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| ORIGINAL

Effectiveness of ozone therapy in the treatment of periodontal diseases: a systematic review

Eficácia da ozonioterapia no tratamento de doenças periodontais: uma revisão sistemática

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ABSTRACT

The aim of this study was to evaluate the effectiveness of ozone as an adjuvant factor in the treatment of periodontal diseases. A systematic review was carried out using the PubMed, LILACS/BIREME, CoChrane, and Scielo databases and manual searches. Clinical studies published in English, Spanish, Portuguese, and French, between 1950 and 2020 that evaluated the effects of ozone in the treatment of periodontal diseases were included. The search resulted in 178 articles, of which 24 met the proposed eligibility criteria and were selected for this review. The risk of bias was assessed for each selected study in accordance with the Cochrane risk-of-bias tool - version 5.1.0. The selected studies evaluated the effect of ozone therapy on periodontitis, gingivitis, and peri-implant diseases. It was observed that the ozone in its oily form presented the best clinical results. In cases of periodontitis, it was concluded that ozone therapy in the gaseous form did not bring any additional benefit. With respect to gingivitis, ozone provided faster remission compared to the control group. And in peri-implant disease cases, ozone had the capacity to reduce the development of mucositis. Regarding microbiology, it was observed that ozone can continuously and significantly reduce periodontal microorganisms; however, with no difference from control groups. Further studies with adequate control of biases are suggested, using ozone in the oily or aqueous form, which are the most promising forms, also evaluating the possible effectiveness of ozone by-products.

Indexing terms: Ozone. Peri-implantitis. Periodontal diseases.

RESUMO

O objetivo deste estudo foi avaliar a eficácia do uso do ozônio como fator adjuvante no tratamento das doenças periodontais. Foi realizada uma revisão sistemática utilizando as bases de dados PubMed, LILACS/BIREME, CoChrane, Scielo e pesquisa manual. Foram incluídos estudos clínicos publicados em inglês, espanhol, português e francês entre 1950 e 2020, que avaliaram os efeitos do ozônio no tratamento de doenças periodontais. A busca resultou em 178 artigos, destes 24 estudos atenderam aos critérios de elegibilidade propostos e foram selecionados para esta revisão. Foi realizada a avaliação do risco de viés em cada estudo selecionado de acordo

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com a ferramenta de avaliação de risco de viés Cochrane Risk of Bias Tool - versão 5.1.0. Os estudos selecionados avaliaram o efeito da ozonioterapia na periodontite, gengivite e em doenças peri-implantares. Observou-se que a utilização do ozônio na forma oleosa foi a que apresentou os melhores resultados clínicos. Nos casos de periodontite, concluiu-se que a ozonioterapia não trouxe nenhum benefício adicional sob a forma gasosa. Em relação à gengivite, o ozônio proporcionou uma remissão mais rápida do que do grupo controle. E nas doenças peri-implantares, o ozônio foi capaz de reduzir o desenvolvimento da mucosite. Com relação a microbiologia, foi observado que o ozônio pode reduzir contínua e significativamente os microorganismos periodontais, contudo, sem diferença para grupos controle. Sugerem-se mais estudos com controle adequado de vieses, utilizando o ozônio de forma oleosa ou aquosa, formas mais promissoras, além da avaliação de possível eficácia de subprodutos do ozônio.

Termos de indexação: *Ozônio. Peri-Implantite. Doenças periodontais.*

INTRODUCTION

The development of periodontal diseases has been associated with anaerobic bacteria that initially affect the protective periodontium and can later reach the attachment periodontium, leading to bone destruction. As a result of this process, tooth mobility and even total tooth loss can be observed. Periodontitis is an inflammatory, chronic, multifactorial disease that begins with the accumulation of bacteria and their metabolic products. Thus, there is migration of the junctional epithelium in the apical direction, which promotes the deepening of the gingival sulcus and the formation of periodontal pockets associated with attachment loss [1].

Tobacco smoking, diabetes, medication, age, hereditary, and obesity have been related to increased risk of periodontal diseases. Similarly, other studies have suggested association between periodontal diseases and other diseases such as diabetes, hypertension, asthma, liver diseases, among others [2]. Many studies have also suggested important association between periodontal disease and cardiovascular diseases, concluding that periodontal disease is a potential risk factor for cardiovascular events, such as stroke and coronary heart disease. Furthermore, it has been demonstrated that individuals with periodontitis have increased risk of developing cardiovascular diseases, including myocardial infarction, heart failure, peripheral artery disease, atherosclerosis and stroke [3].

In addition, there are a number of factors that favor the accumulation of dental biofilm, such as crowding, unsatisfactory restorations, poor contact point, mouth breathing and caries [4]. For better control of the disease, periodontal treatment should be based on controlling the biofilm and the host response. The initial phase is the supra- and subgingival mechanical debridement, which, although being the most important part of the treatment, cannot completely eliminate periodontal microorganisms, especially in very deep pockets (greater than 5-6mm) and furcation lesions [5].

Subgingival instrumentation failures reflected in periodontium with persistent inflammation can lead to indication of surgical procedure, which, in turn, can cause soft tissue recession and esthetic dissatisfaction [6]. To enhance mechanical debridement, topical or systemic antimicrobial agents have been developed. Long-term use of systemic antibiotics is not recommended, as bacterial resistance may develop, in addition to their undesired adverse effects. The topical use of mouthwashes has some limitations as they do not seem to penetrate more than 3mm into pockets and may have poor substantivity [5].

In literature, there is controversy regarding the synergistic effect of subgingival irrigation combined with scaling and planing of root surfaces. Some authors believe that in this way, it is possible to release antimicrobial agents deep into pockets, thus being more effective in stopping the progression of the periodontal disease, reducing surgical interventions in the future [7,8].

