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SYSTEMATIC REVIEW

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Effects of ozone therapy as an adjuvant in the treatment of periodontitis: a systematic review and meta-analysis

Jiaxuan Liu[1], Yuxiao Huang[1], Jiaqi Huang[1], Wanrong Yang[1] and Renchuan Tao[1*]

Abstract

Background Chronic periodontitis is an infectious disease initiated by plaque, which affects chewing and even general health. Ozone therapy, as a complementary means in the treatment of chronic periodontitis, numerous clinical trials have been conducted. We conducted this review to evaluate the effect of the ozone use accompanied by scaling and root planning (SRP) in periodontal treatment.

Methods Randomized controlled trials investigating the use of ozone therapy in chronic periodontitis. The search was carried out across PubMed, Cochrane Central Register of Controlled Trials, and EMBASE databases with the search period extending to July 2024. The quality of the identified studies was evaluated using the Cochrane Collaboration's Risk of Bias tool. The results were presented as weighted mean differences (WMD) with corresponding 95% confidence intervals (95% CI). Heterogeneity among the studies was assessed using the I^2 test. Data analysis was performed using RevMan 5.4 and Stata 16.0.

Results Thirteen articles meeting the inclusion criteria. The meta-analysis revealed statistically significant differences in probing depth (PD) and gingival index (GI) reduction between ozone-assisted nonsurgical periodontal treatment and placebo-assisted treatment in patients with chronic periodontitis ($P < 0.05$). However, no significant differences were observed in clinical parameters such as bleeding on probing (BOP) percentage, plaque index (PI), and clinical attachment level (CAL) ($P > 0.05$).

Conclusion Ozone therapy combined with SRP is superior to SRP alone in improving PD and GI indexes in patients with periodontitis, without increasing adverse reactions, and the effect is worthy of recognition. The research evidence indicates that ozone therapy in patients with chronic periodontitis has a positive effect.

Keywords Ozone, Periodontitis, Meta-analysis

Background

Chronic periodontitis is an infectious chronic oral disease that is initiated by plaque [1]. The prevalence of moderate-to-severe periodontitis in the global population over 15 years of age is about 19% [2]. In addition to affecting chewing, periodontitis can also adversely affect an individual's general health [3]. Studies have revealed that periodontitis is closely related to a variety of systemic diseases, such as adverse pregnancy outcomes [4], diabetes [5], cardiovascular diseases [6], respiratory diseases [7], Alzheimer's disease [8], and certain types of cancer [9, 10]. Consequently, periodontitis has become a significant public health problem [11]. Chronic periodontitis is caused by the interaction of a variety of microorganisms [12, 13], although the gram-negative

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anaerobe is the principal pathogen that leads to chronic periodontitis [14]. Thus, the treatment of chronic periodontitis first involves the removal of the plaque biofilm and related infections in the periodontal pocket, including periodontal non-surgical treatment and tissue regeneration surgery [15, 16]. Mechanical removal of dental plaque is the most widely used and effective non-surgical method for the treatment of periodontal disease [17]. However, it is difficult to reach deep periodontal pockets, complex subosseous pockets, and root bifurcation lesions through mechanical removal [17], which may lead to disease recurrence [18, 19]. Studies have indicated that the herpes virus levels in the subgingival plaque of periodontitis patients are high [20, 21], while Epstein-Barr virus may also affect the process of periodontitis. Currently, in addition to the simple mechanical clearance method, the basic treatment combined with antibacterial drugs has achieved a satisfactory therapeutic effect in clinical practice [22]. Nevertheless, frequent use of antibiotics easily induces the development of resistant virus strains [23].

Ozone (O_3) is a natural gas molecule with a strong oxidation ability that is composed of three oxygen atoms [24]. Studies have shown that ozone significantly inhibits bacteria such as *Escherichia coli* and *Staphylococcus aureus*, fungi such as *Candida albicans,* viruses, and other microorganisms [25]. Besides, ozone has good biocompatibility with oral epithelial cells and periodontal cells [26]. In the oral field, ozone is used for early caries treatment, root canal disinfection, and tooth bleaching [27]. As an adjuvant systems in non-surgical peri-implant treatment, ozone can improve PI and BOP to some extent [28]. In recent years, it has also been introduced as an adjunct to the conventional non-surgical treatment of chronic periodontitis [29].

Ozone therapy, as an effective complementary means for subgingival curettage and root surface leveling in the treatment of chronic periodontitis, improves the clinical and microbiological indicators of patients [30]. Moreover, ozone has an obvious bactericidal effect on "red complex" periodontal pathogenic bacteria [31] and promotes the healing of affected tissue [32]. However, some studies have shown that the combination of periodontal basic treatment with ozone fails to significantly improve the periodontal status of patients with chronic periodontitis [33] and the level of plasma oxidative stress [34]. These contrasting results have led to strong interest in the effects of ozone therapy on chronic periodontitis. This review aims to answer the following key question, which was developed according to the recognized Patient, Intervention, Comparison, and Outcome (PICO) format: What is the effect of ozone therapy as an adjuvant in the treatment of periodontitis on the clinical indicators?

Materials and methods

This review was compiled according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [35]. This study was logged in the PROSPERO database under the protocol number CRD 42024554179.

Eligibility criteria

The inclusion criteria are: 1) Study design: published randomized controlled trials (RCTs) regarding the ozone therapy application as adjunct to SRP of patients with chronic periodontitis. 2) Participants: patients with chronic periodontitis. 3) Interventions: in the experimental group, the subjects were treated with whole-mouth SRP with ozone treatment. In the control group, the subjects were treated with SRP, supplemented with a placebo or blank control. 4) Outcomes: gingival index (GI), plaque index (PI), bleeding on probing (BOP) percentage, probing depth (PD), and clinical attachment loss (CAL).

The exclusion criteria include: 1) Animal studies and in vitro studies. 2) Subjects with systemic disease or poor systemic state and pregnant or breastfeeding mothers. 3) RCTs involving procedures other than non-surgical periodontal treatment and ozone therapy. 4) Studies where the full texts are unavailable. 5) Research with incomplete data.

Literature retrieval strategies

The databases of PubMed (http://www.ncbi.nlm.nih.gov/sites/pubmed), Embase (http://www.embase.com), and the Cochrane Central Register of Controlled Trials (CENTRAL; http://www.cochrane.org) were searched using a computer with no country or language restrictions. The search period was from the establishment of the databases to July 2024. The search formula was formulated by combining the subject words with free words and Boolean logic operators such as "AND" and "OR". The search formula for the PubMed database was: ((("Ozone" [Mesh]) OR (((((((Tropospheric Ozone [Title/Abstract]) OR (Ozone, Tropospheric [Title/Abstract])) OR (Low Level Ozone [Title/Abstract])) OR (Level Ozone, Low [Title/Abstract])) OR (Ozone, Low Level [Title/Abstract])) OR (Ground Level Ozone [Title/Abstract])) OR (Level Ozone, Ground [Title/Abstract])) OR (Ozone, Ground Level [Title/Abstract])))) AND (("Periodontitis" [Mesh]) OR ((((((Chronic Periodontitis [Title/Abstract]) OR (Chronic Periodontitides [Title/Abstract])) OR (Periodontitides, Chronic [Title/Abstract])) OR (Periodontitis, Adult [Title/Abstract])) OR (Periodontitis, Chronic [Title/Abstract])) OR (Adult Periodontitis [Title/Abstract]))))) AND ((((((((randomized controlled trial [Publication Type]) OR (controlled clinical trial [Publication Type])) OR (randomized [Title/Abstract])) OR

(controlled [Title/Abstract])) OR (trial [Title/Abstract])) OR (random [Title/Abstract])) OR (placebo [Title/Abstract])) OR (groups [Title/Abstract])).

