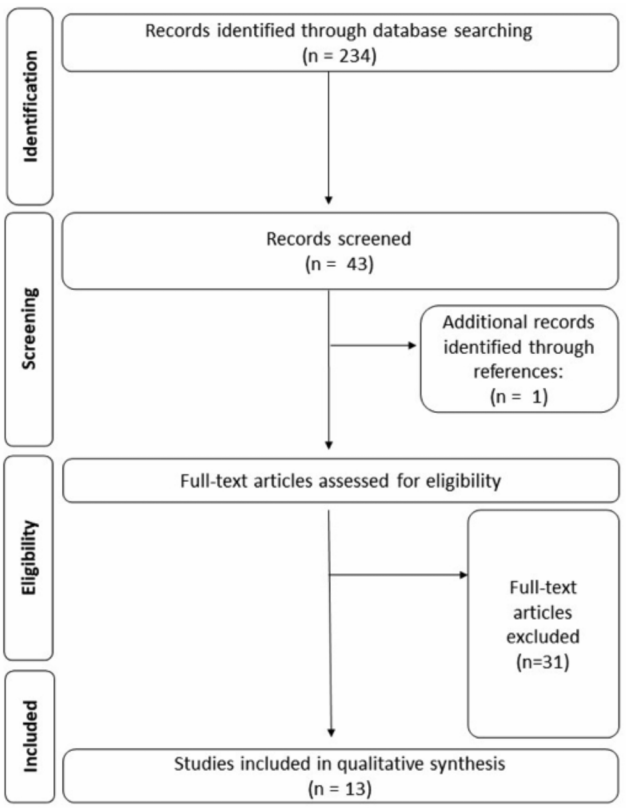

Fig. 1. Review flowchart.

The included studies (Table II) were published in Portuguese, Spanish, and English between 2016 and 2021 and comprise levels II and V of evidence.

Ozone therapy has been used for therapeutic purposes since the XIX century. The first mention of ozone was made by the Dutch physicist Martin van

Table I. Classification of evidence levels of selected studies.

Level I	Evidence from the meta-analysis of multiple randomized controlled trials.
Level II	Evidence was obtained from individual studies with an experimental design.
Level III	Evidence from quasi-experimental studies.
Level IV	Evidence from descriptive (non-experimental) or qualitative studies.
Level V	Evidence from case reports or experience.
Level VI	Evidence-based on expert opinion.

Table II. Studies included in the review.

