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Review

The Use of Ozone Therapy or Blue®M Gel as an Adjunctive Therapy in Patients With Periodontal Disease: A Systematic Review

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Abstract

Background: Conventional treatment of periodontal disease is based on subgingival instrumentation, but its limited effectiveness in eliminating certain pathogens has led to the need for adjuvant approaches such as ozone therapy (OT) or Blue®m gel. **Methods:** A systematic review was carried out between October 2024 and June 2025, using four databases according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Eighteen articles that met the in-clusion criteria were selected from a total of 727. **Results:** Although most articles reported an improvement in periodontal parameters after treatment, significant differences between groups were found in only one article. Furthermore, two articles showed that the use of OT reduced anaerobic bacterial colonisation between 28.5% and 55.0%. Regarding Blue®m, two articles argued that there was a clinical im-provement in periodontal parameters within 14 days to three months. However, an article reported that no significant differences were found between groups. OT and Blue®m oral gel are used as a viable alternative, as they favour wound healing by increasing oxygen levels in periodontal pockets and allowing high concentrations of active oxygen directly in the pocket depth. Oxygen participates in various biological processes, such as bacterial elimination by oxidation, re-epithelialisation, angiogenesis, and collagen synthesis, which appear to be promising new alternatives to conventional approaches. **Conclusions:** Despite promising results, significant intragroup differences were observed, but not intergroup differences, demonstrating that the use of these therapies does not have a negative effect as a complement to conventional treatment.

Keywords: Periodontal diseases, ozone therapy, Blue®m, non-surgical periodontal therapy, active oxygen, oral biofilm.

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Introduction

Periodontal disease (PD) is a chronic inflammatory disorder characterized by the destruction of the periodontium, the supporting tissues of the teeth, such as the gums, periodontal ligament, and alveolar bone [1–4]. This condition is highly prevalent, affecting approximately 50.0% of adults aged 30 and older, and around 70.0% of adults aged 65 and older [1,2]. Periodontitis, which represents the most severe form of the disease, is a multifactorial disease that results from a complex interaction between several factors: an imbalance in the oral microbiome, host immune responses, and environmental influences [5,6]. Depending on the stage of the PD, its clinical manifestations are: bleeding on probing (BOP), periodontal probing depths(PPD), and alveolar bone loss, which can lead to tooth loss [7,8].

The development of periodontitis is primarily associated with Gram-negative anaerobic bacteria, such as *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, *Fusobacterium nucleatum*, and *Aggregatibacter actinomycetemcomitans* [6,7,9]. The accumulation of microbial biofilm at the gingival margin is one of the main causes of periodontal destruction [7]. The accumulation of anaerobic bacteria in deep periodontal pockets activates the host's inflammatory response, creating a low-oxygen environment [7,9,10].

Despite advances in the field, controlling periodontitis remains a challenge. Professional mechanical plaque removal and subgingival instrumentation are considered standard approaches to reduce bacterial load and improve clinical parameters [1,11]. Nevertheless, it is important to emphasise that increased pocket depth, root concavities, grooves and microgrooves, restoration shapes, degree

of furcation involvement, invasion of root surface irregularities and dentinal tubules decrease the effectiveness of scaling [12]. Therefore, given the limitations of mechanical therapy, the use of adjuvant therapies, particularly in situations of more advanced disease or when the response to traditional treatment was inadequate, becomes an added value, enhancing conventional therapy [13]. The literature has been showing new non-surgical and adjunctive therapeutic approaches to this treatment [1,11].

Numerous investigations on the function of oxygen in wound healing have discovered that elevated oxygen levels stimulate the production of collagen and granulation tissue. Oxygen is a chemical element that plays an important role in cellular metabolism, particularly in energy production. It participates in several biological processes, such as bacterial elimination by oxidation, re-epithelialisation, angiogenesis, and collagen synthesis [9,10]. Oxygen therapies can be applied locally or systemically (hyperbaric) [14]. Topical oxygen therapy comes in a variety of forms, such as toothpaste, mouthwash, mouth foam, and oral gel formulations, and releases regulated active oxygen molecules [7].

Both ozone therapy (OT) and Blue®m oral gel use reactive oxygen species and are used as a viable alternative, as they help in wound healing by enhancing oxygen levels in periodontal pockets [7,11].

OT has been recognized as a promising antimicrobial adjunct due to its immunostimulant, antimicrobial, antihypoxic, and biosynthetic effects [1,11–13,15,16]. It also offers additional benefits, such as tissue healing, improved blood circulation in the gingival tissues, reduced inflammation, and enhanced local immune response. Thus, in addition to its antimicrobial effects, the treatment provides more effective and less invasive results [7,11,17].

In this context, this study explores the use of OT as an adjunct to non-surgical therapies in periodontal treatments. By evaluating its antimicrobial efficacy and its role in tissue regeneration, the aim is to offer a new and promising alternative to conventional approaches. This behaviour is part of an effort to gain a better understanding of the pathogenic mechanisms of PD while developing more effective and less invasive therapeutic strategies.

Blue®m gel, developed by a team of dental surgeons in the Netherlands, is a topical formulation based on carbamide peroxide enriched with active oxygen-releasing enzymes, and has attracted growing interest as a non-invasive therapeutic adjuvant in the treatment of periodontal and peri-implant disease [6,9,18]. This oxygenated alternative is distinguished by its dual mechanism of action: on the one hand, antimicrobial activity via the controlled release of oxygen, capable of disrupting anaerobic biofilms, and on the other, stimulation of tissue repair processes through increased cellular oxygenation [6,9,16]. Therefore, it is possible to anticipate that, during subgingival debridement, mechanical and chemical components act together to break down hard and soft biofilm, which may facilitate the removal of granulation tissue, bacterial elimination through oxidation, and tissue regeneration [12].

Subgingival scaling is the gold standard in non-surgical periodontal treatment. However, anatomical limitations in deep pockets, as well as the complexity of the bacterial biofilm, hinder the complete elimination of pathogens, thereby promoting recolonisation. To overcome these shortcomings and mitigate the risk of bacterial resistance associated with traditional antibiotics, agents based on local oxygenation have attracted considerable clinical interest. This systematic review is justified by the need to gather and compare, for the first time, the available scientific evidence on two adjunctive approaches that share the same biological principle—oxidative stress against anaerobic microorganisms and tissue biostimulation—but with distinct application dynamics. OT, characterised by an immediate and intensive release of oxygen in a clinical setting, was analysed in parallel with active oxygen gel (Blue®m), which acts through sustained and continuous topical release. Therefore, the aim of this study is to conduct a systematic review exploring the use of OT as an adjunct to non-surgical in periodontal treatments and to determine whether Blue®m gel can be considered a viable alternative to conventional treatments in non-surgical periodontal therapy.

Materials and Methods

This systematic review was conducted according to the PRISMA 2020 statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [19].

The study protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD420251143899.

The survey was carried out between October 2024 and June 2025, using databases such as PubMed, Cochrane Library, EBSCOHost, and Web of Science, considering all available articles on the subject, with no time frame for the research.

The search strategy used for each database is listed below:

•PubMed: (Periodontal disease [MeSH Terms]) AND (Periodontal therapy [MeSH Terms] OR nonsurgical therapy [MeSH Terms]) AND ((reactive oxygen species [MeSH Terms] OR oxygen gel OR active oxygen) OR ozone therapy)

Filters: Clinical Study, Clinical Trial, Randomized Controlled Trials

•Cochrane Library: (Periodontal disease [MeSH Terms]) AND (Periodontal therapy [MeSH Terms] OR nonsurgical therapy [MeSH Terms]) AND ((reactive oxygen species [MeSH Terms] OR oxygen gel OR active oxygen) OR ozone therapy)

Filters: Not Applicable

•EBSCOHost: (Periodontal disease [MeSH Terms])

AND (Periodontal therapy [MeSH Terms] OR non-surgical therapy [MeSH Terms]) AND ((reactive oxygen species [MeSH Terms] OR oxygen gel OR active oxygen) OR ozone therapy)

Filters: Not Applicable

•Web of Science: (Periodontal disease) AND (Periodontal therapy OR non-surgical therapy) AND ((reactive oxygen species OR oxygen gel OR active oxygen) OR ozone therapy)

Filters: Topic

Data extraction was performed by two independent examiners (R.C and M.I.d.C) in order to demonstrate intra- and in-ter-examiner reliability. A two-stage screening method was used to ensure rigorous and reliable screening of studies. In the first stage, the two independent reviewers assessed the titles and abstracts of the identified studies against the predetermined in-clusion and exclusion criteria. Each reviewer independently determined whether to include or exclude the article based on the initial screening. In the case of discrepancies or uncertainties, a third reviewer (M.R.) reached an agreement. In the second stage, the same two independent reviewers independently evaluate the full articles of the studies that successfully passed the initial screening, with discrepancies again being resolved by the third reviewer.