Data extraction

In this study, the literature selection process was conducted in strict accordance with the PRISMA process, and two researchers participated in literature screening. The two researchers conducted the preliminary screening of the literature independently and then exchanged their preliminary screening results to establish whether there were any discrepancies. If there was a disagreement, a third researcher assessed the relevant literature. If consensus could not be reached between the three researchers, an expert in the field was invited to make a ruling. The content of the data extraction included the authors of the study, publication time, number of study cases, sex ratio, treatment plan and course of treatment, intervention measures, outcome indicators, and follow-up time.

Risk of bias assessment

The risk assessment of bias in this study adopted the process from the new edition of the Cochrane Bias Risk Assessment Manual, Cochrane Reviewers' Handbook (www.handbook.cochrane.org). It mainly includes the following aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. At the end of the evaluation, the two researchers cross-checked their respective evaluation results to generate the final results.

Data synthesis

The meta-analysis was conducted using Review Manager (version 5.4) and Stata (version 16.0). All effect indicators in this meta-analysis were measurement data. Weighted mean difference (WMD) was used to analyze the measurement data and calculate the 95% confidence interval (95% CI). A P value less than 0.05 was considered to be statistically significant. The I^2 heterogeneity test was carried out to evaluate the heterogeneity. The I^2 value can be divided into three distinct levels: $I^2 = 75\%-100\%$, high heterogeneity; $I^2 = 50\%-75\%$, medium heterogeneity; $I^2 = 0-50\%$, low heterogeneity. When $P > 0.10$ and $I^2 \leq 50\%$, the fixed effects model was selected. However, when $P < 0.10$ and $I^2 \geq 50\%$, the random effects model was used. To test the stability of the meta-analysis, a sensitivity analysis was performed by removing individual studies one by one. When the number of RCTs for a certain outcome indicator was greater than ten, publication bias detection was necessary. The methods used in this study included the funnel diagram method and the Egger method.

Results

Study selection

According to the PRISMA process and the inclusion and exclusion criteria, we retrieved 99 related articles from PubMed, Embase, and Cochrane Library. Following the exclusion of 37 duplicates and a further 40 articles after reading the titles and abstracts, 22 articles remained. Subsequently, a comprehensive evaluation of the full texts led to the rejection of nine more articles. Ultimately, 13 articles fulfilled the inclusion criteria and were included in the meta-analysis. The PRISMA flow diagram is presented in Fig. 1.

Study characteristics

The 13 articles included in the screening were all randomized controlled trials published in English between 2013 and 2023. The studies included a total of 655 subjects, 328 in the experimental group and 327 in the control group. In all 13 papers, the intervention methods were local adjuvant treatment after non-surgical periodontal treatment. After scaling and root planing treatment, the periodontal pocket was washed with ozonated water or injected with gaseous ozone. The times and frequencies of local applications varied, but most of them were 30–60 s each time. Of the 13 RCTs, eight used ozonated water [29–31, 36–40]and five utilized gaseous ozone [41–45]. Statistics and records of the ozone applied in the experiments were made for each study, while the usage, dosage, and intervention time were also detailed. To make the data more intuitive, we produced the following table (Table 1), which describes the general characteristics of each RCT included in this study.

Risk of bias across studies

According to the results of the Cochrane bias risk assessment tool, five articles used random methods but did not explicitly state which random methods were employed. The remaining trials reported the use of computer numerical randomization or the random number table method. Moreover, five articles did not state whether or not distribution hiding was implemented, while the others specified the implementation of distribution hiding. The results of the 13 RCTs included in this study were complete with no missing data. Besides, none of the studies had selective reporting bias and none of them clarified whether reporting was biased by other sources (Figs. 2 and 3).

Study outcomes

PD

In total, twelve studies assessed probing depth. The heterogeneity test indicated heterogeneity among all the studies ($P < 0.00001$, $I^2 = 78\%$). The random effects model

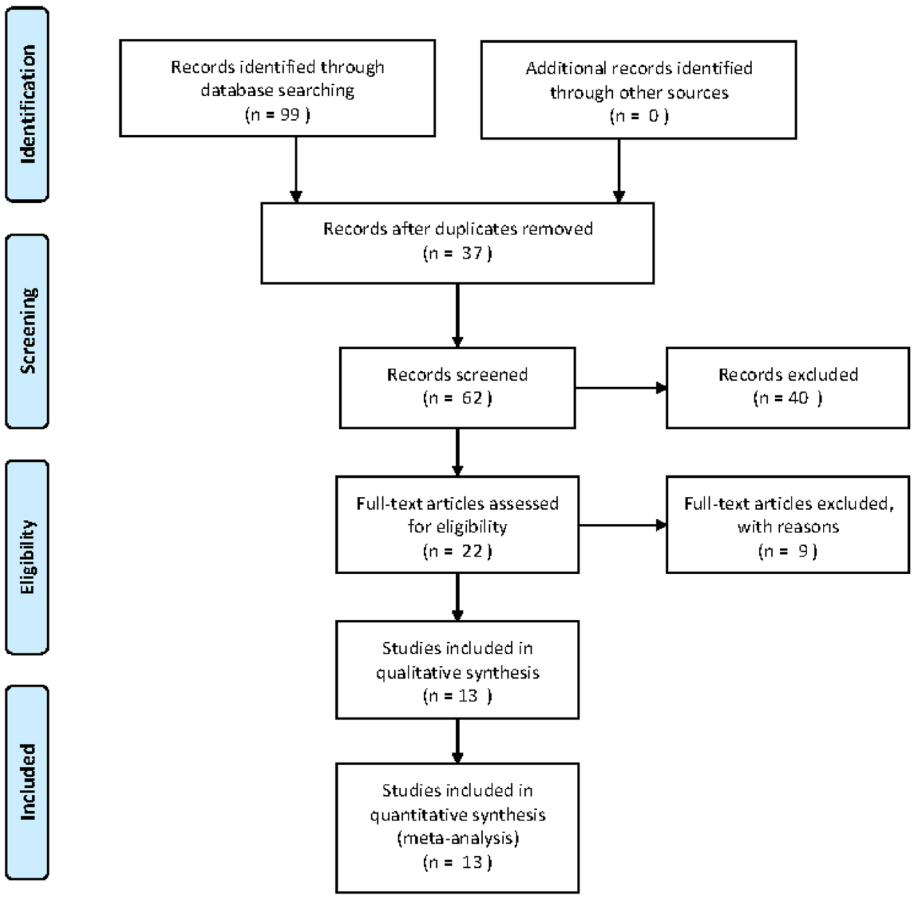

Fig. 1 PRISMA flow diagram

was used for the meta-analysis and the results revealed that there was a statistically significant reduction in PD between the ozone treatment group and the placebo group [WMD = −0.26, 95% CI = (−0.48, −0.05), Z = 2.44, $P = 0.01$] (Fig. 4).

