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COMPARATIVE CLINICAL EVALUATION OF PHOTODYNAMIC THERAPY WITH OR WITHOUT VITAMIN D AS AN ADJUNCTIVE TO NON-SURGICAL PERIODONTAL THERAPY FOR MANAGEMENT OF STAGE II GRADE B PERIODONTITIS: A RANDOMIZED CONTROLLED CLINICAL TRIAL

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ABSTRACT

Aim: The objective of this study was to evaluate the efficacy of Photodynamic Therapy (PDT) alone versus PDT with Vitamin D adjunctive to Non-surgical Periodontal Therapy (NSPT) in treatment stage II Grade B periodontitis adult patients, and explores whether conventional NSPT and Photodynamic therapy with Vitamin D will remain necessary in the future.

Subjects, materials and methods: A total of 24 patients (12 patients per group) were diagnosed with Stage II Grade B periodontitis. The control group: Non- Surgical Periodontal Therapy (NSPT) + Photodynamic Therapy (PDT) alone and the test group: Non- Surgical Periodontal Therapy (SRP) + Photodynamic Therapy (PDT) with Vitamin D were performed. This randomized controlled clinical trial study examined the efficacy of PDT with or without vitamin D as an adjunctive to NSPT by comparing their effects on clinical outcomes (CAL- PI- GI). Radiographic bone loss was taken at baseline for confirming the diagnosis. NSPT was performed for the two groups. PDT was carried out using a blue halogen curing light with a wavelength of 470nm and an intensity of 620mW/cm2, running continuously for five minutes. Using an applicator, the bottom of the periodontal pocket was treated with 2% methylene blue (the photosensitizer). After five minutes, saline was used to rinse the photosensitizer before it was subjected to a blue halogen curing light on day zero. This process was repeated on days seven, fourteen and twenty-one. Prior to intervention, blood samples were taken from each group to measure serum vitamin D levels.

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Results: A statistically significant difference was observed between the two groups employing Vitamin D supplements in conjunction to photodynamic therapy with NSPT regarding CAL, PI and GI especially at 6 weeks follow-up, where p value= 0.0270, p< 0.0001 and p< 0.0001 respectively. Regarding CAL in test group, statistically significant improvements from baseline (3.583 mm) to 6 weeks (2.583) and p value= 0.0003. However, no statistically significant difference in control group p= 0.1068 although there was measurement improvement from baseline (3.625 mm) to (3.167 mm). Regarding PI, test group demonstrated statistically significant and dramatically better results at 4 and 6 weeks to be (1.167 Vs 2.250) and (0.1667 Vs 1.333) respectively. In addition, GI in test group exhibited greater reduction at both 4 weeks and 6 weeks to be (1.083 Vs 2.333) and (0.250 Vs 1.583) respectively. The progressive improvement pattern in both groups (indicated by different letters A, B, C for each time point).

Conclusion: Considering the restrictions of this randomized controlled clinical trial study, it can be concluded that the PDT and Vitamin D supplements gave the best clinical results in comparison to PDT alone as an adjunct to NSPT in Stage II Grade B Periodontitis Patients.

KEY WORDS: Periodontal Disease; Periodontitis; Inflammation; Vitamin D

INTRODUCTION

Periodontitis is an inflammatory disease that affects the tooth's alveolar bone, cementum, and periodontium. Between 20% and 50% of people worldwide are thought to have periodontitis.[1] A variety of periodontal bacteria can thrive in periodontal pockets that form when the attachments between the tooth and supporting periodontal tissue are damaged.[2]

A number of novel approaches have been created to prevent the growth of biofilm on the surface of teeth. Photodynamic therapy (PDT),[3] a non-invasive chemical technique that was initially developed in 1990 for cancer treatment, is one of the therapeutic approaches. By eliminating aberrant cells, PDT may be able to treat a number of illnesses, including microbial infections.[4] The two primary elements of PDT are a photosensitizer (PS) and a light source. The photosensitizer is excited from the ground state to the triplet state when light at a certain wavelength is released after it has been inserted at the infection site. Following a contact with organic molecules, the excited photosensitizer will generate two forms of hazardous reactive oxygen metabolites: Type-I (superoxide, hydrogen peroxide, and free hydroxyl radicals) and Type-II (singlet-oxygen). Microbial or selectively aberrant cell death may result.[5]

Photodynamic therapy is quicker, less costly, and has a more potent bactericidal effect than SRP alone.[6] Furthermore, PDT's antibacterial activity is restricted to the treated locations because of the singlet-oxygen's extremely short half-life.[7]