First Author, year	Level of Evidence	Objective	Conclusions
Al-Omiri *et al.,* 2017	Level II	To evaluate the use of ozone in the treatment of recurrent aphthous stomatitis.	The application of ozone for 60 seconds led to a reduction in pain levels as well as improved healing of ulcers, reducing the size and duration of the lesions.
Tiwari, 2016	Level IV	Highlight the various treatment modalities of ozone therapy and their possible clinical applications in the future.	Ozone therapy has a wide range of applications in almost all areas of dentistry. Its unique properties include immunostimulating, analgesic, antihypnotic, detoxifying, antimicrobial, bioenergetic, and biosynthetic actions. Its atraumatic, painless, non-invasive nature and the relative absence of discomfort increase patient acceptability and compliance, making it an ideal treatment choice, especially for pediatric patients.
Alkan, 2017	Level II	To evaluate the effects of ozone application and prophylactic antimicrobials on the shear strength and rupture interfaces of orthodontic brackets.	The shear strength of orthodontic brackets and ARI scores was not negatively impacted by ozone application.
Beretta & Federici, 2017	Level II	To evaluate the clinical efficacy of a new procedure for the treatment of deep caries in posterior primary teeth.	The proposed procedure has a high success rate if the dental pulp is not affected and uncovered, with rates comparable to those of pulpotomy, but with considerable savings in healthy tissue and surgical time.
Caixêta, 2019	Level IV	Review about ozone therapy in infection control in oral surgery.	Ozone therapy is a low-cost, long-term therapeutic option with predictable results. Ozone treatment has been more favorable than traditional therapeutic modalities and can bring great benefits to dentistry. Subjecting patients to ozone therapy can shorten treatment time and eliminate unwanted microorganisms. Treatment is usually painless and has minimal adverse effects. However, one must be aware that, currently, ozone, in most protocols, is a complementary therapy to other therapeutic modalities.
Cosola *et al.*, 2019	Level III	To compare the clinical efficacy of chlorhexidine and ozonated water in maintaining oral hygiene in orthodontic patients.	Ozone showed better results than chlorhexidine in the treatment of gingivitis in orthodontic patients. Ozone should be investigated in longitudinal studies with larger samples.
Gandhi *et al.,* 2019	Level II	To evaluate and compare the clinical and microbiological efficacy of ozone and chlorhexidine as an adjunct to scaling in patients with chronic periodontitis.	Ozonated olive oil can be used as an adjuvant subgingival irrigant in patients with chronic periodontitis.
Monzillo *et al.*, 2020	Level III	Antimycotic efficacy of an ozonated oil as a possible therapeutic alternative in the local treatment of these infections, compared to chlorhexidine digluconate.	No significant differences were found between the growth inhibition zone of ozonated gel and chlorhexidine. The results indicated that the ozonized gel can help fight Candida infections. In addition, user applications can be used to counteract Candida colonization of endosseous implants.
Oldoini *et al.,* 2020	Level V	To report an ulcerative lesion located in the soft palate treated with ozone as adjuvant therapy in a leukemic patient undergoing an intensive chemotherapy regimen.	Ozone therapy should be considered a useful tool for the adjuvant therapy of oral complications in cancer patients.
Santos *et al.,* 2020	Level I	Investigate the efficacy and safety of ozone therapy for the treatment of dental caries.	Most of these results were imprecise and should be interpreted with caution due to clinical and methodological concerns, small sample size, and wide confidence interval, preventing the determination of the true direction of effect.
Colombo et al., 2021	Level II	To evaluate the effectiveness of the subgingival application of an experimental ozone gel in addition to standard scraping, as well as comparing this protocol with scraping plus a conventional chlorhexidine gel.	In addition to scraping, the use of ozonated gel can be considered a substitute for chlorhexidine, especially considering the main deficiencies associated with it.
Serrano Corrales *et al.*, 2021	Level IV	To evaluate the effectiveness of ozone therapy in the treatment of chronic gingivitis in adolescents.	Ozone therapy was considered an effective treatment for chronic gingivitis in the adolescents studied.
Faccini, 2021	Level II	To histologically evaluate the effect of ozone therapy on the induction of orthodontic force in an animal model.	Ozone therapy increased the number of osteoclasts on the pressure side and osteoblasts on the tension side, at a concentration of 10 _g/mL, demonstrating favorable histological parameters for bone remodeling. The ozone concentration of 60 _g/mL accelerated the periodontal ligament reorganization process.

Marun in 1785, but it was Christian Friedrich Schonbein in 1839 who demonstrated the changes in the properties of oxygen with the formation of the specific gas called ozone (Naik *et al*., 2016). Ozone is an unstable molecule composed of three oxygen atoms that can quickly decompose into oxygen and a single oxygen atom acting as a strong oxidant to kill microorganisms. Therefore, in adequate concentrations, it serves as an ideal drug. Notably, due to its easy dissolution, ozone can be used safely in health, although it is released into the blood, where it has a potent antioxidant capacity composed of a series of lipophilic, hydrophilic compounds, and a variety of antioxidant enzymes (Zeng & Lu, 2018).

Medical ozone preparations were mainly classified as ozone hydrotherapy, externally used ozonated oil and ozone autohemotherapy. Recently, it has been used to treat four types of skin diseases: (1) infectious skin diseases containing viruses, bacteria, and fungi, such as herpes zoster, abscess, and athlete's foot; (2) allergic diseases such as atopic dermatitis, eczema, urticaria (ozone autohemotherapy) and pruritus; (3) diseases with scaly erythema, such as psoriasis and pustulosis palmoplantar; (4) wound healing and ulcer recovery (Borges *et al*., 2017; Zeng & Lu, 2018).

The mechanisms of action of ozone are common to all species involved in the direct antimicrobial effect, immunoregulation, antioxidant defenses, and epigenetic modification, yet other potent properties such as biosynthetic, analgesic, and vasodilatory effects. First, ozone directly disrupts the nucleic acid or liposomal layer of microorganisms. After the membrane is damaged, permeability increases, and ozone molecules can easily enter cells (Zeng & Lu, 2018). Furthermore, it generates molecular level reactions in the medium where it releases oxygen free radicals and then indirectly destroys the microenvironment. Ozone immunoregulation in the treatment of diseases is generally accepted that, on the one hand, it increases the number of leukocytes, increases the phagocytic capacity of granulocytes, facilitates the formation of monocytes, and activates T cells. antibody-dependent cellular cytotoxicity. And on the other hand, it increases the production of hydrogen peroxide derived from the body's immune cells to destroy pathogens (Kucuksezer *et al*., 2014).