GI

Seven RCTs evaluated the gingival index. According to the heterogeneity test, there was heterogeneity among the studies ($P = 0.07$, $I^2 = 48\%$). A meta-analysis using a fixed effect model showed that the GI in the ozone treatment group was significant reduction from that in the placebo group [WMD = −0.15, 95% CI = (−0.24, −0.07), Z = 3.43, $P = 0.0006$] (Fig. 5).

BOP

A total of six studies explored the BOP parameter. There was heterogeneity among the studies ($P = 0.11$, $I^2 = 45\%$), while a meta-analysis using a fixed effect model revealed no significant difference in BOP between the ozone treatment group and the placebo group [WMD = −3.29, 95% CI = (−8.65, 2.06), Z = 1.20, $P = 0.23$] (Fig. 6).

PI

The plaque index was considered in seven articles. The heterogeneity test showed that there was heterogeneity among the studies ($P = 0.77$, $I^2 = 0\%$). A meta-analysis using a fixed effect model revealed no significant difference in PI between the ozone treatment group and the placebo group [WMD = −0.05, 95% CI = (−0.15, 0.04), Z = 1.09, $P = 0.27$] (Fig. 7).

CAL

In nine studies, CAL was measured. The heterogeneity test showed that there was heterogeneity among the studies ($P = 0.0005$, $I^2 = 72\%$). A random effects model was used for meta-analysis, and the results indicated that there was not a significant difference in CAL between the ozone group and the placebo group [WMD = −0.27, 95% CI = (−0.56, 0.01), Z = 1.87, $P = 0.06$] (Fig. 8).

Sensitivity analysis

In this study, there was significant heterogeneity among the studies regarding the PD and CAL effect indicators ($P < 0.00001$, $I^2 = 78\%$; $P = 0.0005$, $I^2 = 72\%$). A sensitivity

Table 1 General characteristics of included studies

	N (T/C)	Male/Female		Intervention		Usage	Assessment method	Follow-up period
		T	C	T	C			
Al Habashneh 2015 [29]	41 (20/21)	6/14	7/14	Ozonated water, 75–85μg/ml	Distilled water	Rinse for 30-60s	PI、GI、BOP、CAL	3m
Alsakr 2023 [30]	92 (46/46)	31/15	31/15	Ozonated water, 5–20μg/ml	Normal saline	Rinse for 5-10min	PD、BOP、CAL	6w
Ranjith 2022 [40]	42 (22/20)	11/11	13/7	Ozonated water, ozone concentration 2ppm	Normal saline	Rinse for 30s	PD、CAL	4w
Rapone 2022 [41]	90 (45/45)	35/6	35/10	Gaseous ozone	Ozone-free gas	Rinse for 2min	PD、CAL、BOP	3m
Seydanur Dengizek 2019 [42]	37 (19/18)	11/8	10/8	Gaseous ozone	Ozone-free gas	Rinse for 1min	PI、GI、CAL	4w
Issac 2015 [37]	60 (30/30)	19/11	19/11	Ozonated water, water output ≥ 150ml/min, ozone output 0.082mg/h	Distilled water	Rinse during treatment	GI、PD、CAL	4w
Katti 2013 [38]	60 (30/30)	-	-	Ozonated water	Normal saline	Rinse 40s, 3 times a week for 2 weeks	PI、GI	4w
Nardi 2020 [39]	96 (48/48)	-	-	Ozonized olive oil mouthwash	Blank control	Rinse for 30s for 3 days	PD、BOP	4w
Hayakumo 2013 [36]	21 (10/11)	-	-	Ozone nanobubble water	Tap water	Rinse during treatment	PD、BOP、CAL	4w
Yılmaz 2013 [45]	20 (10/10)	5/5	3/7	Gaseous ozone	Blank control	Twice a week for 2 weeks	PI、PD、CAL	3m
Uraz 2019 [44]	36 (18/18)	9/9	9/9	Gaseous ozone of 2100 ppm with 80% oxygen	Ozone-free gas	3 times for 30 s for 1 week	PI、GI、PD、BOP	3m
Vasthavi 2020 [31]	24 (12/12)	-	-	Ozonated water	Distilled water	Rinse during treatment	PI、GI、PD	2m
Tasdemir 2019 [43]	36 (18/18)	-	-	Gaseous ozone, 75mg/ml	Placebo gas	3 times for 30 s for 1 week	PI、GI、BOP、PD、CAL	3m

Abbreviations: *N* number, *T* test, *C* control, *s* second, *PI* Plaque index, *GI* Gingival index, *BOP* Bleeding on probing, *CAL* Clinical attachment loss, *PD* Probing depth, *m* mouth, *w* week

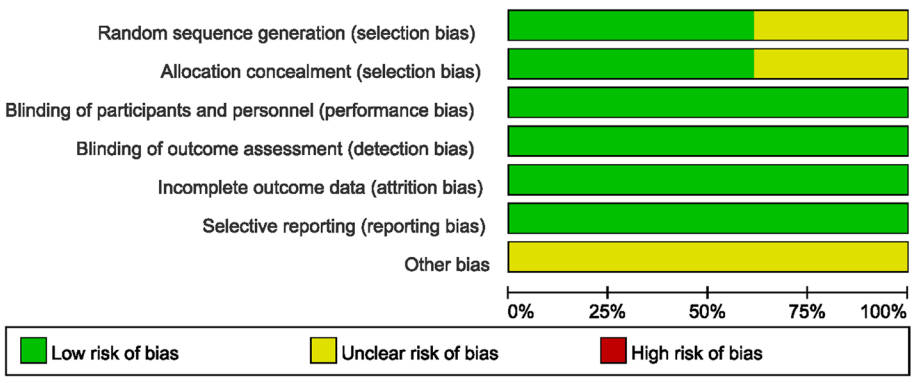

Fig. 2 Risk of bias graph: review of authors' judgements regarding each risk of bias item

analysis using Stata 16.0 software showed that although the combined effect size of some studies deviated from the median line, this study [37] be the source of heterogeneity. However, the combined effect of these studies was still within the 95% confidence interval. Therefore, no studies were excluded as a result of the sensitivity analysis (Figs. 9 and 10).

