Iran J Orthod. 2022 December; 17(2):e1080. doi:10.22034/IJO.2022.556100.1080.
Published online 2022 December 1 Review Article

The Effect of Antimicrobial Photodynamic Therapy on the Management of Gingivitis Induced by Orthodontic Treatment: a Systematic Review

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Received: 2022 June 19; **Revised:** 2022 July 23; **Accepted:** 2022 August 1

Abstract

Aim: Hygiene is a challenge of orthodontic treatment due to its appliances and can lead to periodontal diseases. Antimicrobial photodynamic therapy (aPDT) is a preventive technique for periodontal diseases owing to its antimicrobial and anti-inflammatory properties. The present study reviews the effect of aPDT on the management of gingivitis induced by orthodontic treatment.
Methods: The research was conducted using databases such as Scopus, PubMed, Google Scholar, and Cochrane via inputting keywords such as photodynamic therapy, photo-activated chemotherapy, photoactivated disinfection, antimicrobial photodynamic therapy, laser-activated disinfection, light-activated disinfection, laser therapy, gingivitis, gingival inflammation, and orthodontic patient. The time frame for searching articles was from January 2010 to July 2022.
Results: In terms of anti-inflammatory properties, aPDT technique is associated with reductions in clinical parameters (probing depth, bleeding on probing, plaque score, and plaque index) as well as paraclinical parameters (levels of the inflammatory cytokines IL-6, TNF- α, IL-1β, and human beta defensin-2). Also, this technique has caused a decline in the number of Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, and Prevotella intermedia, although the effect was short-term (one month).
Conclusion: The results of the study demonstrated that aPDT is an effective and safe method in reducing gingivitis induced by orthodontic treatment via its reduction effect on dental plaque, gingival inflammation, inflammatory reactions, and infective pathogens load.

Keywords: Antimicrobial photodynamic therapy, Laser-activated disinfection, Photo-activated chemotherapy, Photoactivated disinfection, Photodynamic therapy.

1. Background

If oral hygiene precautions are not strictly observed, treatments such as fixed orthodontic therapy (FOT) can contribute to excessive plaque accumulation on teeth (1). In FOT, brackets and wires are attached to the surfaces of teeth to move them (2). Subsequently, patients undergoing FOT may find it difficult to floss and remove plaque from their teeth (3).

Plaque on the teeth is a type of biofilm composed of a polymer matrix adhered to the teeth and containing a large number of bacteria (4). Dental plaque is the primary cause of gingival inflammation, which is characterized by gingival redness, bleeding, and swelling in the margin of the gingiva (5, 6). Inflammatory cytokines, such as interleukin 1 beta (IL-1β), are released by bacteria in dental plaque, such as *Aggregatibacter* actinomycetemcomitans, Porphyromonas gingivalis, and Fusobacterium nucleatum. This causes gingivitis by increasing the permeability and perfusion of periodontal tissues (7, 8).

One standard treatment consists of a toothbrush with bristles and a mouth rinse containing 0.2% chlorhexidine digluconate (9).

Essential oils, phytotherapy, probiotics, and even antibiotics have been used to treat gingival inflammation (10- 12). Currently, laser treatments for infectious oral diseases are being researched (12, 13). Antimicrobial photodynamic therapy (aPDT), wherein a photosensitive dye is activated by laser light in an aerobic environment, is gaining popularity (14). Utilizing a photosensitizing agent and a light source of the proper wavelength, the aPDT generates reactive oxygen species to eliminate target cells.

The aPDT utilizes numerous photoactive components. Ideal photosensitizers are nontoxic and only activate when exposed to light. The ideal photosensitizer should possess a broad spectrum of photophysical, chemical, and biological properties (15, 16). Photosensitizers used to treat periodontal infections may stain the gingiva or other soft tissues in the mouth, causing unintended side effects (16). To avoid such side effects, only bacteria and plaque should be attached to the substances. Additionally, it must be palatable to both the patient and dental staff, and it must be able to reach pathogens in deeper pockets (17).

A specific wavelength and low-intensity visible light can also activate photosensitizers. Red light with wavelengths between 630 nm and 700 nm can penetrate human tissue to a depth of 5 to 15 millimeters. With a visible light source, it is easier to see the target area, locate the photoinactivation without harming the host tissue, and minimize operator risk. The total light dose, dose rate, depth of penetration, and location of the target area all influence the stimulation of photosensitizers (18-20).

In addition to reducing inflammation, aPDT can have an antimicrobial effect via production of reactive oxygen species, resulting in the inhibition of bacterial re-cloning and gingival curettage, which inhibits the production of the bacteria's protein synthesis (20-22).