In the presence of disagreements, the third reviewer independently assessed the articles using the same eligibility criteria defined for the review. The Kappa coefficient test provided almost perfect agreement (0.81–0.99) during the search and article selection process.

The articles were analyzed first based on the title, then the abstract, and finally the full text. Listed above is how the PICOS ("Population", "Intervention", "Comparison", "Outcomes", and "Study design") method was used to arrange the eligibility criteria:

– P- Population- Patients with PD requiring treatment.

– I- Intervention- The use of OT or Blue®m as an adjunct to periodontal treatment.

– C- Comparison- The use of conventional periodontal treatment (scaling and root planing (SRP)).

– O- Outcomes- To analyze the use of oxygen therapy (OT or Blue®m) in adjunctive periodontal treatment.

– S- Study Designs- Clinical studies, clinical trials, randomized controlled trials, and case reports.

The inclusion criteria were articles in English, Portuguese, and French; clinical or experimental studies comparing con-ventional periodontal treatments with those combining these treatments with oxygen-based therapy (OT or Blue®m) existing in the literature.

For exclusion, articles without abstracts, studies that did not involve the use of OT or Blue®m. Studies including pregnant or breastfeeding females, individuals with systemic diseases (diabetes, hypertension, thyroid disorders), treatment with drugs (antibiotics, anti-inflammatories), systematic reviews, and meta-analyses. Studies limited to monotherapy with oxygen (without SRP) were not selected, and animal and *in vitro* studies were also excluded.

Study Quality and Risk of Bias

The Joanna Briggs Institute (JBI) was used to analyze the study quality and the risk of bias for randomized controlled trials and case reports. In this classification, the following acronyms were used: (Y) for "Yes" indicating that the criterion is met; (N) for "No" indicating that the criterion is not met; and (UN) for "Unclear" meaning that the information is either insufficient or not clearly reported in the study.

Results

A total of 727 articles were identified in the initial search. The remaining papers were thoroughly examined after duplicates were eliminated and the title and abstract were reviewed (Fig. 1). Eighteen articles were finally included.

Characterization of the Sample for the Quality of the Study

Quality assessments are shown in Table 1 for randomized controlled trials, Table 2 for case reports, and Table 3 for case control studies.

The degree of quality of the studies on the relational index used and the number of positive responses to the questions were mostly high, including 8 articles (Barahim *et al.* [20], 2024; Cetiner *et al.* [21], 2024; Alayadi *et al.* [7], 2024; Ramirez-Peña *et al.* [22], 2022; Rapone *et al.* [1], 2022; Tasdemir *et al.* [23], 2019; Uraz *et al.* [24], 2019; Alsakr *et al.* [25], 2023). Although we could also find 10 studies with moderate evidence (Scribante *et al.* [26], 2024; Mehortra *et al.* [27], 2023; Colombo *et al.* [28], 2021; Piva *et al.* [29], 2020; Koul *et al.* [6], 2020; Seydanur Dengizek *et al.* [30], 2019; Al Habashneh *et al.* [31], 2015; Niveda and Gurumoorthy [32], 2020; Tetè *et al.* [5], 2023 and Issac *et al.* [33], 2015).

Extraction of Sample Data

The following information was collected from the included studies, when available: author names, study design, follow-up period, number of participants per group, mean age, gender, and type of ozone application. Furthermore, clinical parameters were also recorded, including: Plaque Index (PI), Gingival Index (GI), Clinical Attachment Loss (CAL), PPD, and BOP between baseline and final follow-up.

Tables 4 and 5 contain all the studies' characteristics related to ozone-based therapy and Blue®m gel respectively.

Discussion

The aim of this systematic review was to assess the clinical efficacy of reactive oxygen species, including ozone or Blue®m gel, as non-surgical adjuvant therapies in

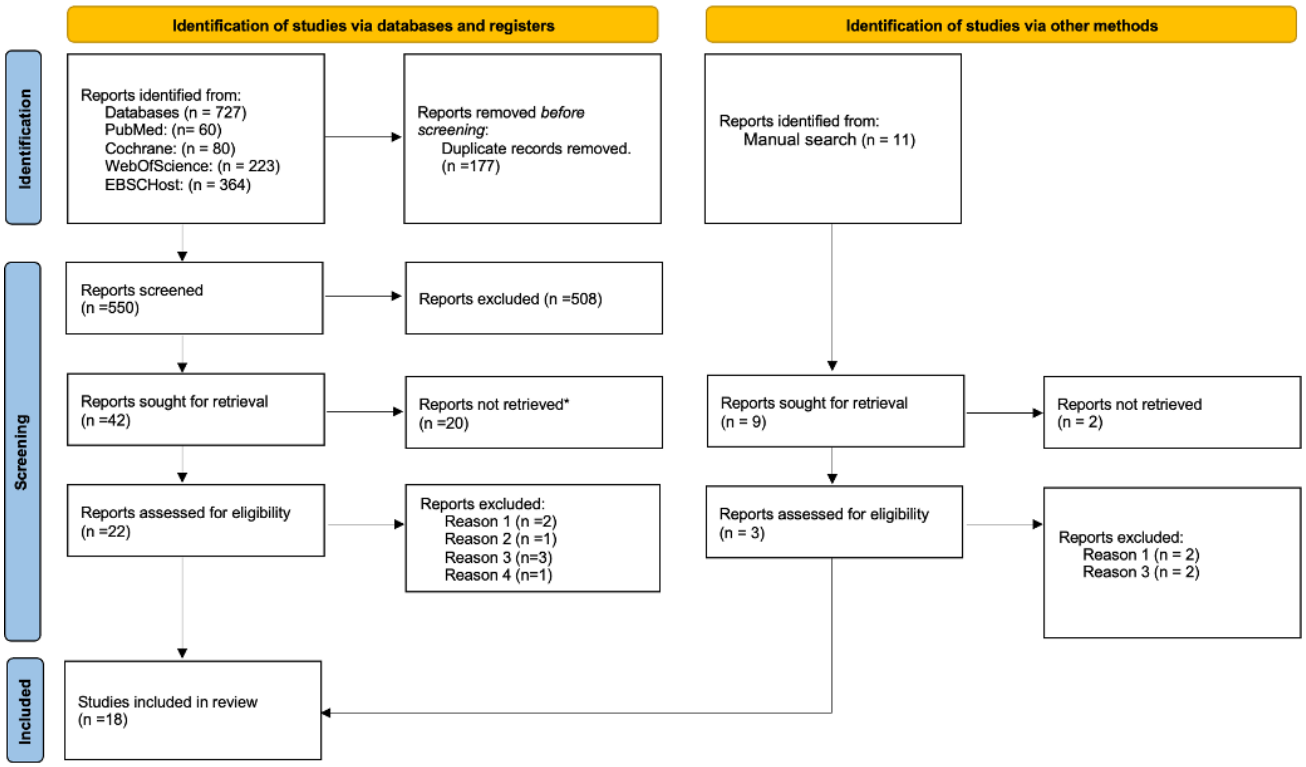

Fig. 1. PRISMA flow diagram of study selection. Reason 1: Irrelevant to the topic; Reason 2: Animal studies; Reason 3: After reading the abstract; Reason 4: *In vitro* studies; * Number of articles whose full text could not be found after attempting to obtain it through various resources. Tables 4 and 5 contain all the studies' characteristics related to ozone-based therapy and Blue®m gel respectively.

the treatment of PD. The data obtained from 18 included studies, including randomized controlled trials, microbiological studies, and case reports, indicate a generally positive trend in favor of the use of these agents as adjuncts to conventional treatments.

According to our results, 10 articles (Cetiner *et al.* [21], 2024; Alsakr *et al.* [25], 2023; Scribante *et al.* [26], 2024; Mehrotra *et al.* [27], 2023; Ramirez-Peña *et al.* [22], 2022; Rapone *et al.* [1], 2022; Colombo *et al.* [28], 2021; Tasdemir *et al.* [23], 2019; Seydanur Dengizek *et al.* [30], 2019; Al Habashneh *et al.* [31], 2015) demonstrated that the efficacy of OT as an adjunct to non-surgical periodontal treatment resulted in an improvement in periodontal parameters, such as PPD, CAL and signs of inflammation after treatment. However, significant differences between groups were found in only one article (Alsakr *et al.* [25], 2023).

Furthermore, two articles (Piva *et al.* [29], 2020; Issac *et al.* [33], 2015), reported that the use of OT reduced anaerobic bacterial colonization.

