

Clinical and Microbiological Outcomes of Topical *Aloe Vera* Gel vs. Photochemotherapy as an Adjunct to Non-surgical Periodontal Treatment in Periodontitis



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ABSTRACT

The present clinical trial aimed to assess the effectiveness of antimicrobial photodynamic therapy *versus Aloe vera* gel as an adjunct to scaling and root planing on periodontal and microbial outcomes in patients with periodontitis. Eligible patients undergoing nonsurgical periodontal treatment were divided into 3 groups: group 1: antimicrobial photodynamic therapy; group 2: *Aloe vera* gel application; and group 3: scaling and root planing only. Clinical periodontal variables included the assessment of plaque scores, bleeding on probing, probing depth, and clinical attachment level gain. Plaque samples were collected to estimate microbial counts of *Tannerella forsythia* (*T. forsythia*) and *Porphyromonas gingivalis* (*P. gingivalis*). All measurements were recorded at baseline, 3 mo, and 6 mo. Statistical analysis of the given data was performed using the chi-squared test and ANOVA for clinical periodontal and microbiological data. Eighty-seven patients completed the trial. Bleeding on probing showed a significant reduction in group 2 compared with the other groups ($p < 0.001$). Group 1 showed a statistically significant reduction in probing depth and gain in clinical attachment level when compared to group 2 and group 3 ($p < 0.05$). Group 1 showed a statistically significant reduction in the counts of *T. forsythia* and *P. gingivalis* over a period of 3 mo ($p < 0.05$). The reduction was seen for *T. forsythia* only following 6 mo ($p < 0.05$). Group 2 showed a significant reduction for only *T. forsythia* at 3 mo ($p < 0.05$). Both antimicrobial photodynamic therapy and *Aloe vera* gel helped in reducing periodontal inflammation. *Aloe vera* gel showed additional benefit in reducing bleeding scores, while antimicrobial photodynamic therapy showed additional enhanced activity against periodontal pathogens and periodontal attachment level gain.

Introduction

Periodontitis is a bacterial and host-mediated inflammatory response of the dental supporting structures that leads to loss of soft tissue connection and bone destruction, eventually leading to tooth loss [1]. The initiation and progression of periodontitis depend on the dysbiosis of microbial niche and multifactorial disease influences, such as diabetes mellitus, cigarette smoking, and stress

[2, 3]. Therefore, to prevent tooth loss and enhance oral health-related quality of life, the disease process must be ceased with appropriate therapeutic interventions.

The standard treatment for periodontitis is the nonsurgical periodontal treatment approach, which includes scaling and root planing (SRP). However, SRP does not always provide successful outcomes in several clinical situations [4]. In addition, manual debride-

ment also involves expertise and does not provide as great efficacy as ultrasonic debridement does [5]. Nevertheless, these flaws can be surmounted by introducing adjunctive therapies with SRP [6]. Several systemic and local adjuncts can amplify the treatment of periodontitis and produce better clinical results when compared with SRP only. Some of the adjunctive agents that are commonly used include antimicrobials, statins, bisphosphonates, and anti-diabetic agents [7–10].

Aloe vera, which belongs to the family Asphodelaceae, is one of the oldest medicinal plants used in medicine [11]. Numerous beneficial compounds such as enzymes, vitamins, polysaccharides, and proteins are present in *Aloe vera*. These bioactive components present in *Aloe vera* are believed to exert a variety of health benefits such as wound healing, as well as antiseptic, antiviral, antibacterial, antifungal, and antioxidant properties [12]. Ample data in periodontal medicine shows that *Aloe vera* has a significant impact on periodontal tissues. *Aloe vera* shows considerable anti-inflammatory properties by reducing bleeding and the amount of microbiome in and around gingival tissues [13]. However, the effect of *Aloe vera* on probing depth (PD) and periodontal attachment level remains uninvestigated.