Photodynamic therapy may be able to treat gingivitis and periodontal disease by inhibiting the activation of the cytokine-induced inflammatory pathway, thus; researchers are becoming increasingly intrigued by this possibility (23-25). The aim of this study was to review the effect of aPDT on the management of gingivitis induced by orthodontic treatment considering the role of laser therapy in periodontal diseases.

2. Methods

Study design

The analysis method and inclusion criteria were determined beforehand based on the PRISMA guideline.

Focused question? Is antimicrobial photodynamic therapy useful for the management of gingivitis induced by orthodontic treatment?

The search strategy was done based on PICO. (Population: patients with gingivitis due to orthodontic treatment; Intervention: antimicrobial photodynamic therapy; Comparison: control groups receiving another therapy; and Outcome: anti-inflammatory and antimicrobial effect).

Information sources and search strategy

In this review and meta-analysis study, accurate search strategies for each database were prepared to identify eligible articles published from January 2010 to July 2022. The searches on Scopus, PubMed, Google Scholar, and Cochrane were performed using the following keywords: photodynamic therapy, photo-activated chemo-therapy, photoactivated disinfection, antimicrobial photodynamic therapy, laser-activated disinfection, light-activated disinfection, laser therapy, gingivitis, gingival inflammation, and orthodontic patient. Also, the search included grey materials (conference proceedings, study protocols, post-graduate dissertations) done for relevant studies. Next, the eligible articles were assessed by reviewing all the titles and abstracts, and the relevant items were chosen by the two writers (RB, NCH).

When there was missing data in the title or the abstract, the full texts were accurately studied to determine whether the article should be entered for future analysis. The references of relevant systematic reviews and studies were also hand searched for further eligible studies.

Selecting the articles

The two authors evaluated the collected articles in terms of inclusion and exclusion criteria (RB, NCH), and a discussion with the third author (AM) solved any possible disagreement. The inclusion criteria included the clinical trials that studied the effects of photodynamic therapy with different photosensitizers in orthodontic patients with gingivitis and the clinical (probing depth, bleeding on the probing, plaque score, plaque index) and paraclinical parameters (measuring the number of cytokines and number of bacteria) to assess the anti-inflammatory and antimicrobial properties of this method. Articles without inclusion criteria, narrative and systematic reviews, and case series and case reports were excluded.

Moreover, to prevent several publications of data, only the original articles were studied.