Conversely, 3 studies (Colombo *et al.* [28], 2021; Barahim *et al.* [20], 2024; and Tetè *et al.* [5], 2023) showed no significant clinical benefit of ozone compared with mechanical treatment alone or with other antiseptic agents, calling into question its systematic efficacy in the management of PD.

Blue®m Gel: A Promising Oxygenated Alternative

The healing process has been shown to be facilitated by oxygen supplementation during wound healing, as it improves the oxidative elimination of bacteria, stimulates angiogenesis, accelerates the formation of the extracellular matrix, and increases fibroblast proliferation and collagen deposition [34,35]. Due to its topical carbamide peroxide-based formulation, enriched with enzymes that release active oxygen, Blue®m gel has been used by dentists, oral surgeons, and implantologists, as it selectively eliminates the anaerobic bacteria associated with periodontitis and promotes the restoration of healthy oral flora. Sodium perborate, a component of Blue®m gel, may serve as a reliable supply of active oxygen. It is an essential active ingredient that controls plaque and promotes wound healing. It initiates a chemical process of hydrolysis upon contact with tissue fluids, releasing hydrogen peroxide and boric acid at low concentrations. In addition to acting as an antibacterial, hydrogen peroxide further releases the nascent oxygen to promote wound healing. Thus, Blue®m gel boosts cellular metabolism and collagen synthesis, facilitates the release of growth factors, including Vascular Endothelial Growth Factor (VEGF) and Fibroblast Growth Factor (FGF), stimulates angiogenesis, and possesses antibacterial properties, thereby enhancing the efficacy of oxygen therapy [35–37].

Table 1. Joanna Briggs Institute Critical Appraisal Checklist for randomized controlled clinical trials.

Joanna Briggs Institute Critical Appraisal Checklist for randomized controlled trials	1	2	3	4	5	6	7	8	9	10	11	12	13
Barahim *et al.* [20], 2024	Y	UN	Y	N	N	UN	Y	Y	UN	Y	Y	Y	Y
Cetiner *et al.* [21], 2024	Y	UN	Y	N	N	UN	Y	Y	UN	Y	Y	Y	Y
Tetè *et al.* [5], 2023	UN	Y	Y	N	UN	UN	Y	Y	Y	Y	Y	N	N
Alsakr *et al.* [25], 2023	Y	UN	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y
Scribante *et al.* [26], 2024	Y	UN	Y	N	N	UN	Y	Y	UN	Y	Y	Y	Y
Mehrotra *et al.* [27], 2023	Y	UN	Y	N	N	UN	Y	Y	UN	Y	Y	Y	Y
Ramirez-Peña *et al.* [22], 2022	Y	UN	Y	N	N	UN	Y	Y	Y	Y	Y	Y	Y
Rapone *et al.* [1], 2022	Y	UN	Y	N	N	UN	Y	Y	UN	Y	Y	Y	Y
Colombo *et al.* [28], 2021	Y	UN	Y	N	N	UN	Y	Y	UN	Y	Y	Y	Y
Niveda and Gurumoorthy [32], 2020	Y	UN	Y	UN	UN	UN	Y	Y	Y	Y	Y	N	Y
Piva *et al.* [29], 2020	Y	UN	Y	N	N	UN	Y	Y	UN	Y	Y	Y	Y
Koul *et al.* [6], 2020	Y	UN	Y	N	N	UN	Y	Y	UN	Y	Y	Y	Y
Tasdemir *et al.* [23], 2019	Y	UN	Y	Y	Y	UN	Y	Y	UN	Y	Y	Y	Y
Seydanur Dengizek *et al.* [30], 2019	Y	UN	Y	N	N	UN	Y	Y	UN	Y	Y	Y	Y
Uraz *et al.* [24], 2019	Y	UN	Y	N	N	UN	Y	Y	UN	Y	Y	Y	Y
Al Habashneh *et al.* [31], 2015	Y	UN	Y	N	N	UN	Y	Y	UN	Y	Y	Y	Y

1. Was True Randomization Used for Assignment of Participants to Treatment Groups? 2. Was Allocation to Treatment Groups Concealed? 3. Were Treatment Groups Similar at the Baseline? 4. Were Participants Blind to Treatment Assignment? 5. Were Those Delivering Treatment Blind to Treatment Assignment? 6. Were Outcomes Assessors Blind to Treatment Assignment? 7. Were Treatment Groups Treated Identically Other Than the Intervention of Interest? 8. Was Follow up Complete and If Not, were the differences between Groups in Terms of Their Follow up Adequately Described and Analyzed? 9. Were Participants Analyzed in the Groups to Which They Were Randomized? 10. Were Outcomes Measured in the Same Way for Treatment Groups? 11. Were Outcomes Measured in a Reliable Way? 12. Was Appropriate Statistical Analysis Used? 13. Was the Trial Design Appropriate, and any Deviations from the Standard RCT Design (Individual Randomization, Parallel Groups) Accounted for in the Conduct and Analysis of the Trial?

Table 2. Joanna Briggs Institute Critical Appraisal Checklist for case reports.

Joanna Briggs Institute Critical Appraisal Checklist for case reports	1. Were the patient's demographic characteristics clearly described?	2. Was the patient's history clearly described and presented as a timeline?	3. Was the current clinical condition of the patient on presentation clearly described?	4. Were diagnostic tests or assessment methods and the results clearly described?	5. Was the intervention(s) or treatment procedure(s) clearly described?	6. Was the post-intervention clinical condition clearly described?	7. Were adverse events (harms) or unanticipated events identified and described?	8. Does the case report provide takeaway lessons?
Alayadi *et al.* [7], 2024	Y	Y	Y	Y	Y	Y	N	Y

Table 3. Joanna Briggs Institute Critical Appraisal Checklist for case control studies.

Joanna Briggs Institute Critical Appraisal Checklist for randomized controlled trials	1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	2. Were cases and controls matched appropriately?	3. Were the same criteria used for the identification of cases and controls?	4. Was exposure measured in a standard, valid, and reliable way?	5. Was exposure measured in the same way for cases and controls?	6. Were confounding factors identified?	7. Were strategies to deal with confounding factors stated?	8. Were outcomes assessed in a standard, valid, and reliable way for cases and controls?	9. Was the exposure period of interest long enough to be meaningful?	10. Was an appropriate statistical analysis used?
Issac *et al*. [33], 2015	Y	N	Y	Y	Y	N	N	Y	Y	Y

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Table 4. Relevant data collected from studies related to ozone-based therapy.

Author	Study design	Inclusion criteria	Sample	Local/Topical therapy based on	Results	Conclusion
Barahim *et al.* [20], 2024	Randomized controlled clinical trial	- Patients with stage III grade B periodontitis	24 type II diabetic patients with periodontitis (18 women, 6 men) CG: SRP alone (n = 12 [11 females and 1 male]) with a mean age of 46.7 ± 4.7 TG: SRP + Ozone (n = 12 [7 females and 5 males]) with a mean age of 44.3 ± 5.5	Ozone gel	CG vs TG (Mean ± SD): 0M: BOP % (58.5 ± 8.7) vs (61.2 ± 13.4) PI% (70.2 ± 14.4) vs (72.5 ± 15.8) PPD (6.1 ± 0.32) vs (6.44 ± 0.53) 3M: CAL: (2.33 ± 1.08) vs (3.6 ± 1.71) PPD (2.25 ± 1.29) vs (3.3 ± 0.67) 6M: BOP% (10.6 ± 6.8) vs (9.3 ± 7.6) PI% (16.2±6.6) vs (19 ± 8.8) CAL (3.2 ± 1.14) vs (3.89 ± 1.76) PPD (3 ± 1.33) vs (3.33 ± 0.71)	Both groups show improvement, but the CG demonstrates better clinical recovery at 6 months, with shallower pockets and more stable attachment. Statistically significant improvements in PPD reduction at 3 months between TG and CG ($p \leq 0.05$).
Cetiner *et al.* [21], 2024	A randomized controlled clinical trial	- Participants were required to be ≤ 35 years old -Have ≥ 12 teeth - Residual PPD ≥ 6 mm - Inter-proximal defects with ≥3 mm intrabony defects - FMPS and FMBS ≤ 20% - No degree 2 or 3 mobility.	24 patients with periodontitis. CG: Surgical treatment + saline irrigation (n = 12 [9 females and 3 males]) with a mean age of 31.3 ± 6.17 TG: Surgical treatment + Ozone application (n = 12 [9 females and 3 males]) with a mean age of 31.3 ± 5.97	Topical gaseous ozone (OzoneDTA generator, APOZA)	CG vs TG (Mean ± SD): 0M: BOP: (70.0 ± 5.85) vs (67.5 ± 5.85) PPD: (4.35 ± 0.24) vs (4.13 ± 0.24) CAL: (4.55 ± 0.25) vs (4.15 ± 0.25) 6M: BOP: (10.0 ± 5.22) vs (17.5 ± 5.22) PPD: (2.80 ± 0.15) vs (2.25 ± 0.15) CAL: (3.08 ± 0.18) vs (2.35 ± 0.18)	TG demonstrated a greater gain in CAL and a larger reduction in PPD. The differences between the two groups remain moderate and not clinically substantial.
Tetè *et al.* [5], 2023	Randomized controlled trial	Pathological clinical periodontal indices (BOP 20%, PI 20%, PPD 4 mm); presence of at least 20 teeth; absence of any periodontal treatment in the last 12M.	30 Caucasian patients (18 women/12 men) aged between 35 and 65 years CG: SRP alone TG: SRP + ozonated gel (Ozoral) Patients were assessed at four different time points: T0: Screening T1: SRP T2: 1M from SRP T3: 3M from SRP T4: 6M from SRP	Ozone gel (Ozoral)	BOP tends to be significant in TG, $p = 0.06$. From T0 to T4 ozone gel showed a greater influence in decreasing BOP than CG, $p = 0.05$. PPD decreased in TG compared to CG, but not confirmed by statistical analysis $p = 0.07$.	The two groups' reductions in clinical periodontal parameters, such as PI, BOP, and PPD, do not differ statistically significantly. Ozoral gel would not seem to improve NSPT alone.