Subgingival irrigation with antiseptics is described in literature mainly with the use of water, saline solution, povidone iodine, hydrogen peroxide, and chlorhexidine gluconate. The latter is the substance most used for this purpose, as it is an antiseptic with broad bactericidal spectrum, with bacteriostatic and antifungal function, and is also effective against gram-positive and -negative aerobic and anaerobic bacteria, [9,10]. However, it also causes mucosal desquamation, damage to the healing of lesions, fixation of fibroblasts on root surfaces, changes in taste and tooth color [7]. Allergic reactions have also been described, especially using povidone-iodine [8].

Recently, ozone has become an alternative antiseptic with good results in dentistry due to its strong action against bacteria, fungi, viruses, and protozoa, in addition to being a potent oxidant, acting as a metabolic and host response modulator [11]. There are various forms of using ozone, whether gaseous or aqueous, such as in the treatment of early caries lesions; in tooth hypersensitivity, in the disinfection of cavities, root canals, and periodontal pockets; in mouthwashes and also for cleaning full dentures [7]. Its use provides better healing of epithelial lesions such as canker sores and herpetic lesions, promotes hemostasis, and is also capable of sterilizing heat-sensitive medical and dental instruments [12].

Thus, the aim of this work is to carry out a systematic review of the effects of ozone as an adjuvant factor in the treatment of periodontal diseases.

METHODS

To select studies to be included in this review, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) protocol was obtained as reference, registered in the PROSPERO platform (number CRD42020165351), with evaluation of the study design, population under study, types of intervention, presence of control group, and analyzed outcomes (PICO) [13].

Clinical trials comparing the effectiveness of ozone as an auxiliary means of treatment for periodontal diseases in relation to other already established therapeutic modalities were selected.

The population under study was composed of patients with some type of periodontal disease, whether gingivitis, chronic or aggressive periodontitis, and peri-implant diseases.

Clinical trials evaluating the effects of ozone in the treatment of periodontal diseases were included.

Studies that evaluated in vitro ozone therapy related to periodontal diseases or other outcomes (endodontics, periodontal disease not induced by biofilm, gingival graft hypersensitivity), review articles, other types of studies (case studies, quasi-experimental), without description of exposure, those performed with specific populations (pregnant women, diabetic patients), those with missing abstract or with unavailability of the full article, were excluded.

The search strategy adopted was to include articles published in English, Spanish, Portuguese, and French between 1950 and 2020, in order to gather the largest number of scientific articles published in literature, within the inclusion and exclusion criteria.

The following databases were searched: PubMed, LILACS/BIREME, Cochrane, and Scielo. To search the grey literature, the Open Grey platform was used, and a manual search for authors of selected articles was performed. The following Boolean expressions were used: "periodontal diseases" AND "ozone"; "gingivitis" AND "ozone"; "periodontitis" AND "ozone".

To search the articles in literature, three researchers reviewed titles and abstracts. After the first search, titles repeated in different databases were excluded. Finally, studies that did not meet the inclusion criteria were excluded. In cases of doubt, in order to decide whether a study should be included or excluded from this research, full reading was performed and, thus, it was decided by mutual agreement.

The risk of bias was individually assessed for each study according to the Cochrane risk-of-bias tool (version 5.1.0) which determines low, high, or unclear risk of bias, according to the following possibilities: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases not belonging to the aforementioned domains [14].

RESULTS

The database search strategy resulted in 168 articles. Of these, 81 were duplicates and 57 were excluded after analysis of titles and abstracts. Thus, 30 articles were read in full and, based on the proposed eligibility criteria, 24 articles were selected for this review (figure 1).