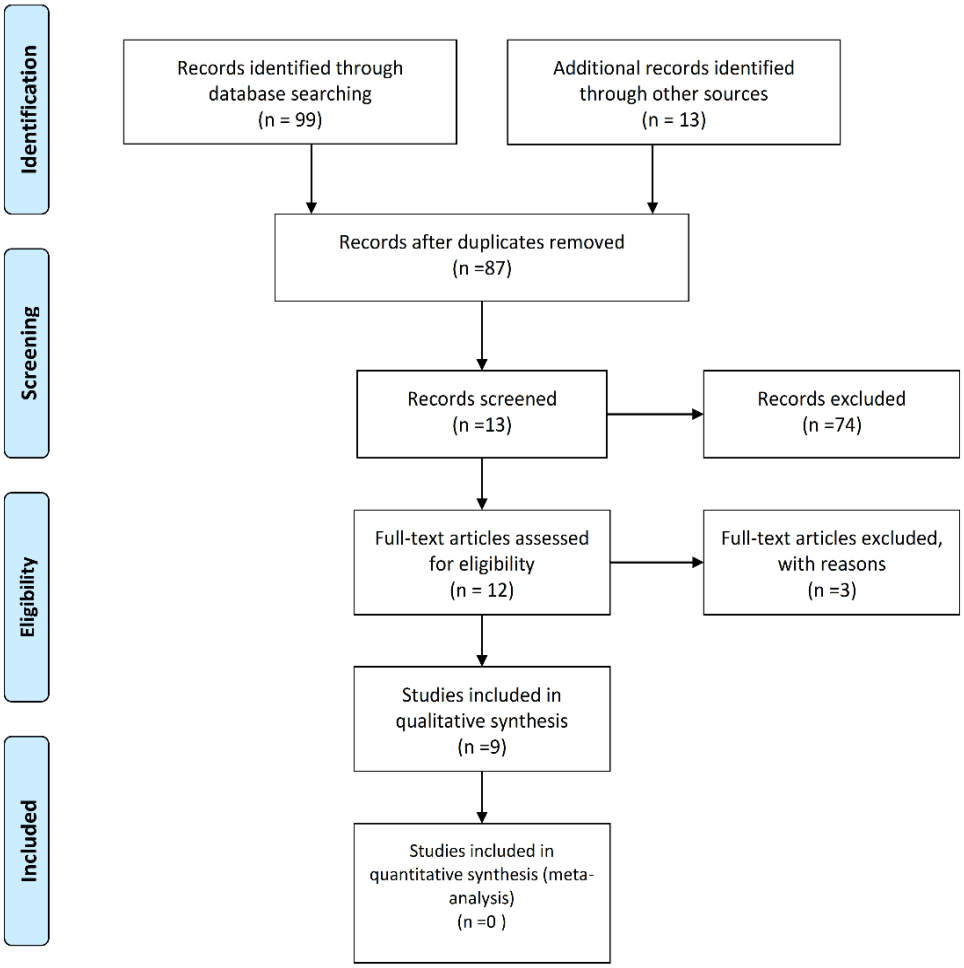

Figure 1. PRISMA flow-chart of selected criteria for the included article reports

Presentation methods of data in this study, including the identification of the research problem, data collection, and analysis and interpretation of data, were conducted according to the checklist for systematic reviews, i.e., PRISMA. The details of inclusion criteria are shown in Fig.1.

Data collection and data items

The studies that fulfilled the inclusion criteria were collected in an electronic database (Excel software). The following data were extracted by each browser in its relevant database: Author, year of publication, title, research design, patients, methods, results, conclusion, and the full text (Yes or No). Then the qualitative quality of the recovered articles was discussed by the authors to reach an agreement. The data results were extracted by two judges to validate and control data.

Data published several times were considered duplicate. In case of any doubts or ambiguity, the original article was always considered the final option. This reduces any overestimation of the effect of the intervention since there are no duplicate data exceptions.

The strategies for missing/defective data in the present study are as follows:

Contact the author if possible

Analyze only the current data (overlooking the missing data)

Discuss the possible effects of the missing data on the understudy findings in the discussion.

3. Results

Initially, 112 references (Fig. 1) were retrieved from the primary databases, among them 25 duplicate references. Additional references were excluded by two independent reviewers based on the abstract and title because the studies were not limited to the effect of photodynamic therapy on

orthodontic treatment-induced gingivitis. Table 1 summarizes these articles. Full texts of the remaining nine articles were obtained.

Table.1. Studies on the application of aPDT in management of gingivitis induced by orthodontic treatment.

Authors/ Year	Type of study/ number of sample	Study Groups	Mean Age (Year)	Laser parameters	Photosensitizer	Sessions	Follow-up	Investigative Parameter: Clinical	Investigative Parameter: Sub-clinical	Results: Anti-inflammatory	Results: Anti-microbial
Malik (2020)[26]	Randomized controlled clinical trial/ 36 patients	Group 1: US + aPDT Group 2: US alone	Group 1: 16.6 ± 0.5 Group 2: 16.8 ± 0.4	660 nm, 0.0125 J/cm2, 150 mW	Methylene blue 400 µg/ml	----	6 months	GI	Oral yeasts analysis	Absence of a significant difference in decreasing gingivitis index with mechanical debridement.	Decreased microbial load more than in mechanical debridement
Alqerban (2020)[27]	A clinic-laboratory study/ 45 patients	Group 1: US + aPDT Group 2: US + PBM Group 3: US alone	Group 1: 14.7 ± 0.8 Group 2: 16.2 ± 0.9 Group 3: 15.8 ± 0.7	670 nm, 22 J/cm2, 1.1 W/cm2	Methylene blue 0.0005 %	----	2 months	PScore BoP PD	Microbiological analysis GCF cytokines assessment	A decrease in hBD-2	Significant decrease in T.denticola
Alshahrani (2020)[28]	Clinical study/ 26 patients	Group 1: FMPD Group 2: FMPD + aPDT	Group 1: 16.3 ± 0.9 Group 2: 16.9 ± 1.0	670 nm, 22 J/cm2, 150 mW	Methylene blue 0.0005 %	---	4 weeks	PScore BoP PD HI	Microbiological analysis GCF cytokines assessment	A decrease in Il-1β and IL-6	A decrease in T. forsythia, P. gingivalis, and T. denticola
Nazeh (2020)[22]	Randomized controlled clinical trial/ 22 patients	Group 1: US Group 2: US + aPDT	Group 1: 17.8 ± 0.7 Group 2: 17.3 ± 0.9	670 nm, 22 J/cm2, 150 mW	Methylene blue 0.0005 %	---	4 weeks	PD PScore BoP	Microbiological analysis	A decrease in bleeding on probing and plaque score as clinical indicators of inflammation	A decrease in P. gingivalis and T. denticola
Baeshen (2020)[29]	Randomized clinical trial/ 30 patients	Group 1: US + aPDT Group 2: US alone	Group 1: 16.1 ± 1.4 Group 2: 15.9 ± 1.3	670 nm, 22 J/cm2, 150 mW	Methylene blue 0.005%	---	4 weeks	PScore BoP PD VAS	Microbiological analysis GCF cytokines assessment	A decrease in BOP (IL-6 and TNF-α)	A decrease in T.forsythia

