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Original Article

Effect of photodynamic therapy as an adjunctive to mechanical debridement on the nonsurgical treatment of peri-implant mucositis: A randomized controlled clinical trial

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ABSTRACT

Background: The use of photodynamic therapy (PDT) has been evaluated as an adjunctive technique for bacterial decontamination of implants with peri-implantitis. Given the controversies over the efficacy of the application of PDT to treat peri-implant diseases, the present clinical study aimed to evaluate the posttherapeutic clinical parameters and cytokine levels in peri-implant crevicular fluid in patients with peri-implant mucosal inflammation, receiving mechanical debridement (MD) alone or in association with PDT.

Materials and Methods: In this double-blinded randomized clinical trial, 52 patients with peri-implant mucosal inflammation were selected and they were randomly assigned to 2 treatment groups: a MD group and an MD + PDT group using an 805 nm laser and indocyanine green (ICG). Although the decrease in bleeding on probing was the primary outcome, pocket depth, PUS, pain on probing, clinical attachment level, gingival recession, tumor necrosis factor-α, interleukin (IL)-1β, IL-6 and matrix metalloproteinase-8 were also evaluated at baseline, 2-week, and 3-month postintervention. Repeated measure analysis of variance was used to analyze inter-group differences and a $P \leq 0.05$ was considered for significant differences between tested parameters.

Results: Statistically significant improvements ($P < 0.001$) were detected for all variables after comparison of baseline data with those collected at each time interval of the study. Nevertheless, the inter-group comparisons of these variables between the baseline, 2-week, and 3-month intervals did not reveal any significant decrease in sites treated with either MD alone or MD + PDT.

Conclusion: The application of PDT using 805-nm laser and ICG as an adjunct therapy to MD did not provide any additional improvements in the clinical or biologic parameters of peri-implant mucosal inflammation.

Key Words: Cytokines, peri-implantitis, photochemotherapy

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INTRODUCTION

Peri-implant diseases consist of inflammatory lesions that may affect the peri-implant mucosa, referred to as peri-implant mucositis or that may result in loss of the implant-supporting bone, referred to as peri-implantitis. Peri-implant mucositis has

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been reported in approximately 80% of patients receiving implants at 50% of implant sites, whereas peri-implantitis has been reported in 28%–56% of implant patients at 12%–40% of implant sites.[1-4]

To manage peri-implant diseases, it is advisable to evaluate the available evidence for treating periodontitis. Therefore, it is important to carry out surface debridement to treat peri-implant mucositis and peri-implantitis.[5,6]

Limited access for plaque control around the implant-supported prosthesis[7,8] and surface roughness of the contaminated implant;[9] cause the decrease in bacterial load at peri-implantitis sites and the resolution of inflammation are incomplete in most cases. However, complete resolution of mucosal inflammation is unpredictable after adjunctive use of antiseptics and antibiotics subsequent to mechanical debridement (MD) of peri-implantitis lesions. The use of photodynamic therapy (PDT) has been evaluated as an adjunctive technique for bacterial decontamination of implants with peri-implantitis.[7]

PDT technique uses a low-power laser with an appropriate wavelength to destroy microorganisms in patients previously treating with photosensitizer, such as toluidine blue O (TBO), which can bind to the target cells. The light-activated photosensitizer takes part in a reaction with the substrate, producing highly reactive oxygen species such as free radicals and/or singlet oxygen, with toxic effects on microorganisms.[10-14]

In a study by Dörtbudak *et al*.,[10] PDT in association with MD resulted in a significant decrease in the counts of pathogens in the sulcus around implants affected by peri-implantitis. An ideal PDT photosensitizer absorbs light at 650–900 wavelengths, i.e., at the visible red and near-infrared region of the electromagnetic spectrum. Maximal penetration of light into tissues is observed at these wavelengths.[11]

Toluidine blue and methylene blue are used as photosensitizers in antimicrobial PDT. These photosensitizers exhibit similar chemical and physicochemical properties.[12] A study showed that TBO resulted in a significant decrease in *Prevotella intermedia* and *Aggregatibacter actinomycetemcomitans* counts, with no effect on *Porphyromonas gingivalis*.[10]