Vitamin D is a fat-soluble hormone that is mostly acquired from sun exposure, but it can also be found in food and dietary supplements. The substance that gives animals the biological activity of cholecalciferol is referred to as (vitamin D3). This vitamin is essential for the regulation of calcium-phosphate balance and the metabolism of mineral bones. In this way, vitamin D promotes intestinal calcium absorption and inhibits parathyroid hormone release, both of which reduce systemic bone resorption. Furthermore, vitamin D maximizes bone remodeling, increases bone matrix proteins to cover bone mass, and stimulates osteoblastic bone formation and alkaline phosphatase activity.[8]

Vitamin D levels' dietary supplements affect periodontal health over the years.[9,10] Lower vitamin D levels have been linked to more severe stages of periodontitis and increased periodontal damage.[11]Other studies corroborated the notion that those with greater vitamin D levels had reduced bleeding on probing (BOP) than those with lower levels.[12] Furthermore, in vitro research showed

that vitamin D may reduce the inflammatory load of periodontitis in mouse models and the quantity of Porphyromonas gingivalis by means of active autophagy.[13]

According to **Mazur et al.**[14], the use of active forms of vitamin D in conjunction with photodynamic therapy enhanced the effectiveness of PDT treatment for actinic keratosis, basal cell carcinoma, and squamous cell carcinoma in situ. Accordingly, the current study was carried out to outline the impact of combining vitamin D supplements with photodynamic therapy in the treatment of periodontitis.

SUBJECTS, MATERIAL AND METHODS

Power analysis and sample size calculation:

The power analysis was conducted for a two-sided, two-sample t-test assuming equal variance between groups. The calculation determined that sample sizes of 12 participants per group (total N=24) would achieve 80.9% power to detect a mean difference of 0.7 units ($\mu1 = 2.6$ vs $\mu2 = 1.9$) between groups, assuming a common standard deviation of 0.6 and using a significance level (α) of 0.05. Accounting for an anticipated dropout rate of 20%, the study should enroll 12 participants per group (total N=30) to ensure adequate evaluable data. This enrollment target allows for up to 3 dropouts per group while maintaining sufficient statistical power.

Study Design:

24 adult patients (12 men and 12 women) between the ages of 30 and 60 were chosen at random from the outpatient clinic's periodontology department (Faculty of Dentistry, MTI University) to participate in this randomized clinical trial study. Based on the inclusion criteria listed below: In accordance with the **Papapanou et al.**[15] World Workshop categorization of periodontal disease, systemic healthy people were diagnosed with stage II grade B periodontitis. Radiographic evidence of bone loss extending to the coronal third of the root in patients with interdental clinical attachment loss (CAL) of 3–4 mm. Using a periapical parallel method, 6 radiographic pictures of the entire mouth—3 for the maxillary arch and 3 for the mandibular arch—including the anterior, canine, and posterior teeth at baseline were used to detect radiographic bone loss (RBL) for confirming the diagnosis. The study excluded smokers who were taking vitamin D as a dietary supplement.

Each of the control and test groups consisted of 12 individuals with Stage II Grade B periodontitis. All groups were randomly selected using a computer-generated randomization table. Patients' age, gender distribution, and level of periodontal disease were standardized using the mean baseline CAL, PI, and GI. Using the Microsoft Excel program, the primary supervisor completed the table and carried out the randomizations.

The control and the test groups were equally prepared for both non-surgical periodontal therapy (NSPT). Then the decision of which group either was received NSPT+ (PDT) that was the control group or was received NSPT+ (PDT) + Vitamin D that was the test group according to the randomized numbers that was picked by the main supervisor and was placed in opaque sealed envelopes. The patients were allocated in a ratio of 1:1. The allocation was concealed using a sealed, coded opaque envelope containing the treatment for each specific subject and were opened immediately the day of periodontal therapy.

All patients received mechanical debridement (supragingival and subgingival plaque control), NSPT employing an ultrasonic scaler (Various 350; NSK, Japan) and a manual universal curette (Gracey; Hu-Friday, Chicago, USA) to the bottom of the pocket of 4 mm or more to preserve any remaining fibers attached and to avoid unintentional curettage. After the subgingival scaling, saline irrigation was done. All teeth were polished with a rubber cup.

In addition to phase I periodontal treatment, the patients' hopeless teeth were extracted and restorative treatment of the teeth with carious lesions were performed.

Furthermore, a blue halogen curing light with a wavelength of 470 nm and an intensity of 620 mw/cm2 was used for photodynamic therapy in a continuous mode for five minutes. Using an applicator, the photosensitizer (Methylene blue 2%) was placed to the periodontal pocket's bottom as seen in **(Figure 1)**. After five minutes, the photosensitizer was washed with saline and exposed to a blue halogen curing light on the "0" day. This process was repeated 3 times till the third week. Then the follow- up was carried out till week 6, then the procedure was carried out in accordance with established safety procedures, which included protective eye protection for the assistant, operator, and patient. The patients were then given instructions on proper oral hygiene on how to brush and rinse with water on a regular basis. Patients were encouraged to follow a soft diet and were informed about any potential problems, such as pressure, soreness, or irritation in the affected area.