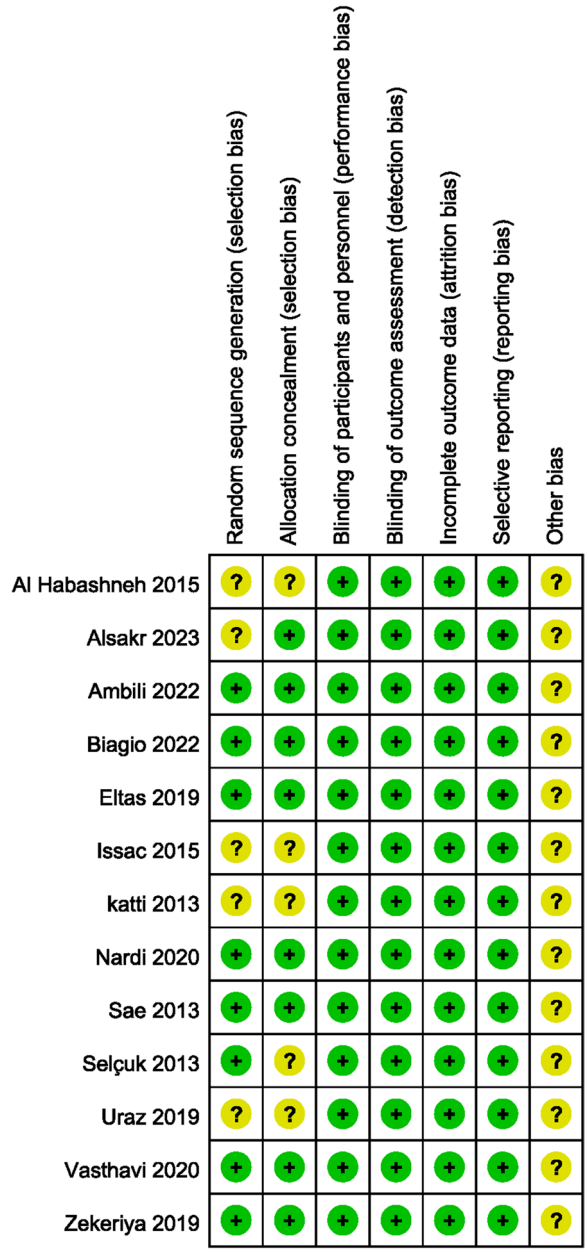

Fig. 3 Summary of risk of bias of the included studies

Publication bias

The PD effect index was appraised in twelve studies, which were tested for publication bias. The funnel plot used for qualitative analysis was not completely symmetrical (Fig. 11). Additionally, the Egger method was used for quantitative analysis of publication bias. According to the results, $p = 0.169$, where $p > 0.10$ indicates that publication bias does not exist (Figs. 12 and 13).

Discussion

As a formidable oxidizing agent, ozone plays a powerful antibacterial function by rapidly releasing newly formed oxygen free radicals to form oxygen [46]. At the same time, ozone also has a regulatory effect on the cellular and humoral immune systems, stimulating the growth of immunoactive cells, production of immunoglobulin [47]. It also reduces inflammation and promotes wound healing by mediating levels of interleukin, leukotrienes, and prostaglandins [48]. Chronic periodontitis is one of the most common infectious oral diseases. In the occurrence and development of periodontitis, pro-inflammatory mediators, reactive oxygen species, and other interrelated molecular pathway networks may all play a crucial role [49]. Traditional antibiotic therapy changes the subgingival microecological environment by inhibiting the growth of subgingival bacteria [50], but it is easy to induce drug-resistant strains. Ozone possesses strong antibacterial, immunomodulator, anti-inflammatory, analgesic, and hemostatic effects [51]. Moreover, compared with commonly used antibiotics, it has the advantages of broad spectrum, rapidity, safety, non-drug resistance, and good biocompatibility [29]. Consequently, numerous randomized controlled trials have applied ozone treatment as an adjunct therapy to explore its role in chronic periodontitis.

Some scholars have discovered that ozone as an adjuvant treatment is extremely effective in reducing dental plaque, gingival inflammation, and bleeding in patients with periodontitis, while it also has an obvious antifungal effect on the *Candida albicans* fungus [52]. Conversely, some researchers believe that ozone therapy does not provide additional benefits in clinical, microbiological, and biochemical parameters during SRP in patients with chronic periodontitis [44]. The 13 articles included in the final meta-screening were English-language randomized controlled trials published between 2013 and 2023. They included 655 subjects, with 328 in the experimental group and 327 in the control group. The results of the meta-analysis revealed that there were significant differences in PD and GI reduction in the ozone treatment group compared with the placebo group ($P < 0.05$). Conversely, there were negligible differences in clinical indicators such as BOP, PI, and CAL ($P > 0.05$). This indicates that ozone therapy enhances the therapeutic effect of non-periodontal surgery in patients with chronic periodontitis to a certain extent. Regarding heterogeneity, there was great heterogeneity in the PD and CAL analyses. To determine the source of the heterogeneity, the RCTs were excluded one by one for sensitivity analysis. For the PD parameter, which comprised more than ten articles, we evaluated publication bias through a funnel plot and the Egger

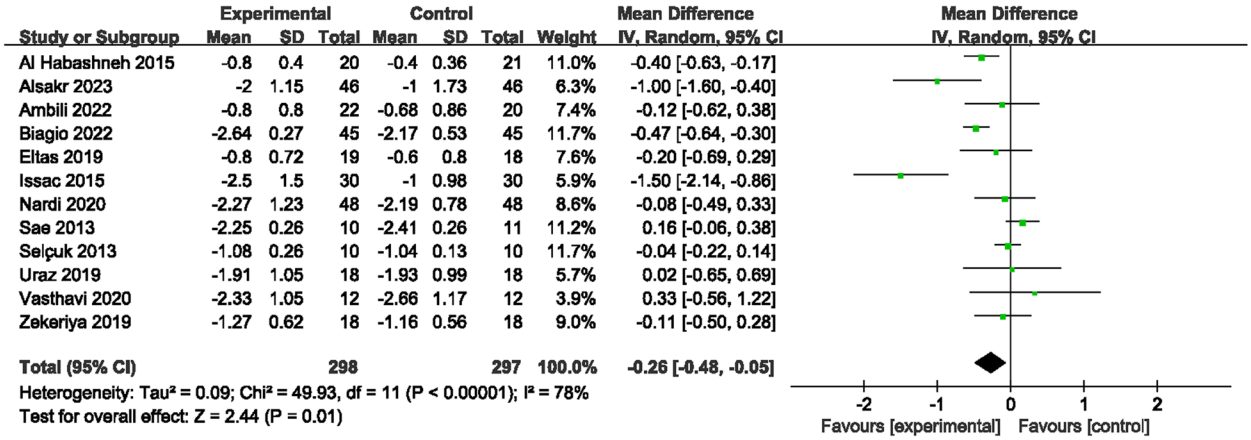

Fig. 4 Forest plot presenting before and after therapy probing depth (PD) by comparing ozone vs. placebo