Table 4. Continued.

Author	Study design	Inclusion criteria	Sample	Local/Topical therapy based on	Results	Conclusions
Alsakr *et al*. [25], 2023	Split-mouth study randomized controlled trial	Patients of both genders aged between 30 and 70 years old; with minimum presence of 12 teeth evenly distributed across the four quadrants; Patients diagnosed with stage II or stage III periodontitis	46 patients 31 males/15 females. CG: side treated with SRP alone TG: side treated with SRP + Ozone	Ozone	CG vs TG: 6W follow-up [Median (IQR)] BOP: 43.50 (26.25) vs 50.00 (30.75), (p = 0.0001) PI: 44.50 (32.25) vs 48 (30.75), (p = 0.042). CAL: 1.00 (0.00) vs 2.00 (1.00), (p = 0.0001). PPD: 1.00 (0.00) vs 2.00 (1.00), (p = 0.0001)	From baseline to 6W of follow-up, PPD, CAL, PI, and BOP showed significant changes ($p < 0.0001$). Significant changes (PPD = 0.0001, CAL = 0.0001, PI = 0.042, and BOP = 0.0001) were observed between the CG and TG.
Scribante *et al*. [26], 2024	A randomized clinical trial (split-mouth study)	-Adult patients aged 18–70 -Bilateral periodontal sites (Severity: Staging I; Complexity: Staging II) -No SD -Compliant with home gel use	30 patients (15 females with a mean age of 59.65 ± 7.52 and 15 males with a mean age of 59.14 ± 11.1 Randomized quadrants (n = 120) CG quadrants treated with CHX (n = 60) TG: quadrants with ozone gel (n = 60)	Ozonated gels (Ozoral Gel and Ozoral Pro)	CG vs TG: (Mean ± SD): Baseline: CAL: (6.47 ± 1.84) vs (6.50 ± 1.81); PPD: (6.13 ± 1.40) vs (6.21 ± 1.61); PCR: (80.73 ± 17.33) vs (81.52 ± 17.73); BOP: (34.20 ± 21.23) vs (33.71 ± 19.46) 6M: CAL (5.27 ± 2.34) vs (4.77 ± 1.86); PPD: (4.65 ± 1.57) vs (4.37 ± 1.52); PCR: (36.13 ± 15.03) vs (31.60 ± 14.95); BOP: (13.16 ± 10.11) vs (8.48 ± 9.27)	CAL, PPD, BOP, and PCR exhibited significant intragroup improvements in both groups ($p < 0.05$), in contrast with intergroup differences ($p > 0.05$). A significantly higher reduction resulted for PPD and CAL values in the group treated with ozone. The number and percentage of residual pockets (PPD ≥ 5 mm) were 68 (33.66%) for the TG and 88 (43.56%) for the CG.
Mehrotra *et al*. [27], 2023	A clinical-microbial study (split-mouth study)	-Patients with chronic periodontitis: systemically healthy patients aged between 30 and 65 years -Patients with PPD ≥ 5 mm -Patients who had not taken antibiotics in the last 6M, -Patients with horizontal bone loss in the OPG.	26 patients with CP (12 females, 14 males) with an age between 30 and 65 years. Group A: n = 26 quadrants (SRP + OT) Group B: n = 26 quadrants (SRP + photodynamic therapy)	OT	Group A vs Group B (Mean ± SD) Baseline: PI (1.96 ± 0.34) vs (1.93 ± 0.38); GI (1.91 ± 0.25) vs (1.91 ± 0.27); PPD (5.27 ± 0.45) vs (5.23 ± 0.43) CAL (5.31 ± 0.47) vs (5.27 ± 0.45) 1M: PI (1.66 ± 0.37) vs (1.57 ± 0.37) GI (1.41 ± 0.42) vs (1.33 ± 0.39) PPD (4.42 ± 0.76) vs (4.12 ± 0.59) CAL (4.46 ± 0.81) vs (4.15 ± 0.61) 2M: PI (1.36 ± 0.33) vs (1.28 ± 0.35) GI (1.19 ± 0.23) vs (1.11 ± 0.28); PPD (3.50 ± 0.51) vs (3.23 ± 0.51); CAL (3.54 ± 0.58) vs (3.27 ± 0.53)	Group A showed a significant decrease in periodontal parameters (PI, GI, PPD, and CAL) from baseline to 1 and 2M post treatment. The χ^2 test showed that there was no statistically significant difference between groups regarding periodontal pathogens in the two groups at 2M ($p > 0.05$).

Table 4. Continued.

Author	Study design	Inclusion criteria	Sample	Local/Topical therapy based on	Results	Conclusion
Ramirez-Peña *et al.* [22], 2022	A clinical and microbiological study (split-mouth study)	- Selected patients had to have a minimum of 12 teeth evenly distributed in the four quadrants of the mouth	32 patients (10 men, 22 women) aged 34–64 with generalized periodontitis. CG: SRP + air TG: SRP + ozone	OT	CG vs TG: (Mean) Baseline: GI (1.42) vs (1.37) CAL (3.91) vs (4.05) MOV (0.23) vs (0.38) 3W: GI (1.47) vs (0.57) CAL (3.99) vs (2.24) MOV (0.21) vs (0.19) 6W: GI (1.40) vs (0.48) CAL (4.09) vs (2.00) MOV (0.23) vs (0.14)	Significant intragroup differences were found between each time point for both the TG and CG ($p < 0.05$); No significant intergroup differences were found between locations ($p > 0.05$).
Rapone *et al.* [1], 2022	A randomized controlled clinical trial	-Adult patients diagnosed with moderate-to-severe periodontitis with at least 16 teeth (four in each quadrant) -Aged $\geq$ 18 years -Able to provide informed consent.	90 patients with moderate or severe generalized periodontitis, with a mean age of 51.56 $\pm$ 10.35 years. TG: SRP + ozone (n = 45 [87% males and 13% females]) CG: SRP alone (n = 45 [78% males and 22% females])	Gaseous ozone	TG vs CG (Mean $\pm$ SD) Baseline: PPD (5.39 $\pm$ 0.31) vs (5.37 $\pm$ 0.2); CAL (5.53 $\pm$ 0.27) vs (5.78 $\pm$ 0.3) BOP (49 $\pm$ 14.74) vs (50.83 $\pm$ 18.11) 3M: PPD (2.75 $\pm$ 0.59) vs (3.2 $\pm$ 0.6) CAL (2.99 $\pm$ 0.53) vs (3.38 $\pm$ 0.6); BOP (8.12 $\pm$ 4.6) vs (17.78 $\pm$ 7.05) 6M: PPD (2.67 $\pm$ 0.48) vs (3.28 $\pm$ 0.71): CAL (2.85 $\pm$ 0.48) vs (3.42 $\pm$ 0.75); BOP (6.27 $\pm$ 3.32) vs (12.83 $\pm$ 5.7)	A significant statistical difference was observed between the groups in respect to baseline values in CAL ($p \leq 0.0001$), PPD ($p \leq 0.0001$), and BOP ($p \leq 0.0001$). SRP combined with OT revealed an improved outcome than SRP alone.