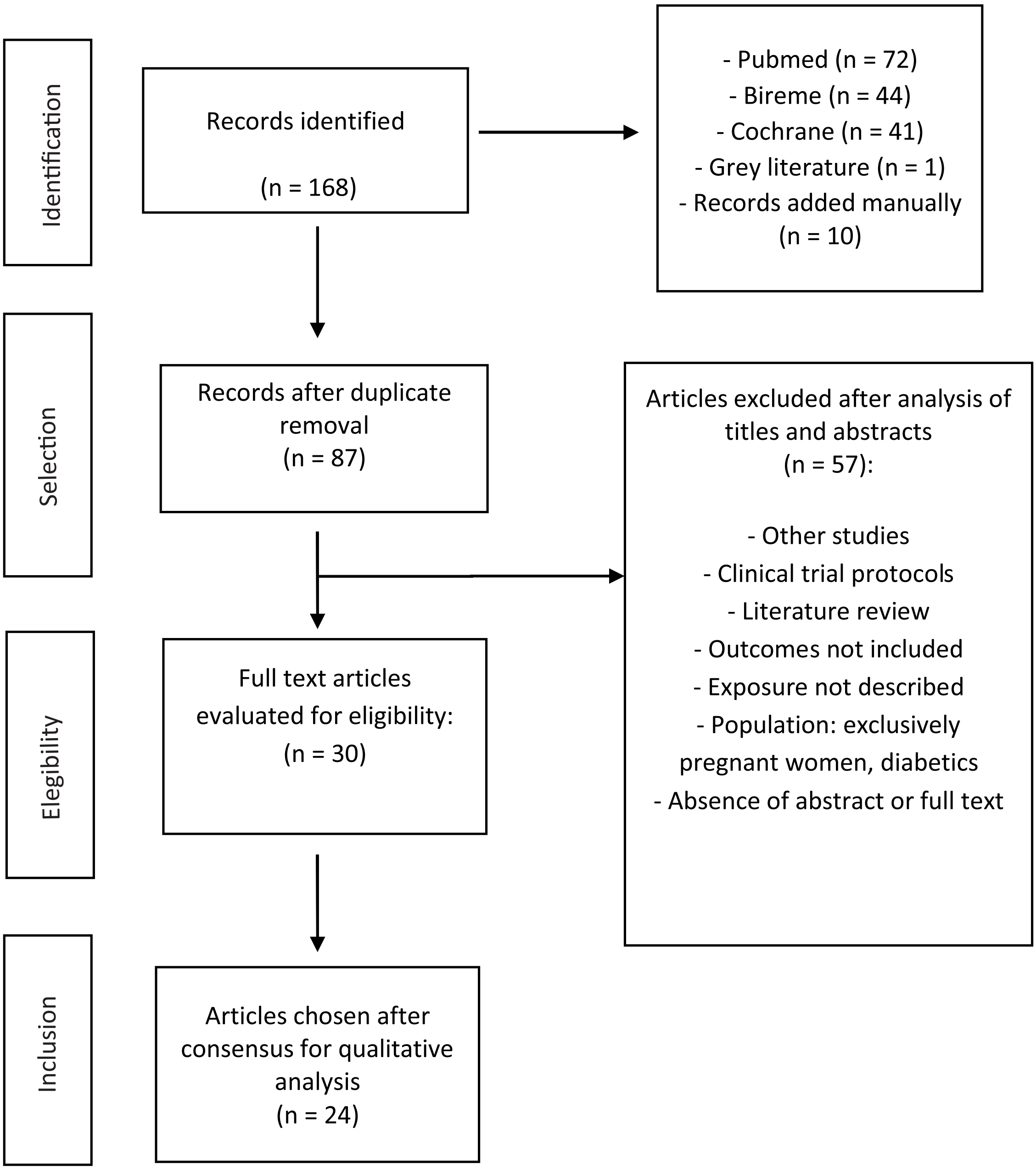

Figure 1. Article selection flowchart.

Included articles were published between 2005 and 2020 and carried out in the following countries: India (7 studies), Turkey (6 studies), Cuba (4 studies), Egypt (2 studies), United Kingdom (1 study), Italy (1 study), Poland (1 study), Jordan (1 study), and Japan (1 study).

Individual data for each study were obtained from publications, as well as from their protocols and registrations in clinical trials registry platforms (U.S. National Institutes of Health Clinical Trials Registry).

Most included studies analyzed the relationship between ozone therapy and periodontitis. Only three studies evaluated gingivitis, one peri-implant mucositis, and one peri-implantitis. The follow-up time of studies ranged from 7 to 180 days, with wide variation within this range depending on the study.

Interventions were performed with gaseous ozone in eight studies, topical in the oily form in seven studies, and liquid (ozonated water) in nine studies. In all cases, the manufacturer's instructions regarding time, potency, pressure, and quantity were followed.

In most studies, interventions performed were accompanied by hygiene instructions to participants, being well described in the articles, with the exception of seven studies [4,7,15-19], which did not provide information in this respect.

In relation to the control group, in 33% of studies, only scaling and root planing were performed, without the use of any irrigation substance. In another 33%, isolated chlorhexidine gluconate was used. In addition, the use of common water, distilled water, oxygen, indocyanine green (photosensitizing agent), combined with laser, hydrogen peroxide, and saline solution was also observed.

The general characteristics of studies in relation to intervention and control groups are described in table 1, which also show the main characteristics of the population of selected studies, the outcomes analyzed, and the results obtained.

Table 1. Characteristics of studies (population, interventions, and results).

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Study/ year of publication/ country	Number and characteristics of participants	Intervention Group: Number of subjects and type of intervention	Control Group: Number of subjects and standard intervention	Outcome analyzed Results (Statistically significant difference)
		GINGIVAL DISEASES		
Martínez Abreu et al. (2006) [4] Cuba	100 patients with chronic edematous gingivitis*	N = 50 Scaling, root planing, and application of ozonated oil in the affected region.	N = 50 Scaling, root planing, and 0.2% chlorhexidine mouthwash.	Patients in the intervention group had faster remission compared to those in the control group (p=0.004).
Rosell et al. (2019) [20] Cuba	60 patients with chronic edematous gingivitis*	N = 30 Application of ozonated oil in the gingival sulcus or pocket twice a week.	N = 30 Rinse with 0.2% aqueous chlorhexidine for 1 minute, once a day for 2 weeks.	No significant differences were found between groups of patients treated with ozonated oil and chlorhexidine, with remission of the condition in both groups.
Talmaç & Çalişir (2021) [21] Turkey	40 patients with gingivitis	N=40 Scaling and application of gaseous ozone for 60 seconds on each tooth every 2 days for 1 week.	N=40 Scaling and dental polishing.	No statistically significant difference was observed between intervention and control groups in terms of plaque index, gingival index, and probing depth (p>0.05). Statistically significant difference was observed only in the gingival bleeding time index between groups (p=0.0436).
		PERIODONTITIS		
Martínez Abreu & Sardinas (2005) [15] Cuba	84 patients with moderate chronic periodontitis	N = 42 Application of ozonated oil.	N = 42 0.2% aqueous chlorhexidine irrigation.	The reduction of signs and symptoms was faster in the group treated with ozone. The treatment efficacy at 180 days was considered good in 98% of patients in the experimental group and in 78% in the control group (p=0.00239).
Kshitish & Laxman (2010) [9] India	16 patients with generalized chronic periodontitis and aggressive periodontitis	N = 16 Ultrasound scaling and irrigation with ozonated water for 5 to 10 minutes (2nd and 3rd quadrants).	N = 16 Ultrasound scaling and irrigation with 0.2% aqueous chlorhexidine (1st and 4th quadrants).	Higher reduction percentage was observed in the plaque index (12%) (p=0.23), gingival index (29%) (p=0.042), and bleeding index (26%) (p=0.03) using ozone irrigation. The percentage reduction of *Actinobacillus actinomycetemcomitans* using ozone was 25% compared to no change using chlorhexidine. No antibacterial effect was observed on Porphyromonas gingivalis and Tannerella forsythensis with ozone or chlorhexidine. In addition, ozone had antifungal effect at baseline (37%) and on the 7th day (12.5%), unlike chlorhexidine, which showed no antifungal effect.

Table 1. Characteristics of studies (population, interventions, and results).