Table 1. Continued

Kamran (2019)[30]	clinical trial/ 50 patients	Group 1: US + aPDT Group 2: US alone	Group 1: 15.4 ± 0.9 Group 2: 14.2 ± 0.7	670nm, 22 J/cm2, 150mw	Methylene blue 0.0005%	---	6 weeks	PD BoP PScore	Microbiological analysis GCF cytokines assessment	A decreasing trend in clinical indicators of gingivitis (plaque score, bleeding on probing, and plaque index)	First a decrease and then an increase in P. gingivalis and P. intermedia
Gomez (2018)[31]	Randomized clinical trial/ 20 patients	Group 1: aPDT Group 2: US alone	Group 1: 15.0 ± 1.8 Group 2: 14.2 ± 1.3	670 nm, 200 mW	Methylene blue 0.005 %	4	9 months	FMPS FMBS PD ICDAS	Microbiological analysis	A decrease in clinical indicators of gingivitis (full-mouth bleeding score)	A decrease in P. intermedia, P. gingivalis, and mutans streptococci similar to the ultrasonic scaler group
Abellan (2018)[21]	Randomized clinical trial/ 20 patients	Group 1: aPDT Group 2: US alone	14.6 ± 1.6	670 nm, 67.06 J/cm2, 6.05 W/cm2	methylene blue 0.005%	7	9 months	PD PI GI	Microbiological analysis GCF cytokines assessment	Decreased gingivitis as a result of a decrease in IL-1β, IL-10, TNF-α	A decrease in the load of Porphyromonas gingivalis and Prevotella intermedia after 6 months; then shown an increase 9. A load of Fusobacterium nucleatum unchanged for up to 6 months and decreased at least 9 months after photodynamic therapy.
Paschoal (2014)[20]	Randomized clinical trial/ 45 patients	Group 1: 2% CHX varnish Group 2: placebo varnish Group 3: aPDT	13–18 years	450 ± 20 nm, 96 J0/cm2, 165 mW/cm2	curcumin 1.5 mg.mL-1	4	3 months	PI GI	-	A significant decrease in clinical indicators of gingivitis (gingival bleeding index)	-

US— Ultrasonic Scaling, CHX— Chlorhexidine, PBM— photobiomodulation, aPDT— antimicrobial photodynamic therapy, PD—pocket depth, PI—plaque index, GI—gingival index, GCF—gingival crevicular fluid, FMPS—full mouth plaque score, FMBS—full mouth bleeding score, ICDAS—International Caries Detection and Assessment System, PScore—plaque score, BoP—bleeding on probing, HI—hyperplastic index, Human beta defensin-2— hBD-2, Interleukin 1beta— IL-1β, Interleukin 6— IL-6, Tumor necrosis factor alpha—TNF-α, Interleukin 10— IL-10.

4. Discussion

Long orthodontic treatment (2-3 years) leads to complications such as root resorption, gingivitis, periodontal disease, and dental caries (32). Orthodontic appliances are always considered a preventive factor in maintaining oral hygiene and gingival health and a barrier to removing microbial dental plaques (33). Among the periodontal therapies, using aPDT has been proposed as a replacement for antimicrobial chemicals to remove subgingival bacteria and to treat periodontitis with fewer complications (34). Different studies have evaluated and confirmed the use and effectiveness of aPDT in decreasing microbial load, dental plaque, and gingivitis, and improving the patients' quality of life under fixed orthodontic treatment. These studies' findings provide evidence that aPDT is an effective treatment in the management of gingivitis induced by orthodontic treatment. The studies used different metrics and measurements for evaluation; different lasers, and radiation methods (size, duration, interrupted or continuous). Therefore a pooled outcome measurement was not possible.

Paschoal et al. (2015) made a comparison between the impacts of aPDT with curcumin with CHX varnish that was applied to teeth to prevent gingivitis and white spot lesions. Subsequent to applying the above therapies four times a week, the authors made a comparison (20) between the gingival bleeding index (GBI) and plaque index (PI) at baseline at the intervals of one month and three months following the intervention. The follow-up period of one month indicated no statistically significant change in PI values for the entire groups; however, in the aPDT group, the three-month follow-up period showed an increased value for the above-cited index. At first follow-up visit, GBI decrease was observed, which was then returned to its baseline amounts.