Another photosensitizer is indocyanine green (ICG) with an activation wavelength of 805 nm and low-power diode laser radiation, which exerted a similar effect on PDT, eliminating periodontal pathogens, including *P. gingivalis*.[13] Hopp and Biffar combined PDT and ICG, which resulted in stabilization of periodontitis/peri-implantitis in the long term.[14]

Visible red light (650 nm) can penetrate biological tissues up to 3–3.5 mm; however, near-infrared light (800–1100 nm) can penetrate to a depth of 6 mm. Therefore, the ICG with a wavelength of 805 nm can penetrate to a greater depth into biological tissues compared to other substances.[15] In addition, the ICG lacks toxicity and has been approved by the U.S. Food and Drug Administration for medical applications.[16]

Recent studies on subjects with peri-implantitis have shown an increase in inflammatory cytokines levels of interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF-α) compared to healthy subjects, suggesting the possible effect of these cytokines on pathogens involved in peri-implantitis cases.[17] Recent studies have shown that the irreversible destruction of peri-implant tissues might be attributed to an increase in matrix metalloproteinase (MMP) levels. The collagenase subtypes of MMP family include MMP-1, MMP-8, and MMP-13 and they have been identified in periodontitis and peri-implantitis due to their ability to break down fibrillar collagen.[18-21] Previous studies have shown an increase in collagen levels in early periodontitis, chronic periodontitis, and peri-implantitis[22-26] and MMP-8 is known to be the major MMP in periodontitis and peri-implantitis.[27]

Based on experimental results,[28-30] PDT used as an adjunct to and in association with MD is more efficacious for the treatment of peri-implant conditions compared to conventional treatment alone. Nonetheless, clinical studies[7,29,31,32] have yielded contradictory results. Given the controversies over the efficacy of the application of PDT to treat peri-implant diseases, the present clinical study aims to evaluate the posttherapeutic clinical parameters and cytokine levels in peri-implant crevicular fluid (PICF) in patients with peri-implant mucosal inflammation, receiving mechanical therapy alone or mechanical therapy in association with PDT.

MATERIALS AND METHODS

Study design

The protocol of the present double-blinded prospective randomized clinical trial study was

approved by the Research Ethics Committee of Tabriz University of Medical Sciences (protocol number: IR.TBZMED.REC.1395.554). The study was registered with the local World Health Organization Registry Network (IRCT.201609281248N3).

Study participants

A total of 52 participants (21 males and 31 females, aged 26–58 years, with a mean age of 37.5 years) were recruited from the patients referred, for the management of peri-implant conditions, to the Department of Periodontics, Faculty of Dentistry, Tabriz University of Medical Sciences, from October 2015 to December 2016. Written and verbal informed consent was obtained from all the subjects before the study.

Inclusion criteria

Patients were included if they meet the following eligibility criteria:

1. Age ≥18 years
2. Partially edentulous subjects with healthy or treated periodontal conditions, undergoing a regular maintenance care program
3. Initial peri-implantitis defined as (a) pocket probing depth (PPD) of 4–6 mm in association with bleeding on probing (BOP) at ≥1 peri-implant site and (b) radiographic evidence of bone loss with a range of 0.5–2 mm from the time when the prosthetic reconstruction was delivered to prescreening appointment
4. implant in function for ≥1 year.[7]

Exclusion criteria

The subjects were excluded if they had the following conditions:

1. Pregnant or breastfeeding women
2. Use of tobacco
3. Uncontrolled medical conditions
4. Untreated periodontal diseases
5. Use of systemic antibiotics during the previous 3-month period
6. Use of systemic antibiotics for prophylaxis of endocarditis
7. Subjects treated for an extended period (i.e., 2 weeks or more) with any medication affecting soft-tissue conditions (e.g., phenytoin, calcium antagonists, cyclosporine, coumadin, and nonsteroidal anti-inflammatory drugs) within 1 month of the baseline examination
8. Radiotherapy in the head-and-neck region
9. Infectious diseases, such as HIV, tuberculosis, and hepatitis
10. Drug and alcohol abuse
11. Failure or refusal to sign a written informed consent form.[7]

Study interventions

A total of 52 patients were selected based on the inclusion and exclusion criteria of the study and were given an informed consent form before they were enrolled. They were randomly assigned to the study groups. A full-mouth plaque index (O'Leary *et al*. 1972) was obtained at baseline, 2 weeks' and 3 months' postintervention. The same operator (radical prostatectomy [RP]) treated all patients during a single appointment. They were then assigned randomly to receive one of the following treatment protocols using a computer-generated randomization table.