Table 4. Continued.

Author	Study design	Inclusion criteria	Sample	Local/Topical therapy based on	Results	Conclusion
Colombo *et al.* [28], 2021	Randomized clinical trial (split-mouth study)	- Participants of both sexes with periodontitis at stage III and grade B	10 patients (4 males and 6 females. Mean age 50 years old) CG: sites treated with SRP + CHX TG: sites treated with SRP + ozone	Ozonized gel with GeliO3; CHX	CG vs TG (Mean ± SD) Baseline: PPD (5.94 ± 0.89) vs (6.21 ± 0.92); CAL (6.13 ± 0.81) vs (6.00 ± 0.83); GI (1.67 ± 0.39) vs (1.67 ± 0.56); PI (86 ± 16) vs (85 ± 18); BOP (33 ± 13) vs (43 ± 27) 3M: PPD (3.95 ± 0.52) vs (4.20 ± 0.48); CAL (3.99 ± 0.56) vs (4.32 ± 0.47); GI (0.71 ± 0.36) vs (0.91 ± 0.35); PI (36 ± 8) vs (39 ± 7); BOP (9 ± 6) vs (9 ± 4)	Clinical periodontal parameters significantly improve after 1 and 3M, with respective to baseline. However, no significant differences were observed between groups for most parameters ($p > 0.05$). At 3M, CHX was more effective than ozone gel in reducing CAL and GI.
Piva *et al.* [29], 2020	Splitmouth, randomized, controlled clinical trial	-Patients diagnosed with chronic periodontitis with no history of recent periodontal treatment.	10 patients (5 men and 5 women, with a mean age of 55 ± 7 years) Control quadrants: SRP only (right quadrants) Test quadrants: SRP + ozonated water (left quadrants).	Ozonline®	SRP with Ozonline® reduced bacterial load significantly. The test group showed a remarkable reduction compared to the CG. *Tannerella forsythia* and *Treponema denticola* were eradicated. *Porphyromonas gingivalis* showed a 38% reduction, and the total bacterial load decreased by 55.0%.	Ozonline® has been shown to be effective in the treatment of moderate to severe chronic periodontitis.
Tasdemir *et al.* [23], 2019	A randomized placebo-controlled clinical trial (split-mouth study)	-Aged 18 to 64 with moderate-to-severe generalized periodontitis -Systemically healthy -Having more than 20 teeth (excluding third molars).	36 moderate to severe generalized periodontitis patients (18 males and 18 females with a mean age of 43.7 years CG: side treated with SRP + placebo TG: side treated with SRP + ozone	Gaseous ozone	CG vs TG (Mean ± SD) Baseline: PI (2.42 ± 0.4) vs (2.34 ± 0.4); GI (2.30 ± 0.4) vs (2.21 ± 0.4); PD (3.17 ± 0.6) vs (3.24 ± 0.7); BOP (92 ± 6.8) vs (90 ± 5.7) 3M: PI (1.1 ± 0.5) vs (1.2 ± 0.5); GI (1.22 ± 0.4) vs (1.15 ± 0.4); PD (2.01 ± 0.5) vs (1.97±0.5); BOP (31.1 ± 11.9) vs (32.9 ± 12.5)	A significant intragroup improvement was observed in PI, GI, PPD, and BOP after 3M ($p < 0.05$), with no significant difference between them ($p > 0.05$).

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Table 4. Continued.

Author	Study design	Inclusion criteria	Sample	Local/Topical therapy based on	Results	Conclusion
Seydanur Dengizek *et al.* [30], 2019	Randomized controlled trial	- Patients with generalized CP, defined by PPD of 4–6 mm in at least two quadrants, RBL, and at least 20 teeth.	37 patients with a mean age of 42.4 years TG: SRP + ozone (n = 19; 8 females and 11 males) CG: SRP + placebo (n = 18; 8 females and 10 males)	Gaseous ozone	CG vs TG (Mean ± SD) Baseline: PI (2.4 ± 0.6) vs (2.5 ± 0.6); GI (2.1 ± 0.6) vs (2.3 ± 0.7); PD (3.6 ± 0.8) vs (3.8 ± 0.8); CAL (4.1 ± 0.8) vs (4.4 ± 1.1) 1M: PI (0.6 ± 0.2) vs (0.6 ± 0.2); GI (0.9 ± 0.2) vs (0.8 ± 0.2); PD (3.0 ± 0.8) vs (3.0 ± 0.6); CAL (3.8 ± 0.8) vs (4.0 ± 0.7)	Both groups showed significant improvements in clinical parameters after treatment, with no significant difference between them.
Uraz *et al.* [24], 2019	Clinical, microbiological, and biochemical aspects (split-mouth design)	-Good general health -No periodontal treatment or medication in the last 6M -Non-smoker -Not pregnant or lactating -No contraindications for periodontal treatment or ozone application -≥ 30% sites with bone loss, and ≥ 3 sites with PD ≥ 5 mm in 2 quadrants.	18 patients with generalized CP (9 males and 9 females with a mean age 40 ± 6.51 years) TG: SRP + OT (n = 18) CG: SRP alone (n = 18)	Ozone gaseous therapy	CG vs TG (Mean±SD) Baseline: PI (1.27 ± 0.43) vs (1.23 ± 0.46); GI (1.61 ± 0.32) vs (1.58 ± 0.33); BOP (67.42 ± 18.95) vs (69.44 ± 12.54); PPD (5.91 ± 1.05) vs (5.87 ± 1.13) 3M: PI (0.78 ± 0.34) vs (0.73 ± 0.30); GI (1.14 ± 0.24) vs (1.03 ± 0.28); BOP (19.44 ± 22.15) vs (15.55 ± 18.60); PPD (3.98 ± 0.92) vs (3.95 ± 0.96).	Both groups showed significant improvements in clinical parameters after 3M (reduction in PI, GI, BOP, and PPD) ($p < 0.05$). No significant differences were observed between the CG and TG ($p > 0.05$). A statistically significant difference was observed in the baseline values and follow-up values at 3M for PI ($p = 0.049$) and total bacterial count ($p = 0.05$) in the TG ($p < 0.05$).

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Table 4. Continued.

Author	Study design	Inclusion criteria	Sample	Local/Topical therapy based on	Results	Conclusion
Issac *et al.* [33], 2015	A clinical and microbiological study (split-mouth design)	-Healthy adolescents aged 35–55 - CP -Signed informed consent, ethical approval -No therapy in the last 6M -Two sites with PPD ≥6 mm	30 systemically healthy (19 males and 11 females with ages between 35 and 55 years) CG: SRP alone TG: SRP + ozonized water irrigation	Ozonized water	CG vs TG (Mean ± SD) Baseline: GI (2.00 ± 0.21) vs (1.88 ± 0.33); PPD (6.67 ± 0.88) vs (6.43 ± 0.73); CAL (6.80 ± 1.06) vs (6.90 ± 0.92); CFU (606.20 ± 145.63) vs (644.10 ± 108.63) After SRP: AC (114.73 ± 18.95) vs (108.23 ± 20.30) 4W: GI (1.13 ± 0.33) vs (0.73 ± 0.27); PPD (5.67 ± 1.06) vs (3.93 ± 1.72); CAL (5.73 ± 1.11) vs (4.40 ± 1.85); CFU (162.67 ± 15.79) vs (77.43 ± 13.27)	GI, PPD, and CAL showed statistically significant reduction after 4W in both test and control sites ($p < 0.0001$). TG exhibited more significant improvement in the clinical parameters compared to the CG. Microbiologically, the TG showed a 28.5% reduction in anaerobic bacterial colonies, while the CG showed a 41.8% increase.
Al Habashneh *et al.* [31], 2015	Randomized controlled clinical trial	-Patients diagnosed with chronic periodontitis based on modified Machtei's criteria, with PPD >5 mm at more than two interproximal sites -RBL, and CAL >6 mm -Nonsmokers -With at least 20 natural teeth - No periodontal treatment in the last 6M.	41 patients with CP CG: SRP + distilled water (n = 21, 6 males and 14 females with a mean age of 39.0 ± 10.2) TG: SRP + ozonated water (n = 20, 7 males and 14 females with mean age of 39.7 ± 13.7)	Ozonated water	CG vs TG (Mean ± SD) Baseline: GI (1.6 ± 0.5) vs (1.6 ± 0.5); PI (1.5 ± 0.6) vs (1.6 ± 0.5); BOP (72.0 ± 28.0) vs (75.0 ± 26.0); PPD (2.4 ± 0.4) vs (2.8 ± 0.4); CAL (1.7 ± 1.2) vs (1.5 ± 1.2) 3M: GI (1.3 ± 0.6) vs (1.5 ± 0.6); PI (1.1 ± 0.8) vs (1.1 ± 0.7); BOP (26.0 ± 24.0) vs (23.0 ± 20.0); PPD (2.0 ± 0.3) vs (2.0 ± 0.4); CAL (1.1 ± 1.0) vs (1.1 ± 1.1)	Both types of treatment showed statistically significant PPD reduction at 3M after treatment for both levels, with no statistically significant difference between groups. Both groups showed significant clinical improvements from baseline to 3M except for the GI. No significant differences were observed between the TG and CG in any of the evaluated parameters.