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Study/ year of publication/ country	Number and characteristics of participants	Intervention Group: Number of subjects and type of intervention	Control Group: Number of subjects and standard intervention	Outcome analyzed Results (Statistically significant difference)
Skurska et al. (2010) [6] Poland	52 patients with chronic or aggressive periodontitis	Group 2 (N= 25 patients with chronic periodontitis) and Group 3 (N=15 patients with aggressive periodontitis): Scaling and gaseous ozone application.	Group 1 (N= 12 patients with chronic periodontitis): Scaling Group 4 (N= 14 patients without periodontal problems).	All clinical parameters evaluated in the study groups were reduced after treatment. Scaling with ozone therapy provided increase in MMP levels in patients with chronic periodontitis and reduction in MMP levels in patients with aggressive periodontitis. Scaling followed by ozone therapy does not lead to further improvement in clinical periodontal parameters in patients with chronic and aggressive periodontitis.
Hayakumo et al. (2013) [8] Japan	22 patients with mild to moderate chronic periodontitis	N = 11 Mechanical debridement and irrigation with nano ozonated water bubbles.	N = 11 Mechanical debridement and water irrigation.	Significant improvements in all clinical parameters were observed after 4 weeks in both groups. Reduction in pocket depth and clinical attachment gain after 4 and 8 weeks in the intervention group were significantly greater than in the control group. Only the intervention group showed statistically significant reductions in the mean total number of bacteria in the subgingival plaque during the study period.
Yilmaz et al. (2013) [16] Turkey	30 patients with chronic periodontitis	N = 10 Scaling and root planing and gaseous topical ozone.	Group 1 (n=10): Scaling and planing and laser application. Group 3 (n=10): Scaling.	Statistically significant improvements in clinical parameters were observed within each group. All treatments reduced the number of total bacteria and the proportion of obligately anaerobic microorganisms. Although intergroup comparisons of microbiological parameters did not show significant differences, the clinical findings, including attachment gain and pocket depth reduction, were statistically significant in group 1.
Al Habashneh et al. (2015) [22] Jordan	41 patients with chronic periodontitis	N = 20 Non-surgical treatment and irrigation with ozonated water for 30/60 seconds.	N = 21 Non-surgical treatment and irrigation with distilled water for 30/60 seconds.	The use of ozonated water as adjunctive therapy for subgingival scaling did not produce statistically significant benefits compared to subgingival scaling with distilled water irrigation in terms of clinical outcome and hs-CRP level.
Shoukheba & Ali (2014) [11] Egypt	30 patients with aggressive periodontitis	N = 15 Scaling, root planing, and application of ozonated oil.	N = 15 Scaling and root planing.	The results showed improvement in all clinical parameters of the intervention group, which was maintained for up to 6 months ($P < 0.05$). However, this improvement was more perceived after one month, gradually decreasing at 3 and 6 months. Scaling alone resulted in significant improvement only in the first month for parameters bleeding on probing, probing depth, and attachment level, and up to 3 months for parameters plaque index and gingival index, compared to baseline values.
Sisto et al. (2015) [17] Cuba	48 patients with periodontitis	N = 24 Subgingival application of ozonated oil for 7 consecutive days topically and inside the pocket.	N = 24 Subgingival irrigation with 0.02% chlorhexidine for the same period as the experimental group.	Ozonated oil was statistically significant only for the clinical parameter evolution of periodontal pocket depth ($p = 0.0376$).
Chaudhari et al. (2016) [7] India	20 patients with chronic periodontitis	N = 20 Scaling, root planing, and irrigation with aqueous ozone.	N = 20 Scaling and root planing without irrigation.	In the experimental group, statistically significant reduction in the gingival bleeding index, probing depth, and total microbial count was observed. It could be concluded that the application of ozone can be effectively used to treat periodontal diseases non-surgically.

Table 1. Characteristics of studies (population, interventions, and results).

Study/ year of publication/ country	Number and characteristics of participants	Intervention Group: Number of subjects and type of intervention	Control Group: Number of subjects and standard intervention	Outcome analyzed Results (Statistically significant difference)
Pandya et al. (2016) [5] India	10 patients with severe periodontitis	Group 2 (N = 10): Scaling and subgingival irrigation with ozonated water (2nd quadrant).	Group 1 (N = 10): Scaling and irrigation with 0.2% chlorhexidine (1st quadrant). Group 3 (N = 10): Scaling and irrigation with saline solution (3rd quadrant). Group 4 (N = 10): Scaling and root planing (4th quadrant).	Chlorhexidine 0.2% is more effective than ozonated water and can be used as adjunct to mechanical therapy to achieve significant reduction in inflammatory periodontal changes and also in the reduction of periodontopathogenic microflora.
Saeed et al. (2017) [1] Egypt	16 patients with moderate chronic periodontitis	N = 8 Scaling, root planing, and application of ozonated oil gel in the subgingival region.	N = 8 Scaling, root planing, and application of placebo gel.	Intergroup comparison revealed that the group treated with ozonated oil showed more favorable clinical and microbiological results, with continuous and highly significant reduction in P. gingivalis counted up to 3 months and with non-significant deterioration at 6 months.
Uraz et al. (2019) [23] Turkey	18 patients with chronic generalized periodontitis	N = 18 Scaling, root planing, and gaseous ozone application 3 times for 30 s (every 3 days) for 1 week.	N = 18 Scaling and root planing.	Adjuvant ozone therapy did not provide additional benefits to clinical, microbiological, and biochemical parameters in relation to scaling and root planing without irrigation in patients with chronic periodontitis.
Dengizek et al. (2019) [24] Turkey	40 patients with chronic periodontitis	N = 20 Scaling, root planing, and gaseous ozone application in the gingival sulcus on days 3 and 8, after periodontal treatment.	N = 20 Scaling and root planing plus placebo.	The findings indicate that gaseous ozone-associated scaling is not associated with significant improvement in periodontal recovery compared to scaling and root planing treatment without ozone therapy.
Kaur et al. (2019) [10] India	20 patients with chronic periodontitis	N = 20 Irrigation with ozonated water for two hours and 30 minutes.	N = 20 Irrigation with 0.2% Chlorhexidine was performed for two hours and 30 minutes with the same pressure as the other group.	The present study showed significant results in both groups regarding the improvement of clinical parameters. When comparison was made between the two groups, the ozonated water group showed slightly higher improvement than the chlorhexidine group. However, statistically significant difference was observed only for the plaque index.
Tasdemir et al. (2019) [25] Turkey	36 patients with moderate to severe generalized periodontitis	N = 36 Scaling and root planing with topical gaseous ozone applied to periodontal pockets twice a week for 2 weeks.	N = 36 Scaling and root planing with ozone application simulation.	Ozone therapy had no additional effect on periodontal parameters. All inflammatory parameters, PTX-3, Hs-CRP, and IL-1β were reduced at 3 months of follow-up. However, only PTX-3 levels were significantly lower at ozone sites compared to those at control sites at three-months.
Verma & Indurkar (2019) [18] India	22 patients with moderate to severe chronic periodontitis	N = 11 Scaling, root planing, and irrigation with ozonated water (4 mg/L) in the subgingival region.	N = 11 Scaling, root planing, and irrigation with 0.2% chlorhexidine.	Statistically significant reduction was observed in the mean values of plaque index, gingival index, probing depth, clinical attachment level, and in the four periodontal pathogens analyzed in both groups. However, differences were not statistically significant when control and intervention groups were compared.