In order to estimate the long-term antimicrobial and anti-inflammatory impacts of photodynamic therapies, Abellan et al (2019) carried out some investigations on patients treated via fixed braces by determining the effectiveness of US (Ultrasonic Scaling) and aPDT effectiveness on periodontal health. They created two groups of patients aged 12 to 18 years (n=20) receiving seven sessions (days 0, 15, 30, 45, 90, 180, 270) of US or aPDT. In comparison with the starting point in both groups, the authors observed a statistically significant decline in probing depth (PD), gingival index (GI), and PI; however, no difference was observed between US and aPDT. According to the multiplex map of high sensitivity immunoassays of human beings, FGF-2 level increased, the levels of IL-10, IL-1β, and TNF- α decreased, and IL-6 and IL-1 had persistent levels; however, both groups showed no difference. Nearly the same decreases in colony-forming units (CFU) were observed for *P. intermedia*, *F. nucleatum*, and *P. gingivalis* in both groups. According to the authors, one can consider aPDT as a safe substitution for gingivitis therapy with inappreciably longer-lasting impacts. In addition, they ascribed the declined amount of bacteria to cell wall degradation and prevention of re-colonization in Gram-positive bacteria (21). Their findings approved the better long-term functions of aPDT, which agreed with the study results of Gomez et al. (2018). They evaluated the effectiveness of aPDT and US for the prevention of white spot lesions and gingivitis in the course of orthodontic treatment. The seven US and aPDT sessions held for patients included four sessions at two-week intervals at baseline (T0), and then, three boosters once in three months (T1, T2, T3). By beginning from T1, a small increase was detected in the international caries detection and assessment system (ICDAS), which were statistically insignificant. Also, the levels of periodontal indicators decreased. In T1, the PD and full-mouth bleeding score (FMBS) reported the most significant decline; however, in T2, full-mouth plaque score (FMPS) recorded the most significant decline, while no difference was found between the US and the aPDT groups. The investigations on a microbiome showed decreased numbers of cariogenic bacteria and periopathogens with no statistically significant difference between the two groups (31).

Furthermore, in a comparative study by Kamran el al. (2020) on subjects who underwent the US only therapy and those who received aPDT as an adjunctive to the US, the results revealed that the values of PS and bleeding on probing (BoP) reduced in both groups after three to six weeks, as compared to the values of baseline. There was a significant reduction in the values of plaque scores (PS) and BoP in both groups after three, and six weeks, respectively, permanently being advantageous to the US-aPDT group. IL-6 and TNF-α levels were decreased by these two protocols. In the US-aPDT group, the levels of IL-6 and TNF- α decreased significantly in week three and week six, respectively. In this group, the values of *P. gingivalis* and *P. intermedia* in the plaque specimens were largely decreased in both follow-up periods. Moreover, this study found that there was a significant reduction in the number of cytokines and the parameters associated with oral

inflammation after the use of aPDT (30).

In a study by Al Nazeh el al. (2020), 22 patients were categorized into two groups. The first group was only exposed to the US and the second group underwent US and aPDT (22). In the pre-intervention period and one and four weeks after the intervention, the upcoming clinical parameters, including a dichotomous record of BoP and PS, were evaluated. The plaque specimens were gathered by the investigators for conducting a bacterial analysis. The results demonstrated a statistically significant reduction in the values of BoP and PS in both groups in comparison to the values of baseline; however, there was no difference between the two groups. In the first group (US), the CFU of *T. forsythia* reduced after one week. Afterwards, in the second group (US-and-aPDT), a statistically significant reduction was observed in the CFUs of both *T. forsythia* and *P. gingivalis* after one and four weeks. The investigators believed that the reduction in the values of BoP and PS was associated with the antimicrobial impacts of such substance having sensitivity to light, which in turn ruins the bacterial matrix outer wall utilizing singlet oxygen (an extremely active chemical agent).

In a study by Alqerban el al. (2020), the efficacy of US with adjunct photobiomodulation (PBM) and the US with adjunct aPDT was compared to the efficacy of US alone using an anti-gingivitis treatment for patients undergoing fixed appliances. In this study, 45 subjects were categorized into three identical groups by the investigator. Alqerban calculated PS, PD, and BoP in every group and gathered gingival crevicular fluid (GCF) and plaque specimens at baseline and on days 30 and 60. The findings demonstrated a statistically significant reduction in the values of BoP and PS in all groups in comparison to the values of the baseline; however, there was no difference between each group. In the aPDT group, a gradual reduction was observed in the amount of PD, but there was no statistically significant difference between the groups. The human β-defensins level in the GCF was evaluated using the ELISA test, indicating a statistically significant reduction after 30 days for all of the study groups. There was an additional reduction reported after 60 days in the aPDT group and after 30 and 60 days, the T. denticola level in the aPDT group reduced (27).