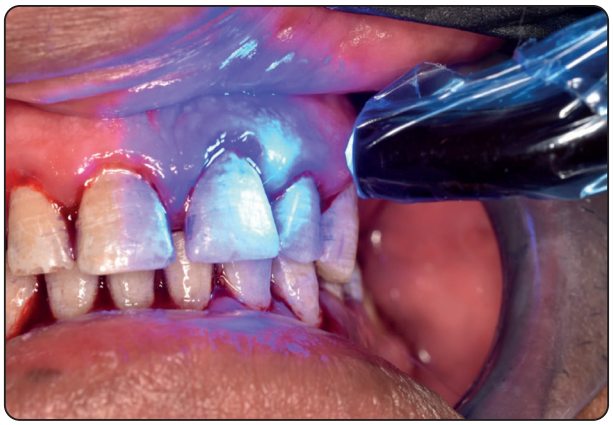

Fig. (1) Clinical picture showed PDT through using photosensitizer (Methylene blue 2%) and a blue halogen curing light with a wavelength of 470 nm and an intensity of 620 mw/cm2 in a continuous mode for 5 minutes.

Blood samples were taken at baseline and six weeks post-intervention to measure serum vitamin D levels in each group. The patients' adherence for taking vitamin D capsules was tracked throughout the length of the treatment by calling them every two weeks to check the bottles for any probable leftover capsules and by requesting information about their supplement use every week.

At one and six weeks following the procedure, oral hygiene instructions were re-affirmed. Every patient was motivated and received thorough information on how to maintain good dental hygiene practices, such as using a soft-bristled toothbrush twice a day and brushing their teeth using a modified Stillman brushing technique. Additionally, once a day, use interdental brushes for large interdental gap and interdental floss for narrow interdental space. Accordingly, three bottles of vitamin D capsules (LIMITLESS OSSOFORTIN D3 5000 IU VITAMIN D3 (CHOLECALCIFEROL 125 MCG)) containing 30 capsules for six weeks were given to the test group.

Outcome assessment

- The main endpoint of this study was Clinical Attachment Loss (CAL), which was assessed both before and after the intervention.
- Plaque Index (PI) and gingival index (GI) changes in relation to the use of PDT with vitamin D supplementation after NSPT on clinical improvement in accordance to the study's secondary main goal.
- All clinical parameters were measured at baseline, 4 weeks and 6 weeks.

Statistical Analysis

1. **Shapiro-Wilk Test**: This is generally preferred for smaller sample sizes (n<50) like this study with 15 participants per group. It tests the null hypothesis that the data is normally distributed.

2. **One-Way Analysis of Variance (ANOVA)**: Used to evaluate differences in gingival index, plaque index, and clinical attachment loss within each group across different time points (baseline, 30 days, and 45 days).
3. **Tukey's Post Hoc Test**: Applied following ANOVA to determine which specific time points significantly differed from each other within each treatment group (indicated by letters A, B, C in the tables).
4. **Independent t-test**: Used to compare differences between the control group (NSPT+ PDT alone) and test group (NSPT + PDT+ Vitamin D) at each measurement time point.

RESULTS

Summary of One-Way Analysis of Variance ANOVA test:

Clinical Attachment Loss (CAL):

1. **Intragroup Comparison:**

- The control group (SRP + PDT alone) showed modest improvement over time (from 3.625mm to 3.167mm at 6 weeks), these changes weren't statistically significant within the group (p=0.1068). In contrast, the test group (SRP + PDT with Vitamin D) demonstrated significant improvement over time (p=0.0003), with measurements decreasing from 3.583mm at baseline to 2.583mm at 6 weeks.

2. **Intergroup Comparison:**

- Table 1 presents the clinical attachment loss measurements across both control and test groups. Initially, both groups showed nearly similar baseline measurements (around 3.6mm), with no significant difference between them.
- The between-group comparison became statistically significant only at the 6-week mark (p=0.0270), suggesting that the addition of Vitamin D to the therapy provides meaningful benefits for reducing clinical attachment loss, but these benefits take time to manifest.

Plaque Index (PI):

1. **Intragroup Comparison:**

- Both groups showed significant within-group improvements over time (p<0.0001). However, the test group demonstrated dramatically better results at both the 4-week mark (1.167 vs 2.250) and especially at 6 weeks (0.1667 vs 1.333).

2. **Intergroup Comparison:**

- Table 2 shows the plaque index results, where both groups started with comparable baseline values (2.833 for control and 2.583 for test group) with no significant difference (p=0.6263).
- These between-group differences were highly significant (p<0.0001), indicating that the addition of Vitamin D substantially enhanced plaque control compared to standard therapy alone. The progressive improvement pattern is particularly noteworthy in the test group, where each time point showed significant differences from the previous one (denoted by different letters A, B, and C), suggesting continued improvement throughout the study period.