Histologically, ozone therapy was able to induce the action of osteoclasts on the pressure side and osteoblasts on the tension side, at a concentration of 10 mg/mL, during the evaluated period, demonstrating histological parameters favorable to bone remodeling. At a concentration of 60 mg/mL, ozone therapy accelerated the periodontal ligament reorganization process (Faccini *et al*., 2021).

Recent studies have proven the analgesic and anti-inflammatory action of ozone therapy. These effects seem to be due to its way of acting on several targets as it decreases the production of inflammation mediators, inactivating metabolic pain mediators. In addition, it improves local blood microcirculation, with an improvement in the supply of oxygen to the tissues, essential for the generation of anatomical structures and the elimination of toxins and, in general, for the resolution of the physiological disorder that generated the pain.

Thus, ozone helps in the synthesis of biologically active substances such as interleukins, leukotrienes, and prostaglandins, which are beneficial in reducing inflammation and pain (Caixêta *et al*., 2019). The study conducted on the anti-inflammatory effects of ozonated water in an experimental mouse model suggested that ozonated water has anti-inflammatory properties and is a potential therapeutic option for acute inflammation.

In Dentistry, ozone therapy has been applied as a therapeutic adjuvant in acute and chronic diseases. Ozone is used in low concentrations and, therefore, can be considered a safe treatment when used correctly by a qualified professional. Shekhar *et al*. (2021) evaluated the effect of ozone therapy on inflammation, pain, and wound healing after implant surgery. They observed that ozone therapy accelerated healing, minimized tissue inflammation, and lessened pain. Osteotomy was performed with saline irrigation in the control group and, in the experimental group, irrigation was performed with ozonated water, together with ozone gas. The assessment was done by measuring C-reactive protein for inflammation, using the Visual Analog Scale for pain and wound healing index for tissue healing.

Al-Omiri *et al*. (2017) investigated the effectiveness of ozone therapy in the treatment of the recurrent aphthous lesion. The test group was exposed to airborne ozone for 60 seconds, while the control received air alone. They observed that ulcer size was reduced from the second day in the test group and pain levels were reduced from the first day in the same group. Ulcer duration, ulcer size after day 2, and pain levels were further reduced in the test group. In

conclusion, the application of ozone to lesions for 60 seconds reduced pain levels and increased ulcer healing, reducing ulcer size and duration. Oldoini *et al*. (2020) reported the importance of ozone therapy in the treatment of oral lesions in cancer patients undergoing chemotherapy.

Ozone therapy proved to be superior to conventional techniques in terms of its ability to neutralize or inhibit bacterial growth in the oral cavity. Therefore, topical application of ozone can be effective in healing oral lesions caused by viruses (Human Herpes virus) and fungi (Candida albicans) that were aggravated by a bacterial infection (Al-Omiri *et al*., 2017; Silva *et al*., 2021). Tiwari *et al*. (2006) state that in vitro studies indicate that ozone can be used as a prophylactic antimicrobial agent before acid attacks and restorations.

Beretta & Canova (2017) found that once ozone was applied, it was possible to maintain a layer of dentin that could be called "ex-carious" that avoided pulp exposure and subsequent pulpotomy. The use of this new technology is more effective for the eradication of cariogenic bacteria than the classic protocol.

The antimicrobial effect of ozonated water on the bacteria that invade the dentinal tubules was observed in the use of ozone as an irrigating agent and as an intracanal medication, and its therapeutic application to the canal system represents a biological treatment, painless to the patient, capable of improving the asepsis of the channels and considered an adjunct to conventional treatment, with antimicrobial action and biocompatibility (Silva *et al*., 2021). Fernandes *et al*. (2021) highlighted that ozone is capable of inactivating microorganisms through the direct oxidation of its structural components and can be proposed as an adjunct in endodontic treatments against Gram-positive and Gram-negative bacteria present in the oral cavity and root canals.

Alkan *et al*. (2017) state that ozone gas as a useful prophylactic antimicrobial application used before acid etching and orthodontic bracket placement had no negative impact on the bond strength values of orthodontic brackets.

In Periodontics, ozone acts as a bactericide and stimulator of the repair process and can be used in the treatment of periodontitis and peri-implantitis, reducing the clinical course of these pathologies. Experimentally, the application of systemic ozone was found to be more effective in reducing alveolar bone loss in rats. It has also been shown to be an effective treatment for chronic fibroedematous gingivitis in adolescents, resulting in healthier gums in less time and a greater number of patients compared to the control group (Serrano Corrales *et al*., 2021). Cosola *et al*. (2019) attest that the oral ozone delivery device had better results than home use of chlorhexidine mouthwash in reducing plaque and bleeding on probing at a 1-month evaluation.