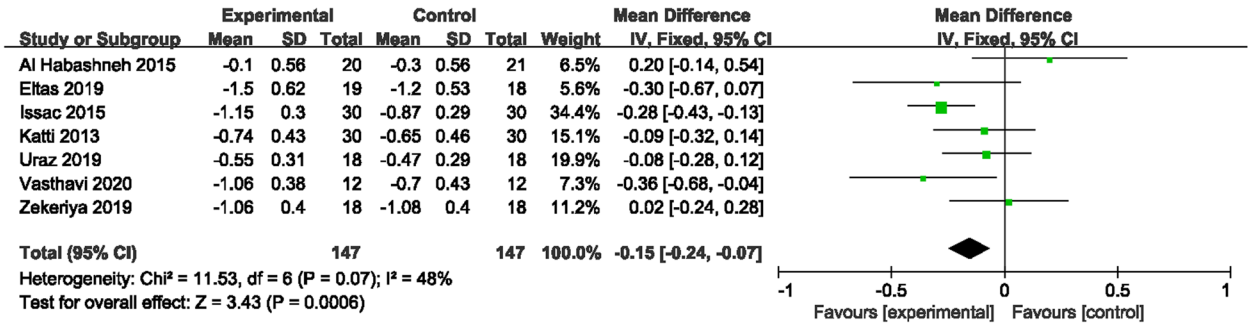

Fig. 5 Forest plot presenting before and after therapy gingival index (GI) by comparing ozone vs. placebo

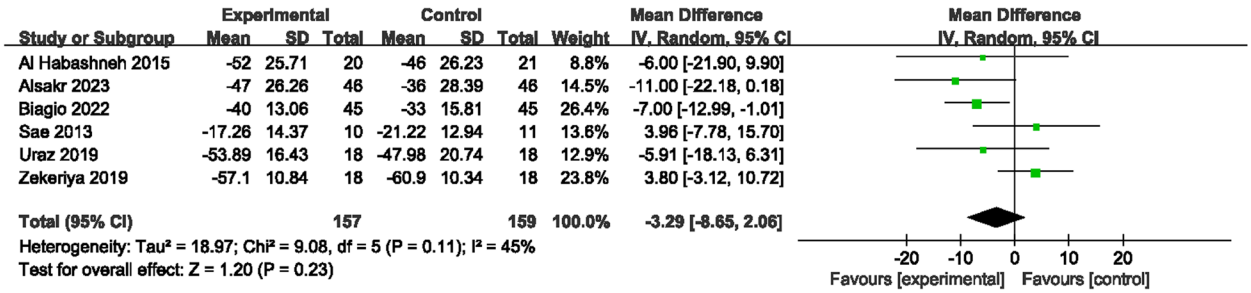

Fig. 6 Forest plot presenting before and after therapy bleeding on probing (BOP) by comparing ozone vs. placebo

test. Ultimately, the results did not reveal any publication bias.

Among the 13 studies included, the intervention measures of the experimental groups involved either ozonated water or gaseous ozone. Depending on the treatment method, there were differences in the outcome indexes for both PD ($P<0.05$) [29, 30, 37, 41] and GI ($P<0.05$) [31, 37]. Additionally, the outcome indexes for BOP ($P<0.05$) [41] and CAL ($P<0.05$) [30, 37]varied. The above four studies [29–31, 37] used ozonated water therapy, one study [41] used gaseous ozone, but it remains unclear whether ozonated water or gaseous ozone is more effective. Therefore, a range of clinical trials are still required to verify which approach is preferable. Furthermore, the ozone concentrations used in both the ozonated water and gaseous ozone studies were not the same, which may have had a certain impact on the test results. In terms of frequency and usage of ozone, local irrigation in the periodontal pocket after periodontal treatment was mostly employed. Nevertheless, the frequency of use varied

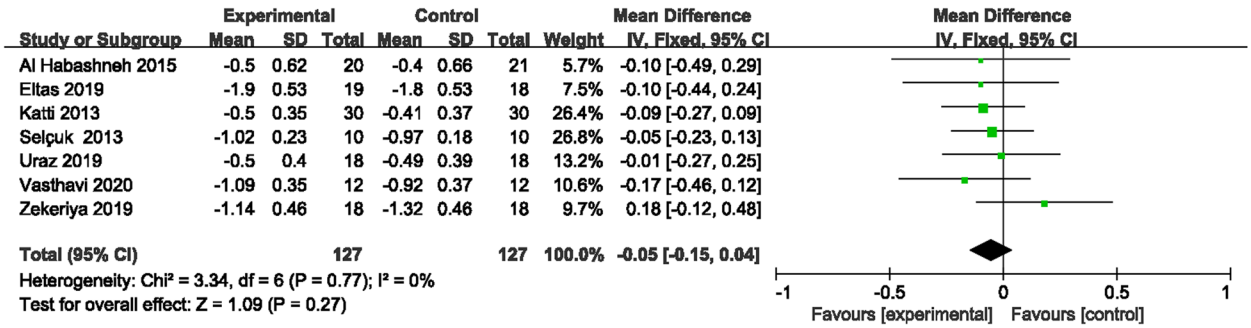

Fig. 7 Forest plot presenting before and after therapy plaque index (PI) by comparing ozone vs. placebo

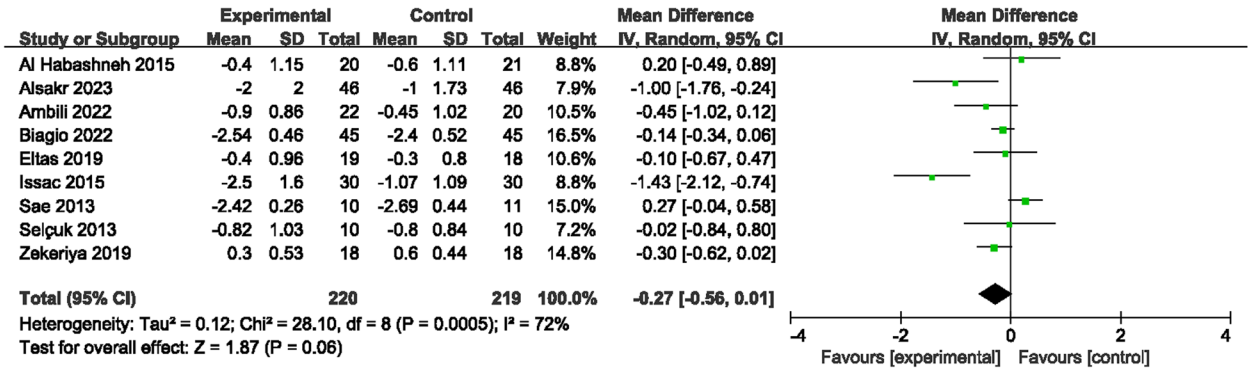

Fig. 8 Forest plot presenting before and after therapy clinical attachment loss (CAL) by comparing ozone vs. placebo