Gingival Index (GI):

1. **Intragroup Comparison:**

- The test group exhibited substantially greater reductions in the gingival index at both 4 weeks (1.083 vs 2.333) and 6 weeks (0.250vs 1.583), with highly significant between-group differences (p<0.0001). The progressive improvement pattern in both groups (indicated by different letters A, B, C for each time point) suggests that while standard therapy helps reduce gingival inflammation, the addition of Vitamin D dramatically enhances this effect, with the test group approaching near-normal gingival conditions by the end of the study.

Intergroup Comparison:

Table 3 focuses on the gingival index, reflecting the severity of gingival inflammation. Similar to the other parameters, baseline measurements were comparable between groups. Both groups showed significant improvements over time ($p<0.0001$ for both groups).

TABLE (1) One Way ANOVA analysis of baseline, 4 weeks and 6 weeks follow up of clinical attachment loss followed by independent t-test between control and test groups:

	Non- Surgical Periodontal Therapy (SRP) + Photodynamic Therapy (PDT) alone (Control Group)	**Non- Surgical Periodontal Therapy (SRP) + Photodynamic Therapy (PDT) with Vitamin D (Test Group)**	**P-value 2**
Baseline	3.625±0.4827 A	3.583±0.5149 A	**0.9965 NS**
4 Weeks	3.333±0.5365 A	2.917±0.5967 B	**0.1672 NS**
6 Weeks	3.167±0.5365 A	2.583±0.5149 B	**0.0270***
P-value 1	**0.1068 NS**	**0.0003***	

M; Mean, SD; Standard Deviation, P1; Using One Way ANOVA, P2; Using Independent t-test
Means with same letters in the same column were insignificant different using Tukey's post hoc test
Means with different letters in the same column were significant different using Tukey's post hoc test
NS; Insignificant difference
****; significant difference***

TABLE (2) One Way ANOVA analysis of baseline, 4 weeks and 6 weeks follow up of plaque index followed by independent t-test between control and test groups:

	Non- Surgical Periodontal Therapy (SRP) + Photodynamic Therapy (PDT) alone (Control Group)	**Non- Surgical Periodontal Therapy (SRP) + Photodynamic Therapy (PDT) with Vitamin D (Test Group)**	**P-value 2**
Baseline	2.833±0.3892 A	2.583±0.5149 A	**0.6263 NS**
4 Weeks	2.250±0.7538 B	1.167±0.3892 B	**<0.0001***
6 Weeks	1.333±0.7785 B	0.1667±0.3892 C	**<0.0001***
P-value 1	**<0.0001***	**<0.0001***	

M; Mean, SD; Standard Deviation, P1; Using One Way ANOVA, P2; Using Independent t-test
Means with same letters in the same column were insignificant different using Tukey's post hoc test
Means with different letters in the same column were significant different using Tukey's post hoc test
NS; Insignificant difference
****; significant difference***

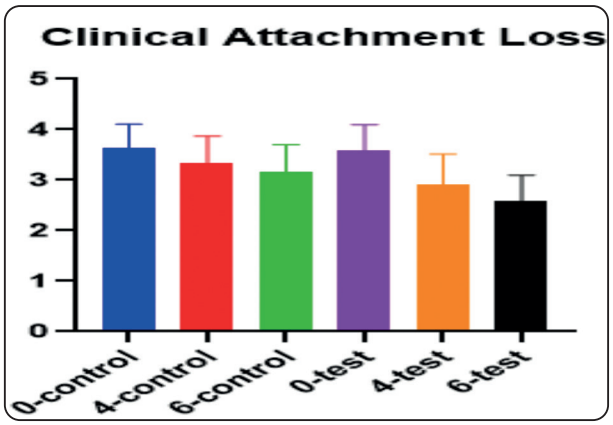

Fig. (2) Bar Chart of clinical attachment loss between control and test groups

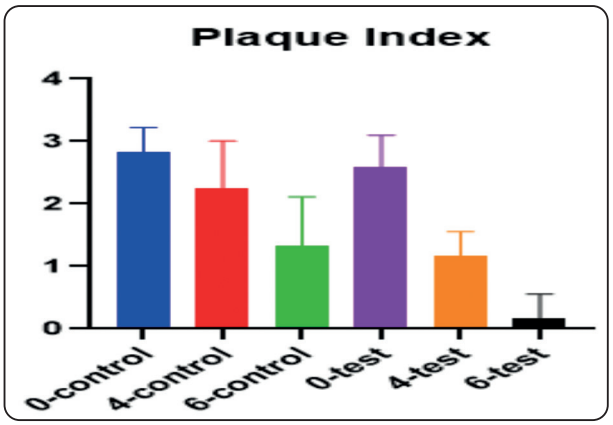

Fig. (3) Bar Chart of plaque index between control and test groups

TABLE (3) One Way ANOVA analysis of baseline, 4 weeks and 6 weeks follow up of gingival index followed by independent t-test between control and test groups:

	Non- Surgical Periodontal Therapy (SRP) + Photodynamic Therapy (PDT) alone (Control Group)	Non- Surgical Periodontal Therapy (SRP) + Photodynamic Therapy (PDT) with Vitamin D (Test Group)	P-value 2
Baseline	2.917±0.2887 A	2.667±0.4924 A	**0.5772 NS**
4 Weeks	2.333±0.7785 B	1.083±0.5149 B	**<0.0001***
6 Weeks	1.583±0.5149 C	0.2500±0.4523 C	**<0.0001***
P-value 1	**<0.0001***	**<0.0001***	

M; Mean, SD; Standard Deviation, P1; Using One Way ANOVA, P2; Using Independent t-test
Means with same letters in the same column were insignificant different using Tukey's post hoc test
Means with different letters in the same column were significant different using Tukey's post hoc test
NS; Insignificant difference ****; significant difference***

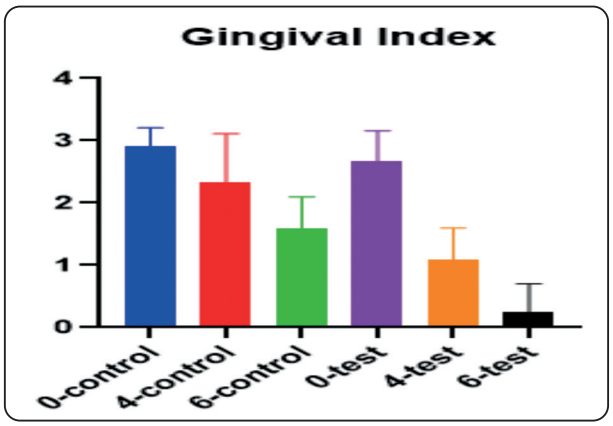

Fig. (4): Bar Chart of gingival index between control and test groups

DISCUSSION

The use of non-surgical methods to treat periodontal disease is currently a popular issue in dental research.[16] Testing adjunctive methods became necessary due to the limits of the traditional non-surgical periodontal therapy (NSPT). The effectiveness of antibacterial, antioxidant, and immunostimulant activities, including photodynamic treatment, has been assessed in earlier recent studies.[17]

In this study, the adjunctive application of photodynamic therapy (PDT) using a blue halogen curing light with a wavelength of 470 nm and an intensity

of 620 mW/cm2 was used in this study as an additional application of photodynamic therapy (PDT) in a continuous mode for five minutes. The effectiveness of non-surgical treatment for periodontitis was significantly increased when methylene blue 2% (the photosensitizer) was applied to the bottom of the periodontal pocket three times in a row over a 21-day period. These findings confirm that PDT causes a deeper disinfection of the periodontal pockets when paired with non-surgical periodontal therapy (NSPT) according to our particular procedure protocol. The null hypothesis was thus disproved.

The statistical results from this current study showed that the use of PDT and vitamin D supplements significantly improved the clinical parameters, such as clinical attachment levels, plaque index, and gingival index in stage II grade B periodontitis cases.

Overall, the clinical attachment levels in the control group (NSPT+ PDT) decreased from (3.625 ±0.4827 A) at baseline to (3.167± 0.5365 A) after 6 weeks, while the test group (NSPT+ PDT+ Vitamin D) significantly improved from (3.583±0.5149 A) at baseline to (2.583± 0.5149 B) after 6 weeks post-intervention. This suggests that PDT appears to have a better reparation of the periodontium because better periodontal tissue disinfection that resulted in better periodontal tissue repair.

According to Mishima and Sharma, PDT was successful because it neutralized host pro-inflammatory cytokines and reduced bacterial harmful byproducts, such as lipopolysaccharides, more thoroughly. When triggered with the 470 nm wavelength light, the photosensitizer penetrates deeply into the periodontal tissues, which is probably why PDT can reduce bacteria at a deeper level. This allows for a broad bactericidal action on the bacteria that live on the non-periodontal mucosal surfaces as well as in the deep periodontal tissues. [18, 19] Additionally, this was aligned with the results of the current study.