AC, anaerobic colony; BOP, bleeding on probing; CAL, Clinical Attachment Loss; CFU, colony forming units; CG, control group; CP, chronic periodontitis; CHX, chlorhexidine; FMPS, full mouth plaque score; FMBS, full mouth bleeding score; IQR, interquartile range; MOV, Miller's mobility index; NSPT, non-surgical periodontal therapy; OPG, orthopantomogram; PI, Plaque Index; PPD, periodontal probing depths; RBL, radiographic bone loss; SD, standard deviation; Sd, systemic disease; SRP, scaling and root planing; TG, test group; 7D, seven days; 14D, fourteen days; 3W, three weeks; 4W, four weeks; 6W, six weeks; 1M, one month; 3M, three months; 6M, six months; 12M, twelve months; GI, Gingival Index; PD, periodontal disease; OT, ozone therapy.

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Table 5. Relevant data collected from studies related to Blue®m gel.

Author	Study design	Inclusion criteria	Sample size	Local/Topical therapy based on	Results	Conclusions
Alayadi *et al*. [7], 2024	A case report	NR	1 patient: 36 years-old women	Blue®m gel	Baseline: PI = 21.0%; GI = 2.0%; BOP = 14.0%; PPD = 5–7 mm 7D: PI = 50%; GI = 2.0%; BOP = 38.0% 14D: PI = 15%; GI = 2.0%; BOP = 9.0%; PPD reduction = 1–2 mm	Blue®m gel proved its effectiveness. A notable improvement in periodontal health was observed within just 14D, with a significant reduction in PPD, PI, and BOP.
Niveda and Gurumoorthy [32], 2020	Splitmouth study randomized controlled trial	Patients with generalized BOP presence of PPD $>$ 5 mm. Healthy patients, without Sd, medication, and non-smokers.	10 patients: 6 males/ 4 females aged between 23 and 53 years 20 sites were assessed for evaluation Group A: Blue®m gel 10 sites Group B: CHX gel 10 sites	Blue®m gel CHX gel	Periodontal parameters on the day of drug delivery vs 6W after drug delivery (Mean $\pm$ SD): Group A: PPD: 7.2 mm $\pm$ 0.42 mm vs 4.7 $\pm$ 0.57 mm CAL : 4.70 mm $\pm$ 0.43 mm vs 2.50 $\pm$ 0.52 mm BOP: 2.30 mm $\pm$ 0.48 mm vs 0.70 $\pm$ 0.48 mm Group B: PPD: 7.0 mm $\pm$ 0.57 mm vs 5.7 $\pm$ 0.64 mm CAL: 4.72 mm $\pm$ 0.45 vs 2.80 mm $\pm$ 0.78 mm BOP: 2.60 mm $\pm$ 0.51 vs 1.40 mm $\pm$ 0.51 mm	There was a significant difference in the reduction of PPD. The mean difference in reduction of PPD (Baseline-6W) Group A: 2.3 mm Group B: 1.5 mm Group A showed better potential in PPD reduction.
Koul *et al*. [6], 2020	A clinical-microbiological study (split-mouth design)	-Age 20–50 years -Both sexes, -CP -PPD $\leq$5 mm -GI and PI	30 patients with chronic periodontitis with an age between 20 and 50 years. CG: SRP + CHX gel TG: SRP + Blue®m gel	Blue®m gel CHX gel	After 1M, both groups showed significant clinical improvements. The results are based on a semi-quantitative scale without numerical data.	Blue®m gel proved to be highly effective and equivalent to CHX gel in the treatment of mild to moderate periodontal pockets. Both the CHX gel and the Blue®m gel had comparable efficacy in the treatment of CP.

BOP, bleeding on probing; CAL, Clinical Attachment Loss; CG, control group; CHX, chlorhexidine; CP, chronic periodontitis; GI, Gingival Index; NR, non referred; PI, Plaque Index; PPD, periodontal probing depths; SD, standard deviation; SRP, scaling and root planing; TG, test group; 6W, six weeks; 7D, seven days; 14D, fourteen days; 1M, one month.

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This gel appears to have exceptional qualities compared to traditional methods of local drug administration, increasing oxygen levels in periodontal pockets, reducing gum bleeding and wounds caused by traumatic extractions, and promoting better healing [6,9].

Regarding Blue®m, two articles, Alayadi *et al.* [7], 2024; Niveda and Gurumoorthy [32], 2020, argued that there was a clinical improvement in periodontal parameters within 14 days to three months. Although the study by Koul *et al.* [6], 2020 argued that no significant differences were found between groups.

The study by Alayadi *et al.* [7], 2024 described the case of a patient with deep periodontal pockets (5–7 mm) successfully treated in just 14 days using Blue®m gel, with a marked reduction in BOP (from 14.0% to 9.0%) and a notable improvement in PI and PPD. These data confirm the rapid, localized action of the gel in the context of active periodontal pockets.

In a split-mouth study by Niveda and Gurumoorthy [32], 2020 of Blue®m gel vs chlorhexidine (CHX), demonstrated that there was a significant difference in PPD reduction between groups, with the group of Blue®m gel showing better results. These findings highlight how comprehensive subgingival cleaning and root planing, in conjunction with topical oxygen adjuvant therapy, aid in the reduction of periodontal pockets. Furthermore, the use of Blue®m gel in an appropriate concentration could be a safe and effective alternative to CHX, with potentially fewer long-term side effects (such as pigmentation or changes in taste).

Finally, in the clinical study by Koul *et al.* [6], 2020, Blue®m gel was compared to CHX as an adjuvant to root planing. Both groups showed significant improvement in GI, PPD, and CFU after one month, with no statistical difference between them. This clinical equivalence between the two agents confirms the value of Blue®m in the management of chronic periodontitis (CP), while highlighting its potentially superior tolerability. These results are consistent with the study by Niveda and Gurumoorthy [32], 2020 in which the Blue®m group showed better potential in reducing PPD.

In summary, current data position Blue®m as an innovative and effective therapeutic option, particularly in cases where a gentle approach, without adverse effects, is preferred. However, the absence of large-scale randomized trials and the predominance of clinical case reports or short-term studies still limit the generalizability of these results. Robust clinical research is needed to refine its exact role in the standardized periodontal treatment protocol and as an alternative to OT.

Clinical Efficacy of OT

The use of OT has been shown to be an effective method for maximizing the healing process of oral wounds. Epithelial cells, fibroblasts, endothelial cells, macrophages, and platelets are all involved in the intricate, multicellular process of wound healing [34,39]. Wounds are regions of tissue that usually have lower oxygen levels, which may be linked to impaired hemodynamics and a lower oxygen delivery to the tissue. It may take months or even years for chronic wounds that are deficient in vital nutrients to heal. Consequently, oxygen is an essential component of wound healing and plays a key role in wound contraction and granulation tissue formation during the secondary healing process [34]. During wound healing treatments, oxygen is rapidly consumed and supplied with ozone or hyperbaric oxygen therapy [40]. All clinical data from this systematic review confirm that OT, when used as adjuvant therapy to mechanical debridement, can lead to significant improvements in clinical parameters in patients with periodontitis. Six studies (Issac *et al.* [33], 2015; Piva *et al.* [29], 2020; Rapone *et al.* [1], 2022; Ramirez-Peña *et al.* [22], 2022; Alayadi *et al.* [7], 2024; Cetiner *et al.* [21], 2024; have demonstrated the clinical efficacy of OT on the periodontium. Two studies (Issac *et al.* [33], 2015; Piva *et al.* [29], 2020) have demonstrated a reduction in anaerobic bacterial colonies using ozone therapy.