In 2020, Alshahrani et al. made a comparison between the use of full-mouth periodontal debridement (FMPD) and FMPD with adjunct aPDT. The authors evaluated the BoP, PD, and PS values and hyperplastic index (HI) at baseline in clinical examinations two and four weeks following the applied therapy. After two and four weeks, a statistically significant decline was observed for the values of the entire items in both studied groups. It is noteworthy that in both time intervals, the FMPD-aPDT group showed a statistically significant decline in the hyperplastic index compared to that of the FMPD group. A significant reduction was observed in *T. forsythia*, *T. denticola*, and *P. gingivalis* from baseline. While, after two and four weeks, a statistically significant higher decline was observed in the mean log CFU/mL for the FMPD-aPDT group for *T. forsythia* and *P. gingivalis*, a significant difference for *T. denticola* occurred only after a two-week follow-up period. After four weeks of follow-up for both groups, IL-1β indicated a significant decline in ELISA.

After a four-week follow-up (28), significant differences were observed in the declined IL-6 levels between the groups to the benefit of the FMPD-aPDT group.

In 2020, Al Malik et al. also made a comparison between the efficacy of using the US alone and that of the aPDT in combination with the US for oral yeast. The gingival index was tested, and the samples of unstimulated whole saliva (UWS) were taken at the start of the research and six months following the intervention. The results were comparable between both groups in terms of GI. From another viewpoint, a significant decline was observed in the CFU/mL value for the yeast for the combined therapy; however, the decline for the US alone regarding the baseline value was not of statistical significance (26).

Baeshen et al. (2020) evaluated the effect of periodontal debridement on pain levels, clinical parameters, bacterial microflora, and cytokine secretion in adolescent orthodontic patients suffering from gingivitis. While group one received aPDT and US treatment via MB as a PS, group two only underwent the US. Nonetheless, no difference was observed in the BoP and PS when the groups were compared. A statistically significant decline was observed in favor of the group with adjunct aPDT. Applying the therapies did not affect the PD values and the perceived pain level. A significant decline in *T. forsythia* was observed for group one in comparison with group two; however, this occurred only after a one-week follow-up. A re-increase was found in microbial counts after four weeks. Compared to baseline, the authors reported a significant decline in IL-6 and TNF-α for both groups. In the case of TNF-α, a significant difference could be detected between the groups at week four, and for the second cytokine, it could be detected at week one (29).

Conclusion

The results of different studies have shown that aPDT is a safe, effective method to reduce periodontal complications induced by orthodontic treatment; it decreases dental plaque, gingivitis, inflammatory reactions, and a load of infectious pathogens, and by reducing pain and increasing the quality of life, increases patient satisfaction when undergoing orthodontic treatment.

Acknowledgments

Supported by Tehran University of Medical Sciences

Conflict of interest

The authors have no conflict of interest to declare.