Protocol 1 (control group)

In a conventional therapy group, all the participants received MD, after administration of local anesthesia, using a sonic scaler (Varios 350, NSK, Tochigi, Japan), which was followed by the use of titanium curettes (Deppeler SA, Rolle, Switzerland) and a glycine-based polishing powder (Air-Flow Master, Perio Powder, Perio-Flow nozzle, E.M.S. Electro Medical Systems SA, Nyon, Switzerland) to remove submucosal biofilm.

Protocol 2 (test group)

In the PDT group, in the sites undergoing PDT, a flexible applicator tip (0.04-mm Endo tip) (0.04-mm Endo tip) was used to fill the peri-implant pocket with ICG photosensitizer (EmunDo®solution (A.R.C. laser GmbH, Nurnberg, Germany) in a coronal direction, initiating in the most apical portion. The photosensitization procedure lasted 60 s. Subsequently, the pocket underwent irrigation with distilled water, followed by laser irradiation (Handy Laser Sprint, RJ-Laser, Reimers and Janssen, Windenim Elztal, Germany) for 120 s at 805 nm of wavelength and an output power of 0.5 W.[17]

Study outcomes

The primary outcome was the reduction of BOP in one positive site in the examined regions. Changes in pocket depth (PD), pain on probing (POP), clinical attachment level (CAL), gingival recession (GR), suppuration, and the level of cytokines IL-1β, IL-6, and TNF-α and MMP-8 were considered as secondary outcomes.

Pre- and post-treatment assessments

Clinical parameters

One examiner (RP) was blinded to the type of treatment rendered to the participants. In an attempt to decrease intraexaminer variability, a customized acrylic stent was fabricated for each patient to provide a stable reference point for carrying out accurate clinical measurements. All the clinical measurements were carried out by one specific type of periodontal probe (UNC-15, Hu-Friedy, Chicago, IL, USA). Before undertaking the study, this examiner was calibrated for measuring clinical parameters for double measurements in two separate sessions, 48–72 h apart, on five patients who were not included in the study. A high level of intra-examiner agreement was achieved (≥90%). This examiner recorded the clinical outcomes at baseline, 2-week, and 3-month follow-ups:

1. BOP: Bleeding after placing the probe apical to the gingival margin at six sites per implant, for the presence or absence of bleeding within 30 s subsequent to probing[29]
2. PD: The depth of the gingival sulcus measured from the gingival margin[29]
3. POP: A simple Visual Analogue Scale (VAS) for evaluation of the patient's perception of pain. VAS consists of a 10-cm horizontal line, punctuated by verbal descriptors of pain severities, with the least severe pain at the left end. The patients mark their pain severities on the line at the point corresponding to their perception of the current state of pain. The numeric value of VAS is determined by measuring the distance between the extreme left end of the line to the point marked by the patient[1]
4. CAL: Measured from a reference point (acrylic stent) to the bottom of the probable pocket[33]
5. GR: Measured as the distance from a reference point (acrylic stent) to the gingival margin[33,34]
6. Suppuration: Presence or absence of suppuration after probing or applying a gentle pressure to the peri-implant gingival tissue with finger (milking).

Collection of samples

Samples were collected from the PICF at implant sites with the deepest PPD at baseline. These predetermined sites were used during the whole study period. The sampling procedures were carried out at baseline and 2-week and 3-month intervals. These sites were isolated with the use of cotton rolls and a saliva ejector and gently air-dried subsequent to the elimination of the supra-mucosal biofilm. The PICF samples were collected using sterile paper strips (Periopaper, OraflowInc, Smithtown, NY, USA) which were placed at crevice entrance and kept there for 30 s. Mechanical irritation was avoided to prevent bleeding and contamination. In cases in which the paper strips were contaminated with blood or saliva, the sampling procedure was repeated the next day.

