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Non-surgical mechanical therapy of peri-implantitis with or without repeated adjunctive diode laser application. A 6-month double-blinded randomized clinical trial

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Abstract

Objectives: The objective of this study is to investigate the outcomes following non-surgical therapy of peri-implantitis (PI) with or without adjunctive diode laser application.

Materials and methods: A double-blinded randomized controlled clinical trial was carried out in 25 subjects with 25 implants diagnosed with PI. Following curettage of granulation tissue, test implants (T) were treated with adjunctive application of a diode laser for 90 s (settings: 810 nm, 2.5 W, 50 Hz, 10 ms), while at control implants (C) non-activated adjunctive diode laser was applied. The entire treatment procedure was performed at days 0 (i.e., baseline), 7 and 14. The primary outcome measure was change in mean pocket probing depth (PPD). Clinical and microbiological outcomes, as well as host-derived inflammatory markers were evaluated at baseline, 3 and 6 months, while radiographic outcomes were assessed at baseline and at the 6-month follow-up.

Results: No statistically significant differences with respect to baseline patient characteristic were observed. After 6 months, both test and control implants yielded statistically significant PPD changes compared with baseline (T: 1.28 and C: 1.47 mm) but without statistically significant difference between groups ($p = .381$). No statistically significant changes in peri-implant marginal bone levels were detected ($p = .936$). No statistically significant differences between test and control implants were observed with respect to microbiological and host-derived parameters ($p > .05$). At the 6-month follow-up, treatment success was observed in 41.7% ($n = 5$) of test and 46.2% ($n = 6$) of control patients, respectively ($p = .821$).

Conclusion: Repeated adjunctive application of diode laser in the non-surgical management of PI failed to provide significant benefits compared with mechanical instrumentation alone.

KEYWORDS
clinical trial, non-surgical therapy, peri-implantitis

1 | INTRODUCTION

Following the last Consensus Conference on periodontal and peri-implant diseases, peri-implantitis was defined as a pathological condition around dental implants characterized by inflammation in the peri-implant connective tissue and progressive loss of supporting bone (Schwarz et al., 2018). Peri-implantitis is a disease with growing incidence (Derks & Tomasi, 2015; Rokn et al., 2017; Romandini et al., 2021; Schwarz et al., 2017) that, if left untreated, leads to implant loss. The etiological factors of peri-implant infections are similar to those involved in periodontal diseases (Heitz-Mayfield & Lang, 2010). Consequently, the goals of peri-implantitis treatment must be the resolution of peri-implant soft tissue inflammation and stabilization of the bony attachment (e.g., the level of osseointegration) (Javed et al., 2013). This can only be achieved under the condition that the majority of bacterial biofilms and hard deposits are eliminated on the implant surface to obtain a biologically acceptable surface conducive to wound healing (Aoki et al., 2015).Conventional non-surgical treatment procedures of peri-implant lesions showed limited predictability (Heitz-Mayfield & Mombelli, 2014; Karring et al., 2005; Renvert et al., 2008, 2009; A. Roccuzzo et al., 2021). On the other hand, surgical interventions, whether resective (Carcuac et al., 2020; Heitz-Mayfield et al., 2018) or reconstructive (M. Roccuzzo et al., 2020, 2021), yielded more promising clinical and radiographic outcomes (Tomasi et al., 2019). Irrespective of the procedure applied (i.e., surgical vs. non-surgical), decontamination of the implant surface is of paramount importance (Koo et al., 2019) even though it is much more challenging when compared with the decontamination of natural root surfaces (Wong et al., 2017). To increase implant surface decontamination, several adjunctive tools have been proposed and investigated both in pre-clinical and clinical studies such as the use of photodynamic therapy (Romanos et al., 2006; Romanos & Nentwig, 2008) and lasers (Bach et al., 2000; Schwarz, Bieling, et al., 2006; Schwarz et al., 2003; Schwarz, Nuesry, et al., 2006; Sculean et al., 2005). Positive outcomes in terms of changes in pocket probing depth (PPD), bleeding on probing (BoP) and suppuration were reported in a 2-year follow-up single group retrospective study (Mettraux et al., 2016). In that study, implant sites were treated with soft tissue curettage to remove the granulation tissue followed by repeated application of diode laser with a wave length of 810 nm (Mettraux et al., 2016). More recently, comparable treatment outcomes were obtained following non-surgical mechanical therapy of peri-implantitis alone or with adjunctive diode laser application with a wave length of 940 nm (Alpaslan Yayli et al., 2022).