Table 1. Characteristics of studies (population, interventions, and results).

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Study/ year of publication/ country	Number and characteristics of participants	Intervention Group: Number of subjects and type of intervention	Control Group: Number of subjects and standard intervention	Outcome analyzed Results (Statistically significant difference)
Ameyaroy et al. (2020) [26] India	22 patients with chronic generalized periodontitis	N = 22 Scaling, root planing, and subgingival irrigation with ozonated water.	N = 22 Scaling, root planing, and photodynamic therapy.	Both subgingival ozonated water therapy and photodynamic therapy improved clinical outcomes after scaling. No statistically significant difference was observed in clinical parameters between ozone therapy and photodynamic therapy when evaluated after 2 months, 4 months, and 6 months, although slightly better clinical outcome was observed with ozone therapy.
Nardi et al. (2020) [27] Italy	96 patients with periodontitis	N = 48 Scaling, root planing, and mouthwash based on ozonated olive oil.	N = 48 Scaling and root planing.	Non-surgical periodontal treatment associated with the use of ozonated oil led to significant and faster reduction in MMP**-8 concentrations in the saliva in patients with periodontitis. Periodontal indices decreased both in the study group and in the control group, without statistical significance.
Vasthavi et al. (2020) [19] India	24 patients with chronic periodontitis	N = 12 Scaling, root planing, and subgingival irrigation with ozonated water.	N = 12 Scaling, root planing, and subgingival irrigation with distilled water.	Statistically significant difference in clinical and microbiological parameters was observed in the study group and in the control group from baseline to 2 months. However, no statistically significant difference was observed in clinical and microbiological parameters between groups.
PERI-IMPLANT DISEASES				
McKenna et al. (2013) [28] UK	20 subjects with 80 implants (4 each)	Group 1 (N = 20): Ozone and saline solution (NaCl 0.9%). Group 3 (N = 20): Ozone and hydrogen peroxide.	Group 2 (N = 20): Hydrogen peroxide (3%) and oxygen. Group 4 (N = 20): oxygen and saline solution.	The trends for significant benefits were in increasing order of effectiveness: oxygen + NaCl; oxygen + hydrogen peroxide; ozone + NaCl, and ozone + hydrogen peroxide. Ozone with or without hydrogen peroxide can reduce the development of peri-implant mucositis and should be considered in clinical trials to assess its effect in the treatment of peri-implantitis.
Isler et al. (2018) [29] Turkey	41 patients with 60 implants	N = 20 Mechanical debridement, implant surface decontamination with saline solution (3 minutes) and ozone (30 seconds per surface) + surgical regenerative therapy.	N=21 Mechanical debridement, surface decontamination of implants with saline solution (3 minutes) + surgical regenerative.	At 12-month follow-up, Plaque index and Gingival index values were significantly higher in the ozone group ($P < 0.05$). Probing depth decreased from 6.27 ± 1.42 mm and 5.73 ± 1.11 mm at baseline to 2.75 ± 0.7 mm and 3.34 ± 0.85 mm at the end of the 12-month observation period in the ozone and control groups, respectively. Likewise, the clinical attachment level values changed from 6.39 ± 1.23 mm and 5.89 ± 1.23 mm at baseline to 3.23 ± 1.24 mm and 3.91 ± 1. 36 mm in the 12-month follow-up, in the ozone and control groups, respectively. According to radiographic evidence, defect filling between baseline and 12 months postoperatively was 2.32 ± 1.28 mm in the ozone group and 1.17 ± 0.77 mm in the control group, which was a statistically significant difference between groups ($P < 0.05$).

Note: *The term chronic edematous gingivitis has been replaced by gingivitis according to the new 2018 Classification of Periodontal and Peri-implant Diseases and Conditions. **MMP = extracellular matrix metalloproteinases.

Table 2 shows the basic form of treatment for all subjects described in the studies, the clinical markers used to assess the disease, and the complementary exams performed.

Non-surgical supra- and subgingival scaling was performed in most studies, with mechanical and/or ultrasonic instrumentation without antibiotic prescription. Some studies reported the use of anesthesia for this procedure [8,23-25]. The duration and number of scaling sessions ranged from 1 to 7 sessions and from 30 min to 1 hour per patient. Irrigation

Table 2. Type of standard treatment, clinical markers, and complementary exams performed in studies.