Cytokine assays

The paper strips that were used to collect PICF samples were weighed before and after the sampling procedures to determine the PICF sample weights. The strips were placed in sealed sterile microtubes separately, which contained 250 mL of phosphate-buffered saline solution and stored at 4°C for 2 h, followed by storage at − 70°C for further analyses of cytokines and MMP levels, using a batch analysis approach. Before cytokine analyses, the samples were kept again under a temperature of 4°C for 2 h. Then 350 mL of phosphate-buffered saline solution was added to the sterile microtubes to achieve a final volume of 600 mL. Then, the samples were transferred into a refrigerator at 4°C for 20 min, followed by centrifugation at 10,000 rpm for 10 min. Subsequent to the elution of proteins from the paper strips, the strips were discarded. Enzyme-linked immune sorbent assays (ELISAs) were applied for cytokine analyze (MMP8 ELISA Kit, Human IL-1b ELISA Kit, Human IL-6 ELISA Kit, and Human TNF-a ELISA Kit; USCN Life Science; Houston, TX). A sandwich ELISA technique was applied according to the manufacturer's instructions. The concentrations of IL-1β, IL-6, TNF-α, and MMP-8 were expressed as pg/μL of PICF.

Standard curves were drawn by plotting the concentrations of IL-1β within a standard range of 4–250 pg/mL, concentration of IL-6 within a standard range of 3–300 pg/mL, concentration of TNF-α within a standard range of 23–1500 pg/mL, and concentration of MMP-8 within a standard range of 39–2500 pg/mL (the amount of enzyme protein, not its activity, were assessed). The minimum level of MMP-8 that could be detected was <14 pg/mL. The concentration of analyses within each sample of PICF was calculated separately by dividing the total concentrations of IL-1β, IL-6, TNF-α, and MMP-8 by the volume of each sample.

Statistical considerations

The sample size was calculated for primary outcome of the study, BOP; at least 22 implants per group were

necessary for a study power of 80% to detect a mean difference of two BOP + sites of six sites per implant between the two groups.[7] The sample size was increased to 25 implants per group to accommodate possible dropouts. The randomization of the patients into control (MD alone) or test (MD + PDT) groups was performed before initiation of the study using an online randomization tool (https://www.randomizer.org/).

Data were kept inaccessible to the operator and only examined by a statistician (MG) blinded to the treatment modalities to prevent disclosure of the patients' data. Data were analyzed with SPSS (SPSS Statistics for Windows, v. 21.0, IBM, Armonk, NY), using the Linear Mixed Model test and Chi-squared test. Paired *t*-test and Wilcoxon signed-rank test were used to calculate levels of significance in each group between baseline and 2-week, and 3-month intervals, with adjustments for multiple comparisons. Repeated measure analysis of variance was used for inter-group differences among the parameters assessed in this study before and after treatment, as indicated. The absolute and relative changes were calculated for each variable, and inter-group comparisons were carried out accordingly. A two-sided $P \leq 0.05$ was considered for significant differences between the tested parameters.

RESULTS

Descriptive results

Sixty-five patients with peri-implant mucositis were included in this study. Nonetheless, 11 patients did not meet the inclusion criteria and two refrained from signing informed consent form. Therefore, 52 patients were randomly assigned to the study groups. Of all these participants, 3 did not present for follow-ups or discontinued intervention (one in the test group due to pregnancy and two in the control group due to moving to other cities). Therefore, only 49 patients, 19 males and 30 females, aged 26–58 years with a mean age of 37.5 years, with 105 implants (29 anterior, 34 premolars, and 42 molars), completed the 3-month follow-up and were included in data analyses. There were no postoperative complications during the follow-up period. The subjects maintained an FMPS of <25%, indicating an acceptable oral hygiene level during the study. There were no significant differences in clinical baseline values and immunologic variables between the study groups.