Antimicrobial photodynamic therapy (APDT), which is highly researched in periodontology, involves the application of laser light of a specific wavelength in the presence of a known concentration of photosensitizer. This technique encompasses the formation of harmful species derived from oxygen that helps to reduce microbial load including the gram-negative bacteria from deep periodontal space in periodontitis [14]. APDT, due to its detoxification and bactericidal potency, is a useful adjunctive therapy to nonsurgical manual periodontal debridement. Numerous systematic reviews have been published that report clinical advantages of APDT as an adjunct to periodontal debridement in periodontal disease [15, 16]. Reports from these reviews suggest that the findings are, in part, contradictory and nondefinitive in terms of clinical periodontal and microbiological data [15, 16]. Further robust investigations are needed to evaluate the significance of APDT and to ascertain the variables and factors affecting the outcomes. Although this technique reports superior results over conventional periodontal debridement, it still has several limitations related to laser parameters, including fiber optic diameter, type of laser, and the number of laser sessions [17]. While most studies report single application

of APDT, other studies have used multiple laser applications [18]. It is still debatable whether multiple applications of APDT proves to be more beneficial than a single application of APDT in periodontitis. The goal of the present study is to compare 2 repeated local applications in the treatment of periodontal infection. Based on our information from the database, there are no studies that have assessed and compared the clinical efficacy of these 2 techniques. Hence, this 6-mo, randomized controlled clinical trial was designed to assess and compare the periodontal and microbiological results with thrice application of adjunctive APDT versus *Aloe vera* gel in patients with periodontitis.

Results and Discussion

Out of 784 patients screened, 90 patients (mean age: 32.57 y) were recruited and randomly divided into 3 groups of equal patients. One patient from group 1 discontinued the follow-up sessions after the baseline visit, while 2 patients from group 2 were lost to follow-up as they moved out of the city. Therefore, a total of 87 patients were included and analyzed. The number of males and females included in the trial are presented in ► **Table 1**.

None of the clinical periodontal parameters showed a statistically significant difference among all groups at baseline (► **Table 2**). For plaque scores (PS) and bleeding on probing (BOP), there was a significant reduction among all 3 groups at 3 mo ($p < 0.01$) and 6 mo ($p < 0.001$) postoperatively. On intergroup comparison, BOP showed a significant reduction in group 2 compared with the other groups ($p < 0.001$). There was a significant reduction in PD and gain in clinical attachment level (CAL) in all the groups. However, group 1 showed a statistically significant difference when compared to group 2 and group 3 ($p < 0.05$).

► **Table 1** Demographic characteristics of the study groups.

Characteristics	Group 1 APDT + SRP	Group 2 <i>Aloe vera</i> + SRP	Group 3 SRP only
Number of patients	29	28	30
Mean age (years)	31.42	33.87	30.59
Gender (males/females)	18/11	15/13	14/16

► **Table 2** Periodontal clinical monitoring at baseline and follow-up.

Groups	Time (months)	PS (%)	BOP (%)	PD (mm)	CAL (mm)
Group 1 (APDT + SRP)	0	24.4 ± 2.9	28.7 ± 2.3	3.9 ± 0.2	4.8 ± 0.2
	3	14.2 ± 2.3 ^b	21.1 ± 2.2 ^c	3.3 ± 0.2 ^a	4.1 ± 0.3 ^a
	6	11.6 ± 1.9 ^a	18.9 ± 2.1 ^b	3.2 ± 0.2 ^{a,*}	4.0 ± 0.3 ^{a,*}
Group 2 (<i>Aloe vera</i> + SRP)	0	26.7 ± 2.8	30.5 ± 2.9	3.6 ± 0.2	4.5 ± 0.2
	3	19.5 ± 2.5 ^b	18.3 ± 2.1 ^b	3.3 ± 0.2 ^c	4.1 ± 0.2 ^c
	6	15.1 ± 2.2 ^a	13.8 ± 2.0 ^{a,*}	3.3 ± 0.2 ^c	3.9 ± 0.3 ^c
Group 3 (SRP)	0	21.9 ± 2.7	26.7 ± 2.5	3.7 ± 0.2	4.4 ± 0.3
	3	14.8 ± 2.3 ^b	21.6 ± 2.7 ^c	3.5 ± 0.2 ^c	4.2 ± 0.2 ^c
	6	12.3 ± 2.0 ^a	19.7 ± 2.5 ^b	3.4 ± 0.2 ^c	4.1 ± 0.3 ^c

All values are reported in mean ± standard deviation. ^a Different from baseline, $p < 0.001$ ^b Different from baseline, $p < 0.01$ ^c Different from baseline, $p < 0.05$ * Difference between groups, $p < 0.05$.