Furthermore, the effectiveness of PDT in conjunction with traditional mechanical debridement was attributed by Lessa et al., Contaldo et al., and Zhao et al. to the disinfectant's ability to penetrate the depth of the periodontal tissues because of the light's deep tissue penetration capabilities and the liquid solution used; this could have led to a more thorough and profound disinfection. [20–22]

Our findings are in contrast to those of Christodoulides et al.[23], Polansky et al.[24], and Balata et al.[25], who found that PDT did not add any benefits for NSPT in management of chronic periodontitis in terms of CAL and PPD reduction. Variations in the technique, photosensitizer, concentration, and exposure period to the chosen wavelength may be the cause of these contentious reports in the literature about the effectiveness of PDT as an adjuvant to NSPT.

Understanding how photodynamic treatment (PDT) works is essential to fully interpreting the findings of our investigation. PDT first entails irradiating a photosensitizer agent with a particular wavelength to activate it from its ground state to a highly energetic triplet state. [26-28] This excited photosensitizer interacts with the surrounding molecules and has a longer lifespan than regular reactive oxygen species (ROS). Cytotoxic species are produced as a result of a series of events that take place in its triplet state. [29, 30]

Type I and Type II are two different paths that have been proposed for the triplet state reactions. [26] The hydrogen atom between the photosensitizer's stimulated state and the organic substrate molecule inside the cells is the focal point of the Type I reaction. Extremely reactive free radicals and radical ions are produced by this process. [26] Superoxide, hydroxyl radicals, and hydrogen peroxide are among the extremely reactive oxygen species that are produced as a result of these free-radical species' further interactions with endogenous molecular oxygen. In essence, these reactive oxygen species "attack"

the cell membrane, rupturing it and resulting in irreversible biological harm. [26, 29, 30]

In contrast, the triplet state photosensitizer and molecular oxygen interact directly in the Type II process. Singlet oxygen (O2), an electrically excited and extremely reactive form of oxygen, is produced as a result of this interaction. Due to its strong chemical reactivity, singlet oxygen reacts with a variety of biological structures, causing oxidative damage and killing bacteria by rupturing their cell walls and membranes.[26]

It's interesting to note that the current study found that several PDT applications over a 21-day period significantly improved clinical parameters, due to sustained release and deeper penetration for bacterial reduction. However, when compared to single treatments, Ramanauskaite et al. showed that several PDT applications did not produce better results.[31]These findings highlight PDT's potential advantages as an adjuvant treatment for periodontitis, especially in diabetic individuals with deep pockets and difficult residual pockets. However, the benefits of PDT in periodontal therapy are exploited by standardizing different parameters.

For many years, researchers have looked for combination therapies that can enhance the effectiveness of PDT method and improving the quality of PDT research. One example of this kind of combination therapy is the application of calcitriol, calcipotriol, and tacalcitol to lesions or diseased cells. According to Mazure et al., vitamin D3 was added to PDT that may increase the method's efficacy by promoting protoporphyrin formation through 5-ALA. Furthermore, these combinations can improve cell differentiation. These findings suggest that PDT combined with vitamin D and D3 has a more effective and focused therapeutic effect.[32]

Additionally, there was a statistically significant difference between the test and control groups in the plaque index calculation. Furthermore, the test group showed significantly better results at the 4- and 6-week follow-up, measuring (1.167 ± 0.3892B) versus (2.250 ± 0.7538 B) and (1.1667 ± 0.3892C) versus (1.333 ± 0.7785 B), respectively. This suggests that both groups maintained good oral hygiene and followed the instructions provided during the first session. Furthermore, Ramanauskaite et al. conducted systematic review and network meta-analysis included comparable findings to the current study.[31]

In the current study, both groups showed an overall decrease in gingival index, which indicated the decrease in the degree of gingival inflammation (p value <0.0001). At the 4- and 6-week follow-up, the test group showed a larger reduction, measuring (1.083 ± 0.5149B) versus (2.333 ± 0.7785 B) and (0.250 ± 0.4523C) versus (1.583 ± 0.5149 C), respectively. A network meta-analysis and systematic review of PDT in periodontal maintenance were published by Ramanauskaite et al.[31]. In contrast to non-surgical periodontal therapy alone, concluded that both one and several additional PDT administrations after NSPT significantly decreased bleeding on probing (BOP).

CONCLUSION

Given the limitations of the current randomized controlled clinical trial, we may draw the following conclusions:

- The addition of Vitamin D to the PDT to NSPT provides meaningful benefits for reducing clinical attachment loss, enhanced plaque control and approaching near-normal gingival conditions but these benefits take time to manifest.

RECOMMENDATION

- Future microbiological analysis with wider sample size and long treatment time are needed to give better results.
- Future selective dyes with selective action of on microbes, prevention modalities of bacterial resistance, multiple easy repeatable treatment options make safer modality with futuristic approach in the field of periodontology.