Clinical parameters

Table 1 presents the peri-implant status and PD, CAL, and GR, areas with pus and frequency distributions of POP at baseline and during follow-up visits. Statistically significant improvements ($P < 0.001$) were detected in both groups in BOP, PD, CAL, POP, and pus after comparison of baseline data with those collected at each time interval of the study [Table 2]. No significant differences were detected between the baseline clinical data in any of the two groups [Table 3]. No statistically significant differences were found in these clinical parameters in any of the two groups during 2-week and 3-month follow-up visits [Table 3]. Clinical parameters were slightly better in terms of the percentage changes in the MD + PDT versus MD group; however, these differences were not significant [Table 2].

Laboratory results

Table 2 presents the numeric values of biomarkers at baseline and 2-week and 3-month intervals.

Table 1: Descriptive statistics of clinical parameters and inflammatory biomarkers (mean±standard deviation) at baseline, 2-week, and 3-month follow-up among the study groups

Parameter	Control			Test MD + PDT		
	Baseline	2 weeks' follow-up	3 months' follow-up	Baseline	2 weeks' follow-up	3 months' follow-up
PD[a]	5.37±0.71	3.91±0.88	3.87±1.19	5.44±0.65	3.2±0.76	3.56±0.58
CAL[a]	6.08±0.71	5.54±0.97	6.12±0.53	6.92±0.81	4.16±0.62	4.8±0.5
GR[a]	1.33±0.86	1.25±0.73	1.5±0.83	1.12±0.78	1.08±0.81	1.4±0.57
BOP[b]	76.62±15.25	24.41±10.25	30.95±10.82	79.40±13.21	28.56±9.63	51.88±17.69
POP	5.5±1.69	4.75±0.67	5.58±1.71	4.52±1.44	3.8±1.11	3.6±1
SUP[c]	13 (54.2)	5 (20.8)	7 (29.2)	19 (76)	4 (16)	9 (36)
TNF[d]	0.61±0.13	0.39±0.11	0.42±0.08	0.62±0.18	0.41±0.13	0.42±0.1
IL-1[d]	62.25±13.86	35.79±10.06	41.75±14.45	48.92±17.96	30.56±16.56	38.44±18.77
IL-6[d]	43.63±15.67	26.67±10.06	27.08±9.35	32.76±9.71	23.08±9.79	26.04±8.64
MMP[d]	3.62±2.14	1.84±0.82	2±0.87	4.09±1.1	2.47±0.85	2.65±0.78

[a]mm; [b]%; [c]*n* (%); [d]pg/mL. PD: Pocket depth; CAL: Clinical attachment level; GR: Gingival recession; BOP: Bleeding on probing; POP: Pain on probing; TNF: Tumor necrosis factor; IL: Interleukin; MMP: Matrix metalloproteinase; MD: Mechanical debridement; PDT: Photodynamic therapy; SUP: Suppuration

Table 2: Absolute and percentage changes (mean±standard deviation) of clinical and inflammatory biomarkers of the study groups at baseline and follow-up visits

Parameter	Control						Test MD+PDT					
	2 weeks from baseline		*P*	3 months from baseline		*P*	2 week from baseline		*P*	3 months from baseline		*P*
	Percentage change	Delta		Percentage change	Delta		Percentage change	Delta		Percentage change	Delta	
PD	27	−1.46±1.06	<0.001	28	−1.5±1.25	<0.001	41	−2.24±0.83	<0.001	35	−1.88±0.83	<0.001
CAL	8	−0.54±1.38	0.099	−1	0.04±0.91	0.999	40	−2.76±1.01	<0.001	31	−2.12±0.75	<0.001
GR	6	−0.08±0.5	0.999	12	0.17±0.48	0.594	4	−0.04±0.79	0.999	−25	0.28±0.73	0.090
BOP	6.8	−52.21±15.6	<0.001	60	−45.67±20.3	<0.001	64	−50.84±17.23	<0.001	9	−27.52±23.41	<0.001
POP	14	−0.75±1.54	0.092	−1	0.08±2.32	0.999	16	−0.72±1.74	0.102	20	−0.92±1.44	0.062
SUP (%)	61	33.4	0.262	31	25	0.594	79	60	<0.001	53	40	0.058
TNF	34	−0.22±0.15	<0.001	29	−0.18±0.14	<0.001	34	−0.21±0.16	<0.001	−196	1.23±7.13	<0.001
IL−1	42	−26.46±15.96	<0.001	33	−20.5±17.98	<0.001	37	−18.36±8.77	<0.001	21	−10.48±12.04	0.032
IL−6	38	−16.95±14.93	<0.001	38	−16.54±15.27	<0.001	29	−9.68±10.54	0.001	21	−6.72±9.43	0.002
MMP	49	−1.78±1.47	<0.001	45	−1.61±1.51	<0.001	39	−1.62±4.45	<0.001	35	−1.43±4.95	<0.001