References

1. Lang NP, Lindhe J. Clinical periodontology and implant dentistry, 2 Volume Set. New Jersey: John Wiley & Sons; 2015.
2. Topaloglu-Ak A, Ertugrul F, Eden E, Ates M, Bulut H. Effect of orthodontic appliances on oral microbiota—6 month follow-up. J Clin Pediatr Dent. 2011;35(4):433-6. doi: 10.17796/jcpd.35.4.61114412637mt661. PMID: 22046705.
3. Černochová P, Augustín P, Fassmann A, Izakovičová-Hollá L. Occurrence of periodontal pathogens in patients treated with fixed orthodontic appliances. Scripta Medica (brno). 2008 Jun;81:85-96.
4. Wennström JL, editor. Mucogingival considerations in orthodontic treatment. Semin Orthod. 1996; 2(1):46-54. doi: 10.1016/s1073-8746(96)80039-9. PMID: 9161283.
5. Bollen AM, Cunha-Cruz J, Bakko DW, Huang GJ, Hujoel PP. The effects of orthodontic therapy on periodontal health: a systematic review of controlled evidence. J Am Dent Assoc. 2008;139(4):413-22. doi: 10.14219/jada.archive.2008.0184. PMID: 18385025.
6. Lee SM, Yoo SY, Kim HS, Kim KW, Yoon YJ, Lim SH, et al. Prevalence of putative periodontopathogens in subgingival dental plaques from gingivitis lesions in Korean orthodontic patients. J Microbiol. 2005;43(3):260-5. PMID: 15995644.
7. Naranjo AA, Triviño ML, Jaramillo A, Betancourth M, Botero JE. Changes in the subgingival microbiota and periodontal parameters before and 3 months after bracket placement. Am J Orthod Dentofacial Orthop. 2006;130(3):17-22. doi: 10.1016/j.ajodo.2005.10.022. PMID: 16979483.
8. Van Gastel J, Teughels W, Quirynen M, Struyf S, Van Damme J, Coucke W, et al. Longitudinal changes in gingival crevicular fluid after placement of fixed orthodontic appliances. Am J Orthod Dentofacial Orthop. 2011;139(6):735-44. doi: 10.1016/j.ajodo. 2009.10.043. PMID: 21640879.
9. Newman MG, Takei H, Klokkevold PR, Carranza FA. Newman and Carranza's clinical periodontology. E-Book: Elsevier Health Sciences; 2018.
10. Sadeghian S, Omrani A, Esnaashari N, Farhad SZ, Kaviani M, Yahyapour F. Effect of 810nm diode laser on the number of periopathogen in gingival crevicular fluid (gcf) of fixed orthodontics patients without gingival inflammation. J Dent Sci. 2020;16(4):62-80.
11. Giannopoulou C, Cappuyns I, Cancela J, Cionca N, Mombelli A. Effect of photodynamic therapy, diode laser, and deep scaling on cytokine and acute-phase protein levels in gingival crevicular fluid of residual periodontal pockets. J Periodontol. 2012;83(8):1018-27. doi: 10.1902/jop.2011.110281. PMID: 22181685.
12. Ishikawa I, Sasaki KM, Aoki A, Watanabe H. Effects of Er: YAG laser on periodontal therapy. J Int Acad Periodontol. 2003;5(1):23-8. PMID: 12666952.
13. Schwarz F, Sculean A, Berakdar M, Georg T, Reich E, Becker J. Clinical evaluation of an Er: YAG laser combined with scaling and root planing for non-surgical periodontal treatment: A controlled, prospective clinical study. J Clin Periodontol. 2003;30(1):26-34. doi: 10.1034/j.1600-051x.2003. 300105.x. PMID: 12702108.
14. Schwarz F, Sculean A, Berakdar M, Szathmari L, Georg T, Becker J. In vivo and in vitro effects of an Er: YAG laser, a GaAlAs diode laser, and scaling and root planing on periodontally diseased root surfaces: a comparative histologic study. Lasers Surg Med. 2003;32(5):359-66. doi: 10.1002/lsm.10179. PMID: 12766958.
15. Sculean A, Schwarz F, Berakdar M, Romanos GE, Arweiler NB, Becker J. Periodontal treatment with an Er: YAG laser compared to ultrasonicInstrumentation: a pilot study. J Periodontol. 2004;75(7):966-73. doi: 10.1902/jop.2004.75.7.966. PMID: 15341354.
16. Sculean A, Schwarz F, Berakdar M, Windisch P, Arweiler NB, Romanos GE. Healing of intrabony defects following surgical treatment with or without an Er: YAG laser: a pilot study. J Clin Periodontol. 2004;31(8):604-8. doi: 10.1111/j.1600-051X.2004. 00525.x. PMID: 15257735.
17. Moslemi N, Heidari M. Is Photodynamic therapy effective in treatment of periodontal diseases? A review of literature. Lasers Med Sci. 2011;8(1):18-24.
18. Mirhashemi A, Janani R, Bahrami R, Chiniforush N. Evaluation of the photodynamic therapy with riboflavin and curcumin on shear bond strength of orthodontic bracket: An in vitro study. Photodiagnosis Photodyn Ther. 2022;38:1-7. doi: 10.1016/j.pdpdt.2022.102787. PMID: 35231617.
19. Bıyıkoğlu B, Buduneli N, Aksu K, Nalbantsoy A, Lappin DF, Evrenosoğlu E, Kinane DF. Periodontal therapy in chronic periodontitis lowers gingival crevicular fluid interleukin-1beta and DAS28 in rheumatoid arthritis patients. Rheumatol Int. 2013;33(10):2607-16. doi: 10.1007/s00296-013-2781-5. PMID: 23728274.
20. Paschoal MA, Moura CMZ, Jeremias F, Souza JF, Bagnato VS, Giusti JS, et al. Longitudinal effect of curcumin-photodynamic antimicrobial chemotherapy in adolescents during fixed orthodontic treatment: a single-blind randomized clinical trial study. Lasers