REFERENCES

1. Garg, A. D., Maes, H., Romano, E., and Agostinis, P. (2015). Autophagy, a major adaptation pathway shaping cancer cell death and anticancer immunity responses following photodynamic therapy. Photochem. Photobiological Sci. 14 (8), 1410–1424.doi:10.1039/c4pp00466c
2. Nazir, M., Al-Ansari, A., Al-Khalifa, K., Alhareky, M., Gaffar, B., and Almas, K.(2020). Global prevalence of periodontal disease and lack of its surveillance. Sci. World J.2020, 1–8. doi:10.1155/2020/2146160
3. Meimandi, M., Talebi Ardakani, M. R., Esmaeil Nejad, A., Yousefnejad, P., Saebi, K., and Tayeed, M. H. (2017). The effect of photodynamic therapy in the treatment of chronic periodontitis: a review of literature. J. lasers Med. Sci. 8 (Suppl. 1), S7–S11.doi:10.15171/jlms.2017.s2
4. Garg, A. D., Maes, H., Romano, E., and Agostinis, P. (2015). Autophagy, a major adaptation pathway shaping cancer cell death and anticancer immunity responses following photodynamic therapy. Photochem. Photobiological Sci. 14 (8), 1410–1424.doi:10.1039/c4pp00466c
5. Kwiatkowski, S.,Knap, B., Przystupski,D., Saczko, J., Kędzierska, E., Knap-Czop, K., et al. (2018). Photodynamic therapy–mechanisms, photosensitizers and combinations. Biomed. Pharmacother. 106, 1098–1107. doi:10.1016/j.biopha. 2018.07.049
6. Jia, L., Jia, J., Xie, M., Zhang, X., Li, T., Shi, L., et al. (2020). Clinical attachment level gain of lasers in scaling and root planing of chronic periodontitis: a network meta analysis of randomized controlled clinical trials. Lasers Med. Sci. 35 (2), 473–485. doi:10.1007/s10103-019-02875-5
7. Joshi, K., Baiju, C. S., Khashu, H., and Bansal, S. (2020). Clinical effectiveness of indocyanine green mediated antimicrobial photodynamic therapy as an adjunct to scaling root planing in treatment of chronic periodontitis- A randomized controlled clinical trial. Photodiagnosis Photodyn. Ther. 29, 101591. doi:10.1016/j.pdpdt.2019.101591
8. Machado V, Lobo S, Proença L, Mendes J 2 and Botelho J. Vitamin D and Periodontitis: A Systematic Review and Meta-Analysis. Nutrients 2020, 12, 2177.
9. Najeeb, S.; Zafar, M.S.; Khurshid, Z.; Zohaib, S.; Almas, K. The role of nutrition in periodontal health: An update. Nutrients 2016, 8, 530.
10. Botelho, J.; Machado, V.; Proença, L.; Delgado, A.S.; Mendes, J.J. Vitamin D deficiency and oral health: A comprehensive review. Nutrients 2020, 12, 1471.
11. Isola, G.; Alibrandi, A.; Rapisarda, E.; Matarese, G.; Williams, R.C.; Leonardi, R. Association of vitamin D in patients with periodontitis: A cross-sectional study. J. Periodontal Res. 2020, 1–11.
12. Dietrich, T.; Joshipura, K.J.; Dawson-Hughes, B.; Bischo_-Ferrari, H.A. Association between serum concentrations of 25-hydroxyvitamin D 3 and periodontal disease in the US population. Am. J. Clin. Nutr. 2004, 80, 108–113.
13. Machado V, Lobo S, Proença L, Mendes J 2 and Botelho J. Vitamin D and Periodontitis: A Systematic Review and Meta-Analysis. Nutrients 2020, 12, 2177.
14. Mazur, A.; Koziorowska, K.; Dynarowicz, K.; Aebisher, D. Vitamin D Supplementation and Photodynamic Therapy. Biol. Life Sci. Forum 2022, 12, 28. https://doi.org/10.3390/IECN2022-12382
15. Papapanou, P. N., Sanz, M., Buduneli, N. et al. (2017): "Periodontitis: Consensus Report of Workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions". J. Periodontol.; Jun; 89 Suppl 1: S173-S182.
16. Butera, A.; Maiorani, C.; Gallo, S.; Pascadopoli, M.; Venugopal, A.; Marya, A.; Scribante, A. Evaluation of Adjuvant Systems in Non-Surgical Peri-Implant Treatment: A Literature Review. Healthcare 2022, 10, 886. [CrossRef]
17. Scribante, A.; Gallo, S.; Pascadopoli, M.; Soleo, R.; Di Fonso, F.; Politi, L.; Venugopal, A.; Marya, A.; Butera, A. Management of Periodontal Disease with Adjunctive Therapy with Ozone and Photobiomodulation (PBM): A Randomized Clinical Trial. Photonics 2022, 9, 138. [CrossRef]
18. Lamont, R.J.; Yilmaz, O. In or out: The invasiveness of oral bacteria. Periodontol. 2000. 2002, 30, 61–69. [CrossRef]
19. Mishima, E.; Sharma, A. Tannarella forsythia invasion in oral epithelial cells requires phosphoinositide 3-kinase activation and clathrin-mediated endocytosis. Microbiology 2011, 157, 2382–2391. [CrossRef]
20. Lessa, A.D.F.N.; de Andrade Celestino, M.; Ferreira, J.M.; Lima, I.V.; Ramos, Y.C.S.; Vieira, F.F.; da Silva Amâncio, A.M.T.; Caldeira, P.C.; de Sousa, S.F.; de Aguiar, M.C.F. Antimicrobial photodynamic therapy for the treatment of oral mucositis—A comparative study. Photodiagn. Photodyn. Ther. 2023, 42, 103543. [CrossRef] [PubMed]
21. Contaldo, M.; Di Stasio, D.; Romano, A.; Fiori, F.; Della Vella, F.; Rupe, C.; Lajolo, C.; Petruzzi, M.; Serpico, R.; Lucchese, A. Oral candidiasis and novel therapeutic