PD: Pocket depth; CAL: Clinical attachment level; GR: Gingival recession; BOP: Bleeding on probing; POP: Pain on probing; TNF: Tumor necrosis factor; IL: Interleukin; MMP: Matrix metalloproteinase; MD: Mechanical debridement; PDT: Photodynamic therapy; SUP: Suppuration

Table 3: Intergroup analysis of clinical and inflammatory biomarkers of the study groups at baseline and follow-up visits

Parameters	Baseline (*P*)	2-week follow-up (*P*)	3-month follow-up (*P*)
PD	0.76	0.01	0.37
CAL	0.09	<0.001	<0.001
GR	0.42	0.69	0.87
BOP	0.51	0.25	<0.001
POP	0.11	0.02	<0.001
SUP	0.9	0.9	0.9
TNF	0.83	0.68	0.80
IL-1	0.09	0.39	0.43
IL-6	0.14	0.24	0.89
MMP	0.33	0.01	0.008

PD: Pocket depth; CAL: Clinical attachment level; GR: Gingival recession; BOP: Bleeding on probing; POP: Pain on probing; TNF: Tumor necrosis factor; IL: Interleukin; MMP: Matrix metalloproteinase; SUP: Suppuration

A total of 315 PICF samples were collected. Similar to the clinical parameters, significant improvements ($P < 0.001$) were detected in IL-1β, IL-6, TNF-α, and MMP-8 from baseline to the 2-week and 3-month intervals in both groups [Table 2]. Nevertheless, the inter-group comparisons of these inflammatory biomarkers between the baseline and 2-week and 3-month intervals did not reveal any significant decrease in sites treated with either MD alone or MD + PDT (*t*-test, $P < 0.001$).

DISCUSSION

Studies have evaluated the clinical effectiveness of PDT for periodontitis and peri-implantitis.[10,35,36] It is demonstrated that PDT has resulted in a significant improvement in clinical parameters of PD, CAL, and BOP,[35] and Bombeccari *et al*. showed that a significantly lower proinflammatory index of periimplantitis was observed in the PDT group (using 810 nm diode laser).[37] In addition, it was concluded that using 810 nm diode laser had significant short-term benefits in the treatment of primary periimplantitis.[38] Furthermore, another study suggested that antimicrobial PDT with a diode laser (670 nm) and phenothiazine chloride could be considered a coadjuvant in the treatment of peri-implantitis associated with mechanical (scaling) and surgical (grafts) treatments.[39] The present randomized clinical trial evaluated changes in clinical parameters and gingival crevicular fluid cytokine profiles in patients with peri-implant mucositis subsequent to treatment with scaling and root planing (SRP) alone or SRP followed by PDT.

The results of this study suggested that PDT (using 805-nm laser and ICG) as an adjunct to SRP did not result in any additional advantages over SRP alone in improving the clinical parameters in patients with peri-implant mucositis. Therefore, the clinical effects seen in both groups at 2-week and 3-month intervals might be attributed only to SRP rather than to the effects of PDT. Apparently, the application of low-level laser does not result in the elimination of sub-mucosal plaque and calculus in peri-implant pockets. Mechanical disturbance and elimination of supra- and sub-mucosal bacterial deposits are absolutely necessary for the treatment of peri-implant infections.[33]