Authors	Standard treatment type	Clinical markers	Complementary exams
		GINGIVAL DISEASES	
Martínez Abreu et al. (2006) [4]	Supragingival scaling. After interventions, all participants were instructed not to eat or wash their mouths until 2 hours after the procedure.	Probing depth, bleed on probing, color, consistency, texture gingival contour.	-
Rosell et al. (2019) [20]	Supragingival scaling and bacterial plaque control.	Signs of inflammation: bleeding, consistency, stippling, size, contour and texture.	-
Talmaç & Çalişir (2021) [21]	Supra- and subgingival scaling and dental polishing.	Plaque index; gingival index; gingival bleeding time index; probing depth.	-
		PERIODONTITIS	
Martínez Abreu & Sardinas (2005) [15]	Not reported.	Presence of chronic gingival inflammation, depth of periodontal pockets.	Microbiological study with a sample of the gingival sulcus or periodontal pocket on the day of admission to the study and at 180 days of postoperative evolution.
Kshitish & Laxman (2010) [9]	Ultrasound scaling and root planing.	Plaque index, gingival index, gingival bleeding index.	Subgingival plaque was collected and analyzed by CRP.
Skurska et al. (2010) [6]	Scaling and root planing in groups 1, 2, and 3 (all with periodontal disease).	Plaque index, bleeding on probing, sulcus bleeding index, probing depth, clinical attachment loss.	On the clinical exam days, saliva at rest was collected for laboratory analysis of MMP-1 enzyme levels.
Hayakumo et al. (2013) [8]	Ultrasound scaling and root planing, supra-and subgingival.	Probing depth, clinical attachment level, probing percentage bleeding recorded at all six sites per tooth (mesial, distal, and middle on the buccal and lingual sides).	Microbiological exam performed immediately before and after treatment and 1 and 8 weeks after treatment.
Yilmaz et al. (2013) [16]	Scaling and root planing.	Plaque index, sulcus bleeding index, probing depth, attachment levels.	Samples from representative periodontal areas were collected for the evaluation of microbiological parameters at time 0 and 90 days.
Al Habashneh et al. (2015) [22]	Scaling and root planing, supra- and subgingival, using manual and ultrasonic instruments.	Probing pocket depth, bleeding on probing, clinical attachment loss, gingival recession (all measured at 6 sites on each tooth - mesial, distal, and middle on the buccal and lingual sides). Plaque index and gingival index (assessed at 4 sites - mesial, distal, buccal, and lingual) in the Ramfjord teeth.	After examining each patient, 5 mL venous blood sample were obtained after a 10-hour fast period, at T0 and T1, to measure highly sensitive serum C-reactive protein concentrations.
Shoukheba & Ali (2014) [11]	Scaling and root planing of all teeth using manual and ultrasonic instrumentation.	Plaque index, gingival index, bleeding on probing, probing depth, and clinical attachment level.	Before treatment, a subgingival plaque sample was collecetd from the deepest periodontal pocket (6 mm probe depth) for real-time CRP analysis.
Sisto et al. (2015) [17]	Not reported.	Color, contour, consistency, texture, edema, position, bleeding on probing, depth of periodontal pockets, corroborated by X-ray; basic periodontal Index.	-
Chaudhari et al. (2016) [7]	Scaling and root planing.	Gingival bleeding index, probing depth, attachment level (all recorded at baseline and at 3 weeks post intervention).	Plaque samples were collected for microbiological study at baseline and immediately at the following day, but without identification of microbiological types.

Table 2. Type of standard treatment, clinical markers, and complementary exams performed in studies.

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Authors	Standard treatment type	Clinical markers	Complementary exams
Pandya et al. (2016) [5]	Scaling and root planing of the entire mouth with irrigation.	Gingival index and probing depth at day 0 and 30 after treatment.	Plaque samples were collected for microbiological analysis from the mesial surface of the 1st molar of each quadrant 20 seconds after the end of the prescribed treatment.
Saeed et al. (2017) [1]	Scaling and root planing with manual and ultrasonic instrumentation, entire mouth polishing in 1 session.	Probing depth, clinical attachment level, bleeding on probing, plaque index (all measured before treatment, and 1, 3, and 6 months after treatment).	Plaque samples collected for CRP analysis.
Uraz et al. (2019) [23]	Scaling and root planing performed under local anesthesia using manual and ultrasonic instruments in a single consultation for each quadrant.	Plaque index, gingival index, bleeding on probing, and probing depth.	In the 3 pockets ≥ 5 mm in depth, gingival fluid and plaque were collected at time 0 and 1 and 3 months after treatment for CRP analysis by Elisa.
Dengizek et al. (2019) [24]	Scaling and root planing, supra- and subgingival, throughout the mouth with irrigation, with manual and ultrasonic instruments.	Plaque index, gingival index, probing depth, clinical attachment level (performed one month after the second ozone application).	Total antioxidant status and total nitric oxide oxidizing status, 8-hydroxy-2’-deoxygguanosine, myeloperoxidase, glutathione, malondialdehyde Transforming growth factors were evaluated from saliva samples collected before and one month after the second application of each treatment.
Kaur et al. (2019) [10]	Scaling and root planing of the entire mouth.	Gingival index, probing depth, clinical attachment level.	-
Tasdemir et al. (2019) [25]	Scaling and root planing through manual instrumentation and local anesthesia.	Plaque index, gingival index, probing depth, bleeding on probing, percentage of sites with bleeding on probing, and clinical attachment level.	Gingival fluid, interleukin-1β, and high-sensitivity CRP protein were evaluated.
Verma & Indurkar (2019) [18]	Half-mouth supra-and subgingival scaling and root planing with irrigation, with manual and ultrasonic instruments.	Plaque index, gingival index, probing depth, and clinical attachment level.	Subgingival plaque samples were collected on the preliminary visit and after 6 weeks, and sent for analysis (CRP). The following periodontal pathogens were analyzed: Aggregatibacteractin mycetemcomitans Porphyromonasgingivalis Tannerella forsythia Prevotella Intermedia
Ameyaroy et al. (2020) [26]	Total scaling and root planing.	Gingival index, probing depth, and clinical attachment level.	-
Nardi et al. (2020) [27]	Scaling and root planing.	Probing depth, plaque index, bleeding on probing.	Active salivary matrix metalloproteinase levels were analyzed by PerioSafe® (Dentagnostics, Jena, Germany), a diagnostic test for the prevention of periodontal and peri-implant disease.
Vasthavi et al. (2020) [19]	Scaling and root planing.	Plaque index, gingival index, and pocket depth.	Subgingival plaque was collected from selected teeth in each patient at sites that showed pocket depth of 5 mm or more at T0, T2, and T3. Samples were analyzed using the BANA-Zyme™ processor to assess periodontal pathogens of the “red complex”.