However, as reported in a best evidence review from the American Academy of Periodontology (Lin et al., 2018), the magnitude of the adjunctive benefits of laser application seems to be limited to short-term changes in BoP.

Therefore, the aim of the present randomized clinical trial was to investigate the adjunctive effects of diode laser application in the non-surgical management of peri-implantitis following a 6-month healing period.

2 | MATERIALS AND METHODS

The study protocol was submitted to and approved by the Ethical Committee of the Canton of Bern (KEK), Switzerland (Nr.: 2019-01163). The investigation was conducted according to the revised principles of the Helsinki Declaration (2013), and signed informed consent was obtained from each patient before entering the study. The trial was registered at ClinicalTrials.gov (NCT04565886).

2.1 | Study design and study group allocation

The present study was designed as a prospective, double-blinded, randomized, controlled, clinical trial with a parallel design of 6-month duration. The study flow chart is reported in Figure 1. Data are reported according the Consolidated Standards of Reporting (CONSORT) guidelines. Patients were randomly allocated to the test and control groups following randomization tables, while treatment allocation was concealed by using opaque envelopes which were labelled with the patient study number and opened immediately after local anesthesia administration by an external investigator not involved in the non-surgical intervention or in the outcome evaluations.

2.2 | Hypothesis

The null-hypothesis (H0) was that no statistically significant difference with respect to the mean change in PPD following non-surgical therapy with adjunctive diode laser application would be detected compared with mechanical instrumentation and non-activated diode laser application.

2.3 | Study population

Subjects attending or referred to the Department of Periodontology at the University of Bern, Bern, Switzerland, were consecutively screened for recruitment. One experienced investigator (G.E.S.) evaluated the subjects and was responsible for the patients' enrollment process following the assessment of the inclusion and exclusion criteria.

2.4 | Inclusion criteria

- Male and female patients aged ≥18 years.
- Patients in systemic health or with controlled medical conditions.
- Patients with healthy or treated periodontal conditions rehabilitated with cemented or screw-retained implant-supported prostheses.
- Tissue level (TL) implants with an SLA surface (Straumann Dental Implant System, Institute Straumann AG, Basel, Switzerland)