strategies: Antifungals, phytotherapy, probiotics, and photodynamic therapy. Curr. Drug Deliv. 2023, 20, 441–456. [CrossRef] [PubMed]

22. Zhao, Y.; Yan, Q.; Wu, X.; Hua, F.; Shi, B. The benefit of antimicrobial photodynamic therapy to mechanical debridement in the treatment of smokers with peri-implant diseases: A systematic review and meta-analysis. Lasers Med. Sci. 2022, 37, 3051–3066. [CrossRef] [PubMed]
23. Christodoulides N, Nikolidakis D, Chondros P, Becker J, Schwarz F, Rössler R, et al. Photodynamic therapy as an adjunct to non-surgical periodontal treatment: a randomized, controlled clinical trial. J Periodontol. 2008;79(9):1638-44.
24. Polansky R, Haas M, Heschl A, Wimmer G. Clinical effectiveness of photodynamic therapy in the treatment of periodontitis. J Clin Periodontol. 2009;36(7):575 80.
25. Balata ML, Andrade LP, Santos DB, Cavalcanti AN, Tunes UD, Ribeiro ED, et al. Photodynamic therapy associated with full-mouth ultrasonic debridement in the treatment of severe chronic periodontitis: a randomized-controlled clinical trial. J Appl Oral Sci. 2013;21(2):208-14.
26. Mielczarek-Badora, E.; Szulc, M. Photodynamic therapy and its role in periodontitis treatment. Adv. Hyg. Exp. Med. Postep. Hig. I Med. Dosw. 2013, 67, 1058–1065. [CrossRef] [PubMed]
27. Takasaki, A.A.; Aoki, A.; Mizutani, K.; Schwarz, F.; Sculean, A.; Wang, C.Y.; Koshy, G.; Romanos, G.; Ishikawa, I.; Izumi, Y. Application of antimicrobial photodynamic therapy in periodontal and peri-implant diseases. Periodontol. 2000 2009, 51, 109–140. [CrossRef]
28. Foote, C.S. Definition of type I and type II photosensitized oxidation. Photochem. Photobiol. 1991, 54, 659. [CrossRef] [PubMed]
29. Bhatti, M.; MacRobert, A.; Henderson, B.; Shepherd, P.; Cridland, J.; Wilson, M. Antibody-targeted lethal photosensitization of Porphyromonas gingivalis. Antimicrob. Agents Chemother. 2000, 44, 2615–2618. [CrossRef] [PubMed]
30. Cosgarea, R.; Ramseier, C.A.; Jepsen, S.; Arweiler, N.B.; Jervøe-Storm, P.M.; Batori-Andronescu, I.; Rößler, R.; Conrad, T.; Eick, S.; Sculean, A. One-Year Clinical, Microbiological and Immunological Results of Local Doxycycline or Antimicrobial Photodynamic Therapy for Recurrent/Persisting Periodontal Pockets: A Randomized Clinical Trial. Antibiotics 2022, 11, 738. [CrossRef] [PubMed]
31. Ramanauskaite, E.; Moraschini, V.; Machiulskiene, V.; Sculean, A. Clinical efficacy of single and multiple applications of antimicrobial photodynamic therapy in periodontal maintenance: A systematic review and network meta-analysis. Photodiagn. Photodyn. Ther. 2021, 36, 102435. [CrossRef]
32. Mazur, A.; Koziorowska, K.; Dynarowicz, K.; Aebisher, D.; Bartusik-Aebisher, D. Vitamin D and Vitamin D3 Supplementation during Photodynamic Therapy: A Review. Nutrients 2022, 14, 3805. https:// doi.org/10.3390/nu14183805