Table 2. Type of standard treatment, clinical markers, and complementary exams performed in studies.

Authors	Standard treatment type	Clinical markers	Complementary exams
	PERI-IMPLANT DISEASES		
McKenna et al. (2013) [28]	Cleaning without using mouthwash two weeks before and at the beginning of the trial. The entire mouth was cleaned with the exception of the implant region, for mucositis induction.	Plaque index, bleeding index, and modified gingival index.	-
Isler et al. (2018) [29]	Regenerative surgical treatment with mechanical debridement, implant surface decontamination with sterile saline solution and ozone therapy and bone graft + PRF.	Plaque index, gingival index, clinical attachment level, gingival recession, probing depth, and bleeding on probing.	CGF: concentrated growth factors.

time varied widely from seconds (20-45) to minutes (1-10). Only in the study by Isler et al. [29], surgical treatment for peri-implantitis was performed, and Amoxicillin (500mg) and Metronidazole (500mg) every 8 hours for 7 days were prescribed.

Bacterial plaque samples were obtained for microbiological analysis in nine studies. Other complementary analyses carried out were blood samples, saliva samples, and gingival fluid samples. The collection frequency varied from before treatment (baseline=t0), the day after treatment, the 4th day, the 15th day, the 18th day, the 21st day, 1 month, 2 months, 3 months, up to 6 months.

After treatment, subjects were recruited within a period of 1 week, 14 days, 1 month, 2 months, 3 months, 4 months, or up to 6 months for the evaluation of clinical parameters.

Regarding methodological quality, the risk of bias results of selected studies are summarized in Figure 2.

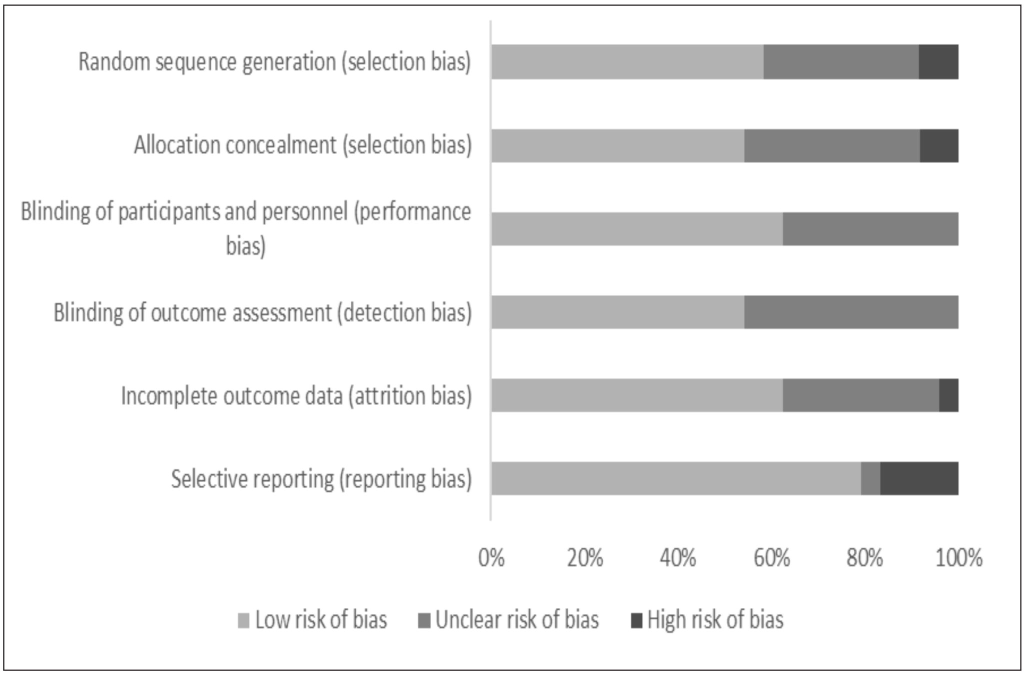

Figure 2. Classification of the risk of bias of selected studies based on the Cochrane risk-of-bias tool - version 5.1.0.

With regard to selection bias, low risk of bias was identified in 58% of studies in the random sequence domain and in 54% in the allocation concealment domain, as details about the randomization process were presented in these studies. As for performance bias, 62.5% of studies presented low risk, as blinding tools were well described in the methodology section. In 37.5% of studies; however, it was not possible to identify forms of blinding, being classified as undefined risk of bias. With regard to detection bias, 54% of studies had low risk of bias. Attrition bias was considered low in 62.5% of studies because, in these cases, when there was loss of follow-up, it was considered small and well justified. Regarding reporting bias, although some studies had not published a protocol, outcomes were reported as proposed in the methodology section and the treatment was well described and reproducible, and thus the probability of bias of this nature was considered low in 79% of studies.

Another bias identified in most studies was the absence of sample calculation parameters, described in only seven studies [18,19,23,24,26-28].

DISCUSSION

It is known that ozone has several physicochemical properties such as immunostimulant and analgesic, anti-hypoxic and detoxifying, antimicrobial, bioenergetic and biosynthetic, by activating the metabolism of carbohydrates, proteins, and lipids [30].

In periodontics, the therapeutic use of ozone has gained popularity due to the antimicrobial properties of ozone against gram-positive and -negative bacteria, viruses, and fungi [5,7,8,23,25], in addition to its ability to stimulate the circulatory system and modulate the immune response [28].

Regarding gingivitis, only three studies were included, and in one of them, ozone provided faster remission compared to the control group [4]. However, these studies were classified as having undefined risk of bias, indicating the absence of relevant information to judge their validity.