There was a gradual reduction in the microbial counts in all 3 groups (► **Fig. 1**). Group 1 showed a statistically significant reduction in the *T. forsythia* and *P. gingivalis* over the period of 3 mo ($p < 0.05$). The reduction was seen following 6 mo post-treatment for *T. forsythia* only ($p < 0.05$). Group 2 showed a significant reduction for only *T. forsythia* at 3 mo of follow-up ($p < 0.05$) (► **Fig. 1a**).

The present study had the purpose of comparing 2 topical therapeutic modalities, one being a light-activated phototherapy and the other one being a phytotherapy. The main findings of the present study showed that APDT significantly improved periodontal attachment level gain, whereas, on the other hand, *Aloe vera* gel application helped to suppress the inflammatory parameters of bleeding in chronic periodontal disease.

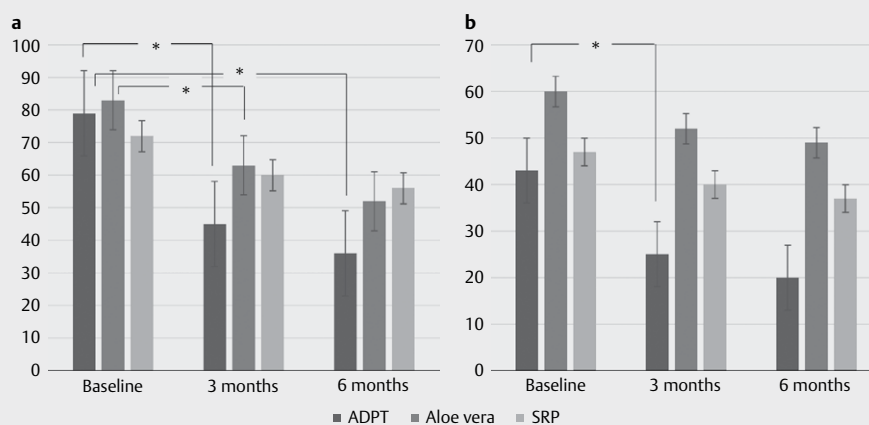
The therapeutic efficacy of photochemotherapy in chronic periodontal disease is well-known. There is a substantial amount of evidence reported in the database that corroborates the findings of our clinical study [15, 19]. For instance, Braun et al. [20] reported increased efficacy of adjunctive APDT on periodontal disease sites compared with hand instruments and ultrasonic debridement. Another study by Alwaeli et al. [21] showed the significant long-term clinical effect of adjunctive APDT in the improvement of clinical periodontal parameters. However, other studies still show some contradictory results. For example, a study by Petelin et al. failed to show significant improvement with regard to PD reduction and gain in CAL [22]. Other studies also showed no statistically significant difference between APDT and SRP groups at 3 mo and 6 mo of post-treatment [23]. These outcomes authenticate the need for novel therapeutic techniques to enhance the clinical efficacy of conventional periodontal debridement. These unwanted side effects create the requirement for a complementary therapeutic approach to limit biofilms and to alleviate periodontal infections [24]. Photodynamic therapy is arbitrated by oxygen (singlet), which could directly influence extracellular molecules. Therefore, the diverse polysaccharides found in the extracellular matrix of polymers of a bacterial niche are also vulnerable to photodamage [24]. This dual role of APDT may not be seen in any other local therapies that put APDT on a higher scale of preference.

Although there are abundant adjunctive topical drugs present to test the clinical efficacy of periodontal outcomes, the most common drugs are generally antimicrobials [25]. However, with several benefits that antimicrobials offer, there are also several well-known drawbacks with antibiotic use. It is a well-known fact that antimicrobials may exhibit microbial resistance, certain GI problems, and allergies [26]. Therefore, we clinically tested *Aloe vera*, which is a safer drug with fewer side effects.