This study used a system which utilizes laser beams at 805-nm wavelength and ICG as a photosensitizer. The majority of the available studies on PDT have used systems with laser beam wavelengths at a range of 630–700 nm and photosensitizers such as toluidine blue, methylene blue, or phenothiazine chloride. Therefore, the results of the present study cannot be directly extended to all the PDT systems. Despite differences, these findings coincide with those in recent systematic reviews and RCTs[6,28,33] indicating that PDT as an adjunct or alternative to SRP does not result in clinically significant benefits. However, Caccianiga *et al*. used PDT based on High-Level Laser Therapy (2.5 W) and reported improvements in all the clinical parameters (perfusion index, BOP, PD).[40] Roncati *et al*.[41] applied an 810-nm diode laser as an adjunct and reported a decrease of 4 mm in PPD, which was attributed to the formation of the long junctional epithelium. In addition, Bassetti *et al*.[7] reported that the decrease in PPD was not statistically significant at 12-month interval; however, they reported significant decreases in BOP-positive sites 12 months after MD with PDT, carried out every 3 months. Although MD with PDT does not appear to predictably result in complete resolution of peri-implant mucositis, these findings should also be interpreted by considering the limitations of assessing BOP around implants. In this context, residual BOP might be partly attributed to mechanical traumas during probing.[42]

It has been suggested that PDT has some putative benefits, including minimal risk of thermal injury, faster and better healing of wounds, lower risk of bacterial resistance to antimicrobials (if used, and not tested here), and rapid elimination of microorganisms in inaccessible areas.[35,39,43,44] However, the results of the present study did not support the application of PDT in association with SRP for additional improvements over SRP alone. Consistent with other studies, the use of PDT did not give rise to any complications.[35,45,46] In the present investigation, the effects of SRP with or without PDT were evaluated and compared in relation to inflammatory biomarkers. Analyses of inflammatory markers showed modest improvements (percentage changes) in the concentration of inflammatory markers such as TNF-α, IL-1β, and MMP-8 in sites receiving both SRP and PDT compared to SRP alone. Consistent with clinical findings, a combination of PDT and SRP did not result in any additional benefits in terms of improvements and decreases in inflammatory biomarker levels. In addition, it has been reported that SRP with adjunct PDT results in a modest decrease in the levels of destructive inflammatory cytokines such as TNF-α, IL-1β, MMP-8, and MMP-9 in the gingival crevicular fluid in comparison to SRP alone.[36] The results of the present study supported the results of a systematic review and an RCT raising doubts about the efficacy of PDT in the treatment of peri-implant diseases.[47,48]

In the present study, evaluation intervals of 2 weeks and 3 months were selected, consistent with previous clinical trials on PDT.[33,46] In this study, PDT was applied as an adjunct to SRP, which was compared with SRP alone, as suggested by the manufacturers and ICG alone (without activation) was not used as a control group since it has proved ineffective.[13,15]

Tavares *et al*. showed in a recent review that photosensitizer properties, wavelength, and the light source have very important roles in the clinical efficacy of PDT.[49] Therefore, future studies should focus on different combinations of photosensitizers and light sources for the determination of the best possible effects in the clinic to establish the optimal parameters for the beams and chemical agents that will result in the highest clinical outcomes.

CONCLUSION

It was concluded that the addition of PDT (using an 805-nm laser and ICG) to mechanical therapy did not provide any additional improvements in the clinical or biologic parameters of peri-implant mucosal inflammation. The additional use of PDT in the treatment of peri-implant mucositis was not supported by this study.

Limitations of study

To minimize the error of the experimenter in evaluating PD and especially BOP, we suggest using automatic probes such as the Florida probe (The Florida Probe® (Florida Probe Corp, Gainesville, FL) in future studies.

In persistent lesions, cytokines should be analyzed by microarray to further examine the safety profile of patients. Furthermore, microbial analysis and antibiogram should be used for persistent lesions.

Recommendations

It is advisable for these clinical studies to consider the application of various PDT protocols, including different laser parameters such as laser type, power, energy, fiber diameter, frequency of treatment appointments, and different photosensitizers or patient parameters such as efficacy, cost-effectiveness, halitosis, patient and operator acceptance, and pre- and post-microbiologic profile assessment to compare pre- and post-treatment levels.

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Ethical approval

The study was approved by the Research Ethics Committee of Tabriz University of Medical Sciences (protocol number: IR.TBZMED.REC.1395.554) and registered with the local World Health Organization Registry Network (IRCT.201609281248N3).

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Conflicts of interest

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