Med Sci. 2015;30(8):2059-65. doi: 10.1007/s10103-014-1700-7. PMID: 25543296.
21. Abellán R, Gómez C, Iglesias-Linares A, Palma JC. Impact of photodynamic therapy versus ultrasonic scaler on gingival health during treatment with orthodontic fixed appliances. Lasers Surg Med. 2019;51(3):256-67. doi: 10.1002/lsm.23035. PMID: 30575059.
22. Al Nazeh A, Alshahrani A, Almoammar S, Kamran MA, Togoo RA, Alshahrani I. Application of photodynamic therapy against periodontal bacteria in established gingivitis lesions in adolescent patients undergoing fixed orthodontic treatment. Photodiagnosis Photodyn Ther. 2020;31:101904. doi: 10.1016/j.pdpdt.2020.101904. PMID: 32622074.
23. de Oliveira RR, Schwartz-Filho HO, Novaes AB, Garlet GP, Freitas de Souza RF, et al. Antimicrobial photodynamic therapy in the non-surgical treatment of aggressive periodontitis: Cytokine profile in gingival crevicular fluid, preliminary results. J Periodontol. 2009;80(1):98-105. doi: 10.1902/jop.2009.070465. PMID: 19228095.
24. Vieira DL, Leite AF, de Souza Figueiredo PT, Vianna LM, Moreira-Mesquita CR, de Melo NS. A conservative approach for localized spongiotic gingivitis hyperplasia using photodynamic therapy: A case report and review of the literature. Photobiomodul Photomed Laser Surg. 2019;37(1):57-61. doi: 10.1089/photob.2018.4454. PMID: 31050937.
25. Mistry A, Pereira R, Kini V, Padhye A. Effect of combined therapy using diode laser and photodynamic therapy on levels of IL-17 in gingival crevicular fluid in patients with chronic periodontitis. J Lasers Med Sci. 2016;7(4):250-5. doi: 10.15171/jlms.2016.44. PMID: 28491261.
26. Al Malik NK, Alkadhi OH. Effectiveness of mechanical debridement with and without antimicrobial photodynamic therapy against oral yeasts in children with gingivitis undergoing fixed orthodontic therapy. Photodiagnosis Photodyn Ther. 2020;31:101768. doi: 10.1016/j.pdpdt.2020.101768. PMID: 32305653.
27. Alqerban A. Efficacy of antimicrobial photodynamic and photobiomodulation therapy against Treponema denticola, fusobacterium nucleatum and human beta defensin-2 levels in patients with gingivitis undergoing fixed orthodontic treatment: A clinic-laboratory study. Photodiagnosis Photodyn Ther. 2020;29:101659. doi: 10.1016/j.pdpdt.2020.101659. PMID: 31945548.
28. Alshahrani A, Togoo RA, Kamran MA, Alshahrani I. Clinical periodontal, bacterial, and immunological outcomes of antimicrobial photodynamic therapy in orthodontic treatment-induced gingival enlargement. Photodiagnosis Photodyn Ther. 2020;31:101934. doi: 10.1016/j.pdpdt.2020.101934. PMID: 32738349.
29. Baeshen HA, Alshahrani A, Kamran MA, Alnazeh AA, Alhaizaey A, Alshahrani I. Effectiveness of antimicrobial photodynamic therapy in restoring clinical, microbial, proinflammatory cytokines and pain scores in adolescent patients having generalized gingivitis and undergoing fixed orthodontic treatment. Photodiagnosis Photodyn Ther. 2020;32:101998. doi: 10.1016/j.pdpdt.2020.101998. PMID: 32916329.
30. Kamran MA. Clinical, microbiological and immunological outcomes with photodynamic therapy as an adjunct to full-mouth scaling in patients undergoing fixed orthodontic treatment. Photodiagnosis Photodyn Ther. 2020;29:101585. doi: 10.1016/j.pdpdt.2019.101585. PMID: 31689513.
31. Gómez C, Abellán R, Palma JC. Efficacy of photodynamic therapy vs ultrasonic scaler for preventing gingival inflammation and white spot lesions during orthodontic treatment. Photodiagnosis Photodyn Ther. 2018;24:377-83. doi: 10.1016/j.pdpdt.2018.11.001. PMID: 30399455.
32. Mohammadi F, Farhad SZ, Feizbakhsh M, Amini S. The Effect of Low Laser Laser Therapy on GCF Level of IL-6 and IL-8 During Orthodontic Treatment. J Isfahan Dent Schol. 2017;13(2):195-201.
33. Aghayan S, Hemmatpoor S, Sadat Mansori S, Mahmoudi Z. Evaluation of Orthokin toothpaste and mouthwash effects on periodontal indexes in fixed orthodontic patients. J Dent Sci. 2018;15(2):56-62.
34. Farhad S, Aryam M, Mohammadi F, Birang E, Barekatain M, Zarei E. Effect of photodynamic therapy as adjunctive periodontal therapy on tnf-⍰ level in gingival crevicular fluid. J Dent Sci. 2015;12(2):78-84.