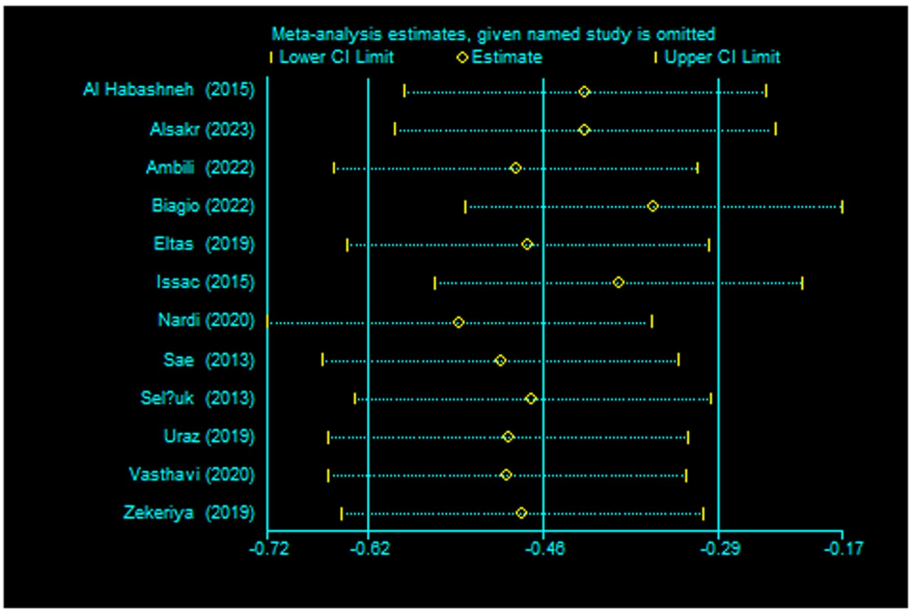

Fig. 9 Sensitive analysis of probing depth (PD)

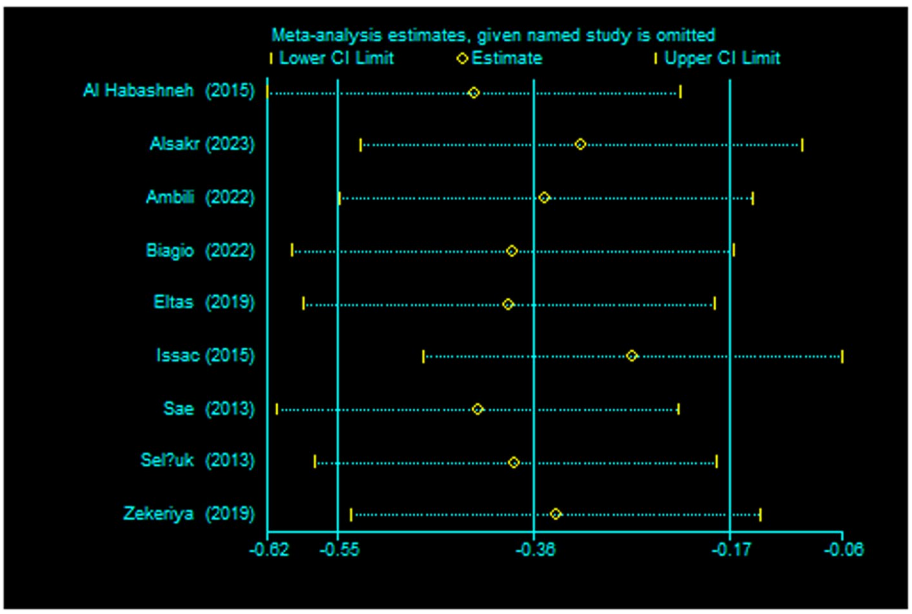

Fig. 10 Sensitive analysis of clinical attachment loss (CAL)

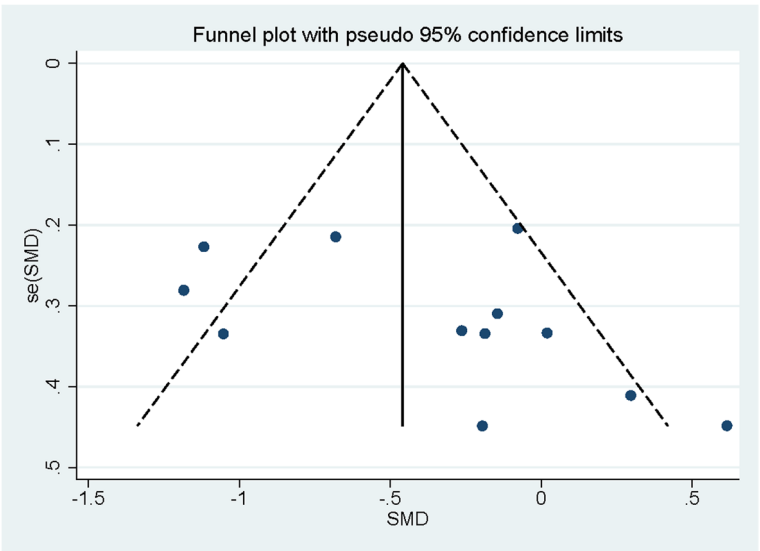

Fig. 11 Funnel plot analysis of published bias of probing depth (PD)

widely; some treatments involved a single application, while others were offered for as long as four weeks. This dissimilarity had a considerable impact on the control of periodontal inflammation, and there was a certain heterogeneity in the outcome indicators of the various studies. Regarding follow-up time, in eight studies it was divided into two categories: 4–6 weeks and 3 months. Longer follow-up times resulted in higher oral hygiene maintenance requirements for the subjects. Besides, the oral hygiene levels of the subjects also had a clear impact on the test results during the follow-up period. In view of the role of ozone in periodontal adjuvant therapy, if the use of ozone-containing preparations in daily oral health care, such as mouthwash, will have a positive effect on the maintenance of oral health and the stability of oral microecological environment [45, 53].

This meta-analysis strictly followed the PRISMA process, including strict inclusion/exclusion criteria and a

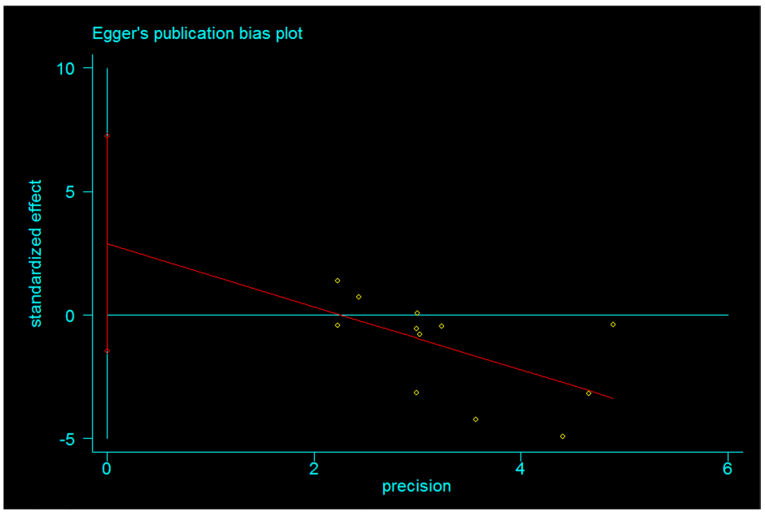

Fig. 12 Egger method detects the symmetry of funnel plot of probing depth (PD)

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-1.281081	.5729226	-2.24	0.049	-2.557632	-.0045297
bias	2.905823	1.958199	1.48	0.169	-1.457317	7.268962

Fig. 13 P-value detected by egger method of probing depth (PD)

publication bias analysis. Nevertheless, the results must be interpreted cautiously because of the following limitations. Firstly, the number of studies included in this meta-analysis was insufficient and the sample size was small. Additionally, there was a risk of bias in some of the included studies, which had a certain impact on the results of the meta-analysis. In the future, it will be necessary to include multi-center RCT studies with large sample sizes.