OT is based on a multifactorial mechanism of action, combining antimicrobial, anti-inflammatory, healing, and regenerative effects, making it a promising adjuvant approach in the treatment of PD. These effects were clinically confirmed by studies of Rapone *et al.* [1], 2022, Cetiner *et al.* [21], 2024, and Alsakr *et al.* [25], 2023, reporting a significant reduction in BOP, PPD, and an improvement in CAL. Because of its high oxidizing power, ozone preferentially targets Gram-negative anaerobic bacteria responsible for periodontal infections, such as *Porphyromonas gingivalis*, *Treponema denticola*, or *Tannerella forsythia*. By oxidizing pathogen phospholipids and membrane proteins, it causes membrane disorganization and rapid cell lysis, leading to a direct reduction in bacterial load. In addition, it inhibits microbial recolonization, as shown by Issac *et al.* [33], 2015, where a decrease of 28.5% in anaerobic colonies was observed in the ozone group, in comparison to an increase in the control group (CG). Ozone also promotes the release of singlet oxygen, which improves tissue oxygenation, stimulates fibroblast proliferation and osteoblastic differentiation, contributing to periodontal and alveolar bone regeneration, as demonstrated by Colombo *et al.* [28], 2021. Thus, ozone acts on several levels, not limiting itself to a simple antiseptic action, but actively participating in the restoration of a healthy periodontal environment.

In the study by Issac *et al.* [33], 2015, subgingival irrigation with ozonated water resulted in a significant reduction in PPD, an improvement in CAL, and a significant decrease in anaerobic bacterial colonies, particularly compared with the CG, where recolonization was observed. In a complementary study, Piva *et al.* [29], 2020 showed that the use of ozonated water (Ozonline®) led to a marked reduction in the bacterial load, particularly of *Tannerella forsythia* and *Treponema denticola*, while being well toler-

ated by patients.

In clinical terms, the most significant results come from controlled trials of good methodological quality. Rapone *et al*. [1], 2022 reported a substantial reduction in PPD (from 5.39 mm to 2.67 mm) and BOP (from 49.0% to 6.27%) after 6 months in the ozone group, compared with a more modest improvement in the CG. Ramirez-Peña *et al*. [22], 2022 also noted a rapid and marked improvement in CAL in the ozone group (from 4.05 mm to 2.00 mm in 6 weeks), contrasting with the absence of any notable change in the CG, suggesting a real and rapid efficacy of ozone in certain indications. Despite these results, in the study by Tetè *et al*. [5], 2023, no differences were found between groups in terms of PI, BOP, and PPD.

Cetiner *et al*. [21], 2024 reinforced these observations by showing that, in the post-surgical context, the application of ozone gas resulted in greater attachment gain and a more marked reduction in BOP and PPD than saline irrigation. This result highlights the potential value of ozone even in more complex situations, such as deep intraosseous defects. Finally, Scribante *et al*. [26], 2024 evaluated the use of ozonated gels in a post-SRP domiciliary approach. Although the results showed significant improvements for all clinical parameters (CAL, PPD, BOP, CRP), no statistically significant difference was observed between the ozonated gel and CHX, highlighting comparable efficacy between the two agents.

Overall, these results support the hypothesis that ozone, in its various forms, represents an effective therapeutic adjunct, helping to improve clinical outcomes in the non-surgical treatment of periodontitis. However, this efficacy remains conditioned by several factors, such as the mode of application, frequency of sessions, severity of disease, and the systemic context of the patient, which justifies an exhaustive analysis of the limitations of this approach.

Limitations to the Clinical Efficacy of OT

Despite the overall positive results, several studies have highlighted clinical limitations to the use of OT as an adjuvant in periodontal treatment. For example, in the randomized controlled trial conducted by Seydanur Dengizek *et al*. [30], 2019, although improvements were observed in both groups (ozone vs. placebo), no statistically significant differences between groups were reported, in terms of PI, GI, PPD, and CAL after one month. This result suggests that the clinical effect of ozone may not exceed that achieved by mechanical instrumentation alone in the short term. Similarly, Tasdemir *et al*. [23], 2019, in a split-mouth study with three-month follow-up, observed a significant reduction in periodontal indices in both groups (ozone vs. placebo), with no statistical advantage in favor of ozone, calling into question the relevance of its routine use.

Colombo *et al*. [28], 2021, in a comparative study between ozone and CHX, found no clinical superiority of ozonated gel at three months, and even reported a better reduction in CAL in the CHX group. These results underline that, under certain clinical conditions, more conventional treatments could offer equivalent or even superior efficacy to OT. Furthermore, a study by Barahim *et al*. [20], 2024 in diabetic patients showed that, despite improvement in both groups (ozone vs. SRP alone), the CG showed a more favorable clinical response after six months, with more stable pocket reduction and greater attachment gain. This may indicate that the effects of ozone can be attenuated in specific systemic contexts, such as diabetes.

Finally, Mehrotra *et al*. [27], 2023 compared ozone to photodynamic therapy in addition to SRP and reported similar improvement in both groups, with no statistically significant difference. These results show that ozone has not demonstrated a superior effect over other emerging adjunctive therapies.

In summary, although OT shows promising potential, these studies serve as a reminder that it is not systematically superior to conventional treatments or other alternative approaches. Its efficacy may vary according to clinical conditions, duration of follow-up, study population, and protocol used.

Blue®m Gel or OT

It would be interesting to compare the clinical efficacy of these two local oxygen-based therapies, but this is not yet possible due to a lack of information from studies comparing the use of these two adjuvant approaches with oxygen.

Clinically, ozone studies (Rapone *et al*. [1], 2022; Ramirez-Peña *et al*. [22], 2022; Cetiner *et al*. [21], 2024; Issac *et al*. [33], 2015 have demonstrated significant effects on PPD reduction, CAL improvement, as well as a reduction in inflammatory signs (BOP, GI), including in complex cases of deep intraosseous sites. However, some trials (Tasdemir *et al*. [23], 2019; Seydanur Dengizek *et al*. [30], 2019; Mehrotra *et al*. [27], 2023) have shown that these benefits are not systematically superior to those achieved by mechanical treatment alone or compared with other adjuvants.

Blue®m gel, on the other hand, although not yet studied in large-scale randomized trials, has shown comparable efficacy to CHX (Koul *et al*. [6], 2020), with better tolerability, and rapid action on clinical signs (Alayadi *et al*. [7], 2024), particularly in peri-implant settings or in at-risk patients. The *in vitro* study by Deliberador *et al*. [9], 2020 confirmed antibacterial activity equivalent to CHX at high concentration, notably against *Porphyromonas gingivalis*.

From a practical point of view, OT requires specific equipment (ozone generator, irrigation, or diffusion devices) and appropriate training and is often reserved for use in dental practice. Blue®m gel, on the other hand, is easy to apply and well tolerated, and can be used at home by the patient in the maintenance phase, promoting long-term compliance without the side effects associated with chlorhexidine.