A study carried out by Gandhi *et al*. (2019) attested that the adjuvant use of ozonated olive oil in the treatment of chronic periodontitis significantly improves clinical and microbiological outcomes and is as effective as chlorhexidine, while being free of adverse effects. Colombo *et al*. (2021) reported that the use of ozonated gel within a protocol for the non-surgical treatment of periodontal disease represents a valid approach, even if without a greater effect compared to the group undergoing standard scaling and root planing plus chlorhexidine. This antimycotic efficacy of the ozonized gel is due to the oxidation of microorganisms by the slow release of peroxides (Monzillo *et al*., 2020). However, it is important to consider that chlorhexidine may have cytotoxic effects, which may be a valid reason to prefer the use of ozone in periodontal therapy.

In the context of Aesthetics, whitening combining ozone and hydrogen peroxide produced better tooth tones than whitening with hydrogen peroxide alone. Bleaching with 38 % H_2O_2 for 20 min combined with ozone for 60 seconds produced similar results regardless of whether ozone was applied before or after H_2O_2. Regarding sensitivity to bleaching, ozone application after H_2O_2 was preferable (Al-Omiri *et al*., 2017).

Berretta & Canova (2017) investigated the application of ozone in carious lesions in primary teeth. They observed that after performing partial removal of carious dentin and sterilizing the remaining tissue with ozone, a high success rate was obtained if the dental pulp was not affected, with considerable savings in healthy tissue and surgical time. However, the technique can only be performed if there is no obvious preoperative pulp exposure. The proposed protocol was effective and efficient in the treatment of deep carious lesions of deciduous teeth.

Furthermore, Nogaleset *et al*. (2008) state that the future of ozone therapy should be focused on the establishment of safe and well-defined parameters in controlled clinical studies, to determine the precise

indication and guidelines for the treatment of various dental pathologies. This highlights the relevance of ozone therapy techniques with safely defined and appropriate protocols in the treatment of various pathological conditions. Despite the diversity of studies that recommend ozone therapy, further investigations are still needed, mainly measuring the antimicrobial effects in long-term follow-up (Santos *et al*., 2020).

CONCLUSION

The literature reports that Ozone Therapy has been applied in several areas of health in the treatment of acute and chronic diseases. In Dentistry, it has been used in preventive dentistry, caries treatments, root canal treatments, gingival treatments, periodontal surgeries, implants, and extractions. It is considered a therapy that uses ozone gas safely and effectively as it does not release chemical residues. As a mechanism of action, it has a direct antimicrobial effect, immunoregulation, antioxidant defenses, analgesic, and vasodilator effects. However, it is contraindicated in patients with heart problems, pregnant or lactating women, and patients with severe anemia and severe myasthenia, thrombocytopenia, and hyperthyroidism. Therefore, it is still necessary for new controlled and randomized clinical studies to investigate new possibilities for its therapeutic use.

CONFLICT OF INTERESTS. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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RESUMEN: El ozono es un gas incoloro de olor característico presente en la naturaleza en forma de oxígeno trivalente. En 2015, el Consejo Federal de Odontología (CFO) aprobó el uso de la ozonoterapia y en 2018 el Ministerio de Salud aprobó la aplicación de la Ozonoterapia como Práctica Integrativa Complementaria en el Sistema Único de Salud. Por lo tanto, el objetivo de este estudio fue verificar la aplicabilidad de la ozonoterapia en la práctica odontológica. Esta es una revisión integrativa de la literatura cuya búsqueda se realizó en las bases de datos Medline/Pubmed, LILACS, SciElo y Google Scholar. Fueron elegibles los estudios publicados en los últimos 5 años en inglés, portugués o español. Después de la búsqueda, se encontraron 312 títulos y después de la exclusión de duplicados y análisis de resúmenes y texto completo, se incluyeron 13 artículos en esta revisión. La literatura reporta la aplicación de la ozonoterapia en varias áreas en el tratamiento de enfermedades agudas y crónicas. Como mecanismo de acción, el ozono tiene un efecto antimicrobiano directo, de inmunorregulación, defensas antioxidantes, efectos analgésicos y vasodilatadores. En odontología su aplicabilidad es principalmente en odontología preventiva y como complemento en procedimientos quirúrgicos, tratamientos endodónticos y periodontales.

PALABRAS CLAVE: ozono, odontología, terapéutica.

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