Conclusion

Ozone therapy combined with SRP is superior to SRP alone in improving PD and GI indexes in patients with periodontitis, without increasing adverse reactions, and the effect is worthy of recognition. The research evidence indicates that ozone therapy in patients with chronic periodontitis has a positive effect and it may be beneficial in daily active oral maintenance.

Abbreviations

SRP	Scaling and root planning
WMD	Weighted mean difference
CI	Confidence interval
PD	Probing depth
GI	Gingival index
BOP	Bleeding on probing
PI	Plaque index
CAL	Clinical attachment lever
PICO	Population, interventions, comparisons, outcomes
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomised controlled trials

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12903-025-05639-6.

Supplementary Material 1.

Supplementary Material 2.

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None.

Authors' contributions

Jiaxuan Liu, Yuxiao Huang, Renchuan Tao concepted and designed the study. Jiaxuan Liu, Yuxiao Huang, Jiaqi Huang, Wanrong Yang reviewed the literature, extracted and analysed the data. Jiaxuan Liu, Yuxiao Huang, Renchuan Tao drafted the paper. All authors reviewed and confirmed the manuscript.

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Data availability
All data generated or analysed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Clin Periodontol. 2018;45(Suppl 20):S162-s170.
2. Benzian H, Watt R, Makino Y, Stauf N, Varenne B. WHO calls to end the global crisis of oral health. Lancet. 2022;400(10367):1909–10.
3. Qi L, Qian Y, Zhu F, Cao N, Lu H, Zhang L. Association between periodontal disease and tooth loss and mortality in an elderly Chinese population. Aging Clin Exp Res. 2020;32(11):2375–82.
4. Figuero E, Han YW, Furuichi Y. Periodontal diseases and adverse pregnancy outcomes: Mechanisms. Periodontol 2000. 2020;83(1):175–88.
5. Lalla EPapapanou P N,. Diabetes mellitus and periodontitis: a tale of two common interrelated diseases. Nat Rev Endocrinol. 2011;7(12):738–48.
6. Sanz M, Del Castillo AM, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Bouchard P, et al. Periodontitis and Cardiovascular Diseases. Consensus Report Glob Heart. 2020;15(1):1.
7. Michaud DS, Liu Y, Meyer M, Giovannucci E, Joshipura K. Periodontal disease, tooth loss, and cancer risk in male health professionals: a prospective cohort study. Lancet Oncol. 2008;9(6):550–8.
8. Jungbauer G, Stähli A, Zhu X, Auber Alberi L, Sculean A, Eick S. Periodontal microorganisms and Alzheimer disease - A causative relationship? Periodontol 2000. 2022;89(1):59–82.
9. Slots J. Periodontitis: facts, fallacies and the future. Periodontol 2000. 2017;75(1):7–23.
10. Tsai CY, Tang CY, Tan TS, Chen KH, Liao KH, Liou ML. Subgingival microbiota in individuals with severe chronic periodontitis. J Microbiol Immunol Infect. 2018;51(2):226–34.
11. Barros SP, Fahimipour F, Tarran R, Kim S, Scarel-Caminaga RM, Justice A, et al. Epigenetic reprogramming in periodontal disease: Dynamic crosstalk with potential impact in oncogenesis. Periodontol 2000. 2020;82(1):157–72.
12. Caton JG, Armitage G, Berglundh T, Chapple ILC, Jepsen S, Kornman KS, et al. A new classification scheme for periodontal and peri-implant diseases and conditions - Introduction and key changes from the 1999 classification. J Periodontol. 2018;89(Suppl 1):S1-s8.
13. Wilson M. Susceptibility of oral bacterial biofilms to antimicrobial agents. J Med Microbiol. 1996;44(2):79–87.
14. Pham TAV, Tran TTP, Luong NTM. Antimicrobial Effect of Platelet-Rich Plasma against Porphyromonas gingivalis. Int J Dent. 2019;2019:7329103.
15. Nibali L, Koidou V, Salomone S, Hamborg T, Allaker R, Ezra R, et al. Minimally invasive non-surgical vs. surgical approach for periodontal intrabony defects: a randomised controlled trial. Trials. 2019;20(1):461.
16. Nibali L, Pometti D, Chen TT, Tu YK. Minimally invasive non-surgical approach for the treatment of periodontal intrabony defects: a retrospective analysis. J Clin Periodontol. 2015;42(9):853–9.
17. Graziani F, Karapetsa D, Alonso B, Herrera D. Nonsurgical and surgical treatment of periodontitis: how many options for one disease? Periodontol 2000. 2017;75(1):152–88.
18. Chatzopoulos GS, Koidou VP, Tsalikis L. Local drug delivery in the treatment of furcation defects in periodontitis: a systematic review. Clin Oral Investig. 2023;27(3):955–70.
19. Gomes EWB, Casarin M, Martins TM, da Silva AF. Local delivery therapies as adjuvants to non-surgical periodontal treatment of periodontitis grade C: a systematic review. Clin Oral Investig. 2020;24(12):4213–24.
20. Arduino PG, Cabras M, Lodi G, Petti S. Herpes simplex virus type 1 in subgingival plaque and periodontal diseases. Meta-analysis of observational studies. J Periodontal Res. 2022;57(2):256–68.
21. Naqvi A, RSlots J. Human and herpesvirus microRNAs in periodontal disease. Periodontol 2000. 2021;87(1):325–39.
22. Zhao H, Hu J, Zhao L. Adjunctive subgingival application of Chlorhexidine gel in nonsurgical periodontal treatment for chronic periodontitis: a systematic review and meta-analysis. BMC Oral Health. 2020;20(1):34.
23. Rams TE, Sautter JD, van Winkelhoff AJ. Comparative In Vitro Resistance of Human Periodontal Bacterial Pathogens to Tinidazole and Four Other Antibiotics. Antibiotics (Basel). 2020;9(2):68.
24. Zeng JLuJ. Mechanisms of action involved in ozone-therapy in skin diseases. Int Immunopharmacol. 2018;56:235–41.
25. Sechi LA, Lezcano I, Nunez N, Espim M, Duprè I, Pinna A, et al. Antibacterial activity of ozonized sunflower oil (Oleozon). J Appl Microbiol. 2001;90(2):279–84.
26. Kist S, Kollmuss M, Jung J, Schubert S, Hickel R, Huth KC. Comparison of ozone gas and sodium hypochlorite/chlorhexidine two-visit disinfection protocols in treating apical periodontitis: a randomized controlled clinical trial. Clin Oral Investig. 2017;21(4):995–1005.
27. Oizumi M, Suzuki T, Uchida M, Furuya J, Okamoto Y. In vitro testing of a denture cleaning method using ozone. J Med Dent Sci. 1998;45(2):135–9.
28. Butera A, Maiorani C, Gallo S, Pascadopoli M, Venugopal A, Marya A, et al. Evaluation of Adjuvant Systems in Non-Surgical Peri-Implant Treatment: A Literature Review. Healthcare (Basel). 2022;10(5):886.
29. Al Habashneh R, Alsalman W, Khader Y. Ozone as an adjunct to conventional nonsurgical therapy in chronic periodontitis: a randomized controlled clinical trial. J Periodontal Res. 2015;50(1):37–43.
30. Alsakr A, Gufran K, Alqahtani AS, Alasqah M, Alnufaiy B, Alzahrani HG, et al. Ozone Therapy as an Adjuvant in the Treatment of Periodontitis. J Clin Med. 2023;12(22):7078.
31. Vasthavi C, Babu HM, Rangaraju VM, Dasappa S, Jagadish L, Shivamurthy R. Evaluation of ozone as an adjunct to scaling and root planing in the treatment of chronic periodontitis: A randomized clinico-microbial study. J Indian Soc Periodontol. 2020;24(1):42–6.
32. Ramirez-Peña AM, Sánchez-Pérez A, Campos-Aranda M, Hidalgo-Tallón FJ. Ozone in Patients with Periodontitis: A Clinical and Microbiological Study. J Clin Med. 2022;11(10):2946.
33. Skurska A, Pietruska MD, Paniczko-Drężek A, Dolińska E, Zelazowska-Rutkowska B, Zak J, et al. Evaluation of the influence of ozonotherapy on the clinical parameters and MMP levels in patients with chronic and aggressive periodontitis. Adv Med Sci. 2010;55(2):297–307.
34. Rapone B, Ferrara E, Qorri E, Inchingolo F, Isola G, Dongiovanni P, et al. Research efficacy of gaseous ozone therapy as an adjuvant to periodontal treatment on oxidative stress mediators in patients with type 2 diabetes: a randomized clinical trial. BMC Oral Health. 2023;23(1):278.
35. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339: b2700.
36. Hayakumo S, Arakawa S, Mano Y, Izumi Y. Clinical and microbiological effects of ozone nano-bubble water irrigation as an adjunct to mechanical subgingival debridement in periodontitis patients in a randomized controlled trial. Clin Oral Investig. 2013;17(2):379–88.
37. Issac AV, Mathew JJ, Ambooken M, Kachappilly AJ, Pk A, Johny T, et al. Management of Chronic Periodontitis Using Subgingival Irrigation of Ozonized Water: A Clinical and Microbiological Study. J Clin Diagn Res. 2015;9(8):Zc29-33.
38. Katti S, SChava V K,. Effect of Ozonised water on Chronic Periodontitis - A Clinical Study. J Int Oral Health. 2013;5(5):79–84.
39. Nardi GM, Cesarano F, Papa G, Chiavistelli L, Ardan R, Jedlinski M, et al. Evaluation of Salivary Matrix Metalloproteinase (MMP-8) in Periodontal Patients Undergoing Non-Surgical Periodontal Therapy and Mouthwash Based on Ozonated Olive Oil: A Randomized Clinical Trial. Int J Environ Res Public Health. 2020;17(18):6619.