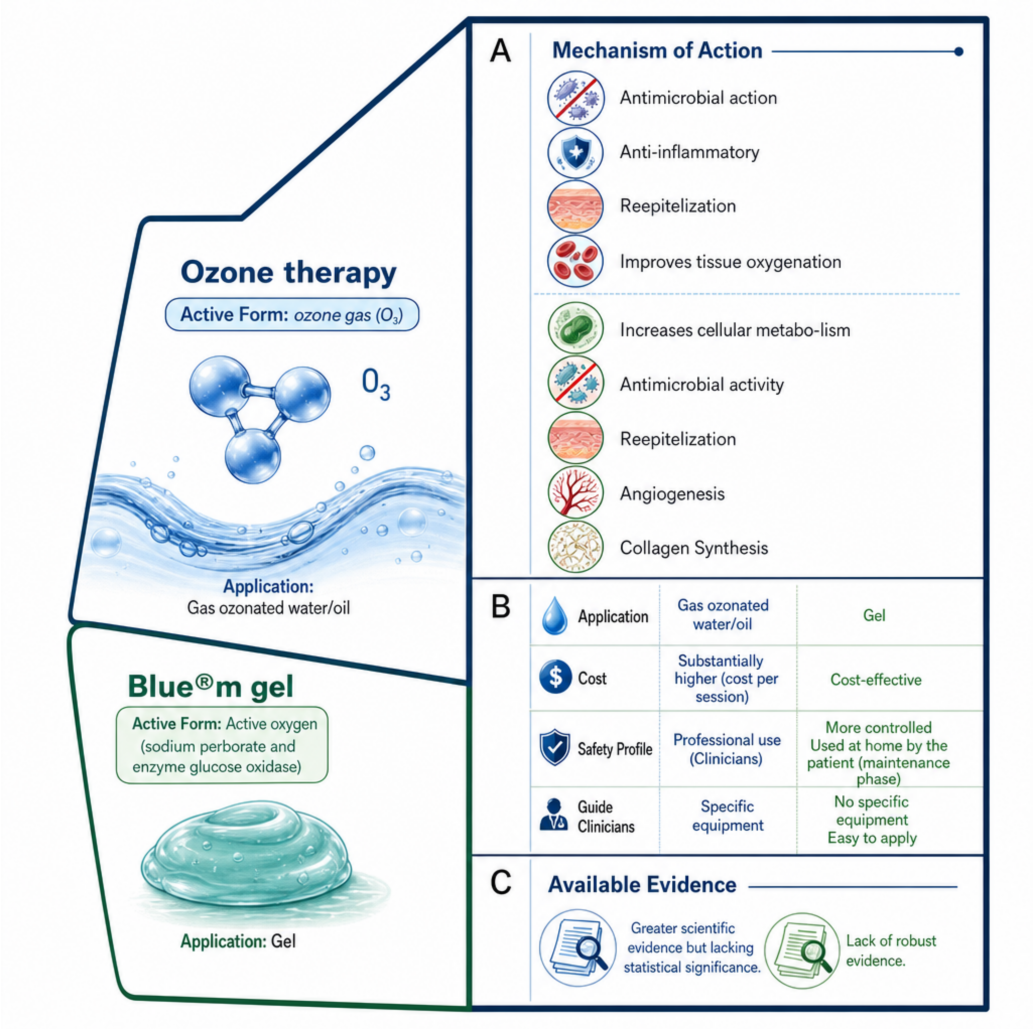

Fig. 2. The main characteristics of ozone therapy vs Blue®m gel. Created using Illustrae.co.

In summary, OT seems best suited to advanced clinical situations requiring rapid, intensive antibacterial and regenerative action, while Blue®m gel offers a gentle, long-lasting and versatile alternative, suitable for both the active phase and periodontal maintenance. Given the information available in the literature, the choice between these two approaches will therefore depend on the clinical context, therapeutic objectives, the patient's systemic terrain, and available resources.

Fig. 2 shows the main characteristics of these two oxygen-based therapies.

The Effects of Blue®m Gel or OT on the Subgingival Microbiota

The effects of oxygenated therapies on the subgingival microbiota have been explored in several studies included in this review, demonstrating real antimicrobial activity against major periodontal pathogens. The study by Piva *et al.* [29], 2020, conducted using a split-mouth protocol, demonstrated that subgingival irrigation with ozonated water (Ozonline®), as a complement to mechanical debridement, resulted in a significant reduction in bacterial load. Specifically, *Tannerella forsythia* and *Treponema denticola* were completely eradicated, while *Porphyromonas gingivalis* was reduced by 38.0%, with an overall bacterial load reduction of 55.0%. These results confirm the targeted bactericidal capacity of ozone in a clinical environment.

In another experimental study, Deliberador *et al.* [9], 2020 compared the *in vitro* antimicrobial efficacy of Blue®m gel with that of CHX against *P. gingivalis*. At concentrations of 75.0% and 100.0%, Blue®m gel showed zones of inhibition comparable to those produced by CHX, suggesting equivalent efficacy against this key pathogen. However, at 50.0%, the gel lost potency, underlining the importance of a sufficient concentration to guarantee optimum effect. Finally, Issac *et al.* [33], 2015 conducted a split-mouth study on patients with CP, where subgingival irrigation with ozonated water not only improved clinical parameters, but also showed a notable microbiological effect. After 4 weeks, the ozone group showed a 28.5% reduction in total anaerobic colonies, while the CG (SRP alone) recorded a 41.8% increase, reflecting rapid bacterial recol-

onization in the absence of adjuvant. These results demonstrate the potential of ozone to limit subgingival recolonization, a key factor in preventing periodontal recurrence.

Thus, microbiological data reinforce the therapeutic interest of oxygenated approaches in periodontology, not only for their anti-inflammatory action, but also for their targeted and long-lasting effect on periodontal pathogens, while preserving the balance of the oral microbiota.

Methodological Limitations

Furthermore, the available data on Blue®m gel also present several notable methodological limitations. The presence of isolated case reports (Alayadi *et al.* [7], 2024) severely limits the clinical transposability of their results. In addition, the lack of large-scale randomized controlled trials, combined with very short follow-up periods (often less than one month), means that it is not possible to assess the gel's real long-term efficacy or measure its impact on periodontal stability.

Several methodological limitations were identified across the studies included in this systematic review. Firstly, there is considerable variability in protocols: ozone concentrations, application methods (gel, water, gas), treatment frequency, and duration differ considerably from one study to another, making inter-study comparisons difficult. Secondly, follow-up times are generally short, with many studies not exceeding 1–3 months. Few studies assess long-term efficacy, beyond 6 months, which limits analysis of the stability of results. Furthermore, some studies, such as those by Colombo *et al.* [28], 2021, Deliberador *et al.* [9], 2020 and Alayadi *et al.* [7], 2024, are based on small samples, which reduces their statistical power and representativeness. Another important limitation is the lack of standardized data: studies use a wide variety of clinical indices (PI, GI, CAL, BOP, RBL) without methodological standardization, making quantitative analysis and meta-analysis difficult. Finally, several publications present a moderate to high risk of bias, due to lack of blinding or incomplete randomization, as shown by the studies by Mehrotra *et al.* [27], 2023, Scribante *et al.* [26], 2024 and Piva *et al.* [29], 2020.

The lack of heterogeneity in the protocols of some of the studies evaluated hindered the interpretation of the results and limited the ability to establish robust and generalisable clinical recommendations.

It is therefore necessary to conduct further studies on this topic, using blinding methodologies to prevent bias and ensure the objectivity of the results. In addition, more randomised clinical studies are needed with an equitable distribution of any known or unknown confounding variables (systemic diseases, smoking) that may, in this case, compromise the results obtained, as they correspond to risk factors for PD. Furthermore, the use of small samples in most of these studies did not, in our view, allow statistically significant results to be obtained, even if a real effect could exist. Similarly, the use of short follow-ups did not allow the long-term durability or effects of using these two adjuvants with oxygen to be assessed.

As a result, it was not possible to perform a meta-analysis on the subject or even compare the efficacy of OT versus the use of Blue®m gel as an adjunctive therapy in non-surgical treatment. However, to our knowledge, this study is an original systematic review of existing data on the use of ozone or Blue®m gel as adjuvant therapy in the non-surgical treatment of PD.

Conclusions

Given the results obtained, we can conclude that OT appears to improve periodontal clinical parameters (PDD, CAL, BOP, and GI) through NSPT. Despite being a recent product and still with few clinical studies, studies related to Blue®m gel have also demonstrated improvements in PPD reduction. These results suggest that the use of these local oxygen-based therapies may be a viable alternative to conventional treatments in NSPT. However, both therapies require further evidence, since most studies report that improvements observed in periodontal parameters were intragroup and not intergroup, which proves that the use of these therapies does not have a negative influence on conventional treatment. For this reason, and given the scarcity of articles with statistical intergroup relevance (the use of SRP alone or in combination with OT or Blue®m gel), further randomized controlled trials with greater methodological robustness (larger sample size, longer follow-up period, inclusion of systemic diseases, lack of information that can be used for quantitative analysis) and statistical relevance are needed to strengthen the results obtained especially for Blue®m.

List of Abbreviations

AC, anaerobic colony; BOP, bleeding on probing; CAL, Clinical Attachment Loss; CFU, colony forming units; CG, control group; CP, chronic periodontitis; CHX, chlorhexidine; FMPS, full mouth plaque score; FMBS, full mouth bleeding score; IQR, interquartile range; JBI, Joanna Briggs Institute; MOV, Miller's mobility index; N, No; NR, non referred; NSPT, non-surgical periodontal therapy; OPG, orthopantomogram; OT, ozone therapy; PD, periodontal disease; PPD, periodontal probing depths; PI, Plaque Index; RBL, radiographic bone loss; ROS, reactive oxygen species; SD, standard deviation; Sd, systemic disease; SRP, scaling and root planing; TG, test group; UN, unclear; Y, Yes; 7D, seven days; 14D, fourteen days; 3W, three weeks; 4W, four weeks; 6W, six weeks; 1M, one month; 3M, three months; 6M, six months; 12M, twelve months.

Availability of Data and Materials

The data and materials on which the conclusions of this article are based are available from the corresponding author upon reasonable request.

Author Contributions

Conceptualization, RC and CC; methodology, RC, CR and MIdC; software, MR and CR; validation, RC and MIdC; formal analysis, MIC; investigation, RC; resources, CR, CC; data curation, FS and MR ; writing—original draft preparation, RC and MIdC; writing—review and editing, RC, CC, MR and MIdC.; visualization, CR, MR and FS; supervision, RC and MIdC; project administration, RC and MIdC. All authors have read and agreed to the published version of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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