The findings of the present study agree with the outcomes of previously published data on *Aloe vera* use that showed a higher reduction in plaque and improvement in gingival inflammation after the use of mouthrinse containing *Aloe vera* combined with toothbrushing [27]. A study by Pradeep et al. demonstrated significant improvement in the plaque and gingival index scores with *Aloe vera* used in the dentifrice [13]. *Aloe vera* gel helped in the significant reduction of bleeding scores in our study. This could be attributed to the active natural ingredients present in the plant. The parenchyma gel of *Aloe vera* is comprised of numerous polymers of carbohydrate, mainly glucomannans or peptic acid, with various inorganic and organic constituents [28]. The immunomodulatory characteristics of the polysaccharides acetylated mannans present in the gel from *Aloe vera* are considered to perform a vital role in the reduction of inflammation. Treatment against diabetes and cancer, as well as the andantimicrobial properties of *Aloe vera*, have been suggested to prove the broader application of *Aloe vera* [29].

With regard to the microbial destruction, there are still debatable reports. Some laboratory studies failed to demonstrate the antimicrobial activity of APDT on periodontal pathogens [30]. However, a positive effect from the use of APDT has been reported by Theodoro et al. [31]. Six mo post-treatment with APDT was seen to significantly reduce the microbial counts (*T. forsythia* and *P. gingivalis* being the 2 of them). Our study indicated a statistically significant reduction of the 2 microbes. This could be attributed to the repeated multiple application of APDT in the deep periodontal pockets, which are housed by late colonizers [22].

The present trial certainly has some limitations. The specific drug concentration was variable. The testing with several drug con-



► **Fig. 1** Microbiological analysis of subgingival plaque samples for 2 periodontal pathogens. Proportion of sites positive for (A) *T. forsythia*, and (B) *P. gingivalis* at baseline, and at 3 and 6 mo after the treatment. * Denotes statistical significance at $p < 0.05$.

centrations may provide different clinical outcomes in periodontitis. The assessment of various proinflammatory biomarkers in the gingival crevicular fluid may suggest the reduction of local inflammation with the use of APDT and *Aloe vera* gel. In addition, the present study did not consider the stratification of periodontal pockets into moderately deep (>4 mm) and deep pockets (>5 mm). Moreover, the 2 sets of treatments were dissimilar, and the initial periodontal assessments could not be blinded. These limitations may surely have an impact on the true clinical findings in the reduction of periodontal inflammation. Further robust clinical trials with long follow-up and stratified data are needed to test the efficacy of the 2 topical treatments in periodontitis.

Both APDT and *Aloe vera* gel helped in reducing periodontal inflammation. *Aloe vera* gel showed additional benefit in reducing bleeding scores, while APDT showed additional enhanced activity against periodontal pathogens and periodontal attachment level gain.

Materials and Methods

Ethical consideration and study design

The study was conducted following the principles described in the Declaration of Helsinki. Ninety dentate patients were included in the study and requested to sign the informed consent. This trial was a single-blinded, parallel, randomized controlled clinical study conducted between March 2018 and July 2019.

Patient eligibility

A total of 784 patients were screened initially for generalized periodontitis. After performing basic periodontal charting, the patients who met the criteria were assessed for full-mouth clinical periodontal charting. Inclusion criteria were: 1) > 18 y of age with no gender predilection, 2) at least 16 natural teeth present (excluding third molars), and 3) diagnosed clinically with generalized periodontitis, defined as PD \geq 5 mm, CAL \geq 3 mm, and presence of BOP. The following patients were excluded: 1) active cigarette smokers, 2) pregnant or lactating women, 3) those with periodontal therapy within the last 6 mo, 4) those who used antimicrobial therapy, and 5) those with medical conditions that could influence the treatment or progression of periodontal condition. The standards of this trial agreed with the Declaration of Helsinki.