40. Ranjith A, Niranjana JM, Baiju KV. Adjunctive benefit of ozonized water irrigation with mechanical debridement in the management of Stage III periodontitis: A randomized controlled clinical and biochemical study. Int J Dent Hyg. 2022;20(2):364–70.
41. Rapone B, Ferrara E, Santacroce L, Topi S, Gnoni A, Dipalma G, et al. The Gaseous Ozone Therapy as a Promising Antiseptic Adjuvant of Periodontal Treatment: A Randomized Controlled Clinical Trial. Int J Environ Res Public Health. 2022;19(2):985.
42. Seydanur Dengizek E, Serkan D, Abubekir E, Aysun Bay K, Onder O, Arife C. Evaluating clinical and laboratory effects of ozone in non-surgical periodontal treatment: a randomized controlled trial. J Appl Oral Sci. 2019;27:e20180108.
43. Tasdemir Z, Oskaybas MN, Alkan AB, Cakmak O. The effects of ozone therapy on periodontal therapy: A randomized placebo-controlled clinical trial. Oral Dis. 2019;25(4):1195–202.
44. Uraz A, Karaduman B, Isler S, Gönen S, Çetiner D. Ozone application as adjunctive therapy in chronic periodontitis: Clinical, microbiological and biochemical aspects. J Dent Sci. 2019;14(1):27–37.
45. Yılmaz S, Algan S, Gursoy H, Noyan U, Kuru BE, Kadir T. Evaluation of the clinical and antimicrobial effects of the Er:YAG laser or topical gaseous ozone as adjuncts to initial periodontal therapy. Photomed Laser Surg. 2013;31(6):293–8.
46. Al-Omiri MK, Alhijawi M, AlZarea BK, Abul Hassan RS, Lynch E. Ozone treatment of recurrent aphthous stomatitis: a double blinded study. Sci Rep. 2016;6:27772.
47. Jakab GJ, Spannhake EW, Canning BJ, Kleeberger SR, Gilmour MI. The effects of ozone on immune function. Environ Health Perspect. 1995;103 Suppl 2(Suppl 2):77–89.
48. El Meligy OA, Elemam NM, Talaat IM. Ozone Therapy in Medicine and Dentistry: A Review of the Literature. Dent J (Basel). 2023;11(8):187.
49. Chapple IL. Role of free radicals and antioxidants in the pathogenesis of the inflammatory periodontal diseases. Clin Mol Pathol. 1996;49(5):M247–55.
50. Wennström JL, Heijl L, Dahlén G, Gröndahl K. Periodic subgingival antimicrobial irrigation of periodontal pockets (I). Clinical observations J Clin Periodontol. 1987;14(9):541–50.
51. Roth A, Krishnakumar A, McCain RR, Maruthamuthu MK, McIntosh M, Chen YX, et al. Biocompatibility and Safety Assessment of Combined Topical Ozone and Antibiotics for Treatment of Infected Wounds. ACS Biomater Sci Eng. 2023;9(6):3606–17.
52. Kshitish D, Laxman VK. The use of ozonated water and 0.2% chlorhexidine in the treatment of periodontitis patients: a clinical and microbiologic study. Indian J Dent Res. 2010;21(3):341–8.
53. Nambiar S, Malothu S, Karmakar S, Varkey A, Chandra D, Chava VK. Comparison of Ozonated Olive Oil and Chlorhexidine Gel as an Adjunct to Nonsurgical Periodontal Therapy for the Treatment of Chronic Periodontitis: A Randomized Controlled Clinical Trial. J Pharm Bioallied Sci. 2022;14(Suppl 1):S94-s98.

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