Based on articles with lower risk of bias in all six categories analyzed [22-25], it could be concluded that ozone therapy did not bring any additional benefit, nor any significant improvement in periodontal parameters in terms of periodontitis. On the other hand, in studies by Hayahumo et al. [8] and Yilmaz et al. [16], which were also classified as having lower risk of bias in five categories (lack of information on concordance for the assessment of clinical parameters), significant improvement was observed only in clinical parameters, for Hayahumo et al. [8], and in clinical and microbiological parameters for Yilmaz et al. [16]. The lack of standardization in the way ozone is applied for the treatment of periodontal diseases, length of use, and frequency could explain differences between results of these studies.

Specifically for peri-implant diseases, two articles were identified [28,29] with low risk of bias in all categories. In both studies, the conclusion was that ozone can reduce the development of mucositis, significantly improving clinical parameters in addition to radiographic evidence of significant improvements. It is noteworthy that the inclusion of peri-implant conditions and diseases in the Classification of Periodontal Diseases and Conditions [31] is recent. Thus, further studies relating these diseases to ozone therapy are needed for a better understanding of its therapeutic effect.

Regarding the form of ozone use, it could be concluded with studies by Skurska et al. [6], Uraz et al. [23], Dengizek et al. [24], and Tasdemir et al. [25] that gaseous ozone therapy does not lead to additional improvement in clinical and microbiological parameters. Only the study by Yilmaz et al. [16] found improvement in clinical parameters such as attachment gain and reduction in pocket depth with this form of administering ozone. This can be explained by the instability of ozone in the gaseous medium, which has half-life from 30 to 40 minutes at 20 °C [32,33].

In the study by Kshitish & Laxman [9], good results using ozonated water under pressure from 350 to 500kPa were obtained. On the other hand, in the study by Pandya et al. [5], chlorhexidine was more effective than ozonated water produced at 0.595-350kPa, suggesting that the absence of pressure standardization interferes with the result obtained. Hayakumo et al. [8] used nanobubbles as alternative, with significant results for clinical and microbiological parameters.

The oily form of ozone was the form that presented the best clinical results in the evaluated studies [1,4,11,15,17,27]. The advantage of this method is that the oil remains in contact with the surface for longer period of time, performing its functions. In addition, it can be stored under refrigeration for several months, eliminating the need for generator. This characteristic is opposed to that of gaseous ozone, which needs to be generated and used immediately, since when exposed to air, the gas decomposes quickly.

On the other hand, the chemical evaluation of the ozonation of some types of oils such as sunflower, castor, olive, almond, and propylene glycol was carried out. The absence of ozone percentages and the presence of formaldehyde were observed in all analyzed samples. It is known that the hydrolysis of ozonated oils can generate hydrogen peroxide, aldehyde, and ketones, which are antimicrobial. This suggests that the bactericidal and curative results of ozonated oils may be related to their by-products rather than to the ozone itself [34].

Regarding microbiology, it was observed in studies by Yilmaz et al. [16], Saeed et al. [1], Verma & Indurkar [18], Hayakumo et al. [8], Shoukheba & Ali [11], Pandya et al. [5], and Uraz et al. [23] that ozone can continuously and significantly reduce periodontal microorganisms. However, there were no significant differences between intervention groups and their controls, indicating that the antimicrobial effect between groups was similar.

In the study by Uraz et al. [23], reduction of potent pathogens of the orange and red complexes such as Porphyromonas gingivalis (Pg) was observed in the first month and Tannerella forsythia (Tf) and Prevotella intermedia (Pi) in three months. Shoukheba & Ali [11] observed significant reduction in Pg and Actinobacillus actinomycetemcomitans (Aa) between 1 and 3 months in the ozone group; however between 3 and 6 months, no significant differences between groups were observed. In the study by Saeed et al. [1], reduction in Pg was observed for three months and Hayakumo et al. [8] also reported a more than 95% reduction in all sites under study. Verma & Indurkar [18] observed reduction in the four periodontal pathogens (Aa, Pg, Pi, and Tf) in both groups, which can be attributed to the fact that repeated subgingival irrigations were performed, interfering with the recolonization of the subgingival microflora. In the work by Kshitish & Laxman [9], percentage reduction was only observed in Actinobacillus actinomycetemcomitans, with no antibacterial effect on Porphyromonas gingivalis and Tannerella forsythensis, using ozone or chlorhexidine.

Two studies [6,27] evaluated the presence of high MMP-8 levels (metalloproteinases) in saliva and gingival fluid. In the study by Nardi et al. [27], it was observed that scaling and root planing, accompanied by subgingival irrigation with ozone in the oily form, was more effective in reducing this metalloproteinase in saliva than scaling and root planing alone, with significant difference between groups. MMP-8 levels are associated with the disease severity and help understanding the pathogenesis, diagnosis, and treatment of periodontal diseases.

CONCLUSION

Works that discuss the use of ozone as a therapeutic alternative in periodontics do not reach any conclusion regarding a protocol to be used. It could be inferred that the antimicrobial effectiveness of ozone is related to the form of presentation, concentration (dose), exposure time, and microorganism evaluated. Thus, well-defined criteria must be implemented to provide the quality and reliability of the ozone produced in any of its forms.

Further studies with adequate control of biases are suggested, using ozone in the oily or aqueous form, as the most promising forms, also evaluating the possible effectiveness of ozone by-products.

Collaborators

Palma PV, substantially contributed in the conception and design, acquisition of data, analysis and interpretation of data; drafted the article and revised it critically for important intellectual content; and approved of the final version to be published. Cunha RO, substantially contributed in the conception and design, acquisition of data, analysis and interpretation of data; drafted the article and revised it critically for important intellectual content; and approved of the final version to be published. Leite ICG, substantially contributed in the conception and design, acquisition of data, analysis and interpretation of data; drafted the article and revised it critically for important intellectual content; and approved of the final version to be published.

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