Power calculation

The sample size estimation was based on the mean differences in PD of 0.5–1 mm. and the standard deviation was assumed to sit at 1 mm between SRP and adjunctive therapies. Therefore, a total sample of 90 patients (30 per group) were needed to offer 80% power for the detection of 0.75 mm of the true difference between the groups.

Groups and test products

All the patients after recruitment were randomly assigned to one of the 3 treatment groups. Group 1 consisted of patients that underwent APDT. Group 2 comprised of participants who were provided the treatment with *Aloe vera* gel, while patients in group 3

were given only SRP. Test treatment modalities were rendered after SRP in groups 1 and 2, respectively.

Aloe vera gel was formulated using the technique described in Velam et al. [32] without the incorporation of piroxicam. In short, the pulp from the leaves of *Aloe vera* was washed with water and 0.1 N NaOH. After blending the pulp, the contents were prefiltered with the help of a cotton sheet and later filtered under vacuum to obtain a transparent solution. Later, 1.25% w/w Carbopol (polymer) and 0.75% w/w methylparaben were mixed and sonicated. Lastly, 0.5 N NaOH was slowly added and gently agitated until the liquid transformed into the gel. The gel was weighted and collected in glass bottles and covered with aluminum foil to prevent photo-oxidation [32].

APDT was carried out using the laser system (Periowave) in deep periodontal pockets. A blunt syringe carrying methylene blue as a photosensitizer was applied inside the pockets for 60 s. The sites were activated using the diode laser with a wavelength of 670 nm and a power output of 280 mW. A total of 3 sessions, at baseline, wk 1, and wk 2 were carried out, respectively.

Clinical monitoring

All clinical assessments were performed by a single expert periodontal examiner (MA). Before performing clinical assessments, 5 patients with periodontitis (not included in the study groups) were invited for the assessment of intra-assessor calibration and intra-class correlation. Full-mouth PD and CAL recordings were taken and repeated after 1 wk. A total of 92% of values were reproducible for both PD and CAL and considered a good agreement. Detailed periodontal charting was undertaken for patients randomized in the 3 groups. Full-mouth PS, BOP, PD, and CAL were charted at 6 points of all the teeth (except third molars). All periodontal assessments were taken using a measuring instrument (UNC-15, Hu-Friedy). All measurements were taken before the treatment, at 3 mo, and 6 mo post-treatment.

Plaque sampling and microbiological techniques

All patients were instructed to rinse and gargle with normal saline to remove food debris. Supragingival plaque was removed carefully. Two plaque samples from each patient were collected using sterile paper points from the deepest periodontal pocket (>6 mm) at baseline, 3 mo, and 6 mo [33]. The plaque was sampled from the same site at each following visit. The paper points were transferred in 1 mL of PBS and vortexed for 10 s. The presence of 2 periodontal pathogens — *P. gingivalis* and *T. forsythia* — was assessed qualitatively in all specimens by performing PCR technique. This was followed by genomic DNA extraction for hybridization using a commercial micro-IDent test (Hain Lifescience). PCR amplification was performed. The process comprised of a primary step of denaturation for 5 min at 95 °C; 10 cycles for 30 s at 95 °C and for 120 s at 58 °C; 20 cycles for 25 s at 95 °C, for 40 s at 53 °C, and 40 s at 70 °C; and a final extension step for 8 min at 70 °C. For the reverse hybridization technique, the steps comprised of the denaturation of biotinylated amplicons were carried out and then stored at 45 °C with hybridization buffer. The strips consisted of coating 2 control lines and 2 microbe-specific probes. Any nonspecifically bound DNA was removed by washing. Next, the steps consisted of the slow ad-

dition of streptavidin-conjugated alkaline phosphatase and then washing again. The hybridized products were seen by the addition of alkaline phosphatase.

Statistical analysis

Statistical analysis of the data was performed using the SPSS software (v20, IBM). The values of all the parameters calculated were reported as means and their standard deviations. Normal distribution tests of all the parameters were performed prior to computation of any testing. Statistical analysis of the given data was performed using chi-squared test and ANOVA for clinical periodontal and microbiological data. P-values, if shown less than 0.05, were considered statistically significant.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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