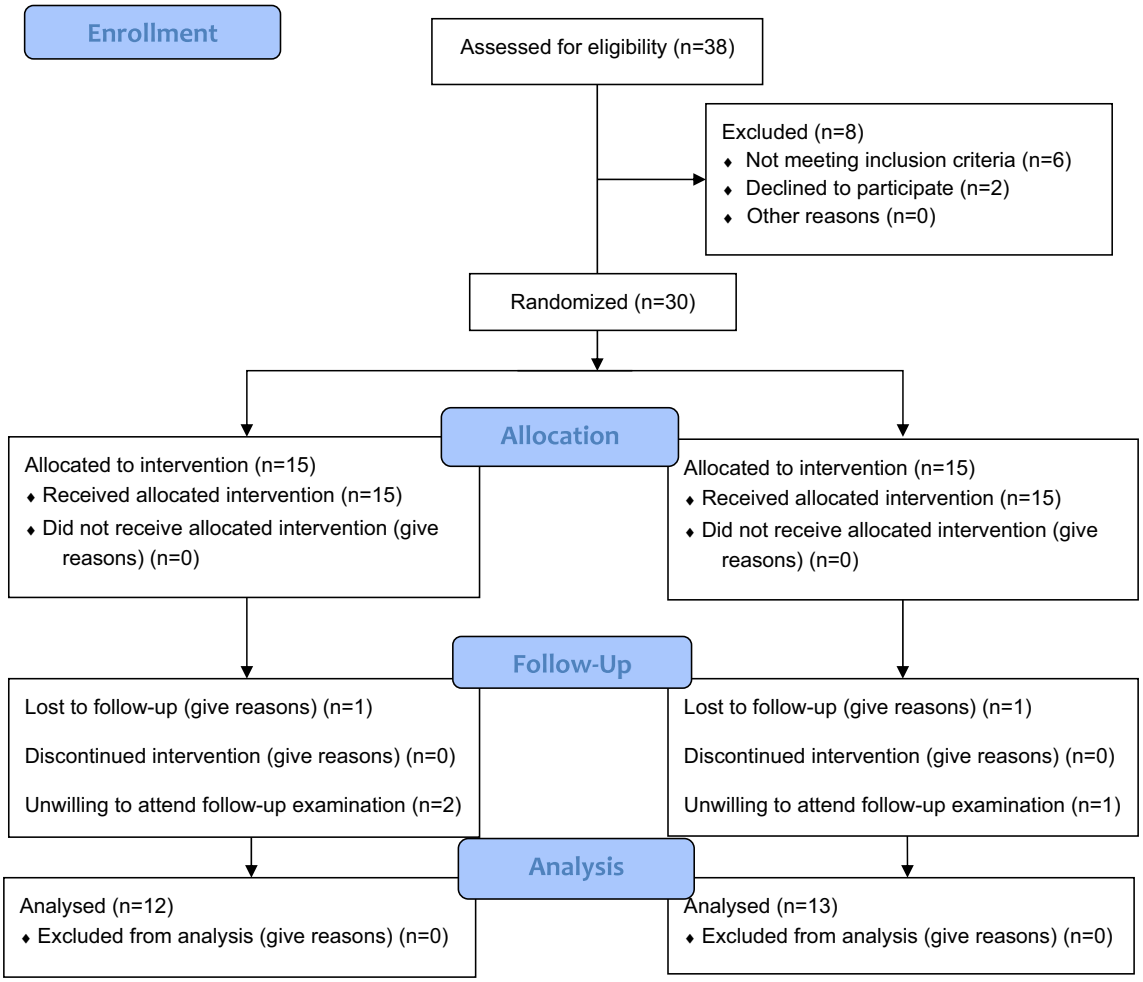

FIGURE 1 Study flow-chart

supporting single-unit crowns (SUCs) or fixed dental prostheses (FDPs).

- PPD > 5 mm.
- Presence of bleeding on probing (BoP) and/or suppuration.
- Radiographic evidence of crestal bone loss ≥2 mm based on periapical radiographs following delivery of the final restoration.
- Implant-supported prostheses accessible for self-performed plaque control.
- Presence of at least 2 mm of keratinized and attached mucosa (KM).

2.5 | Exclusion criteria

- Systemic diseases that could interfere with the treatment outcome (e.g., uncontrolled diabetes mellitus, chemotherapy, etc.).
- Previous peri-implantitis treatment.
- Implant mobility.
- Full-Mouth Plaque Score (FMPS) > 25%.
- Full-Mouth Bleeding Score (FMBS) > 25%.
- Cigarette smoking >10 cig./day.
- Intake of antibiotics in the previous 3 months.

2.6 | Intervention

Instructions on the use of manual or power-driven toothbrushes and interdental brushes were provided during the screening session.

As previously reported (Mettraux et al., 2016), following delivery of local anesthesia (Ubistesin Forte; 3M ESPE), the implant surfaces were debrided from hard deposits (i.e., cement excess and/or calculus) using titanium curettes and the inflamed peri-implant soft tissue wall was curetted with stainless steel curettes (Deppeler SA). Following mechanical debridement, the pockets around the implants were rinsed with sterile saline solution. At test implants, adjunctive diode laser (settings: 810 nm, 2.5 W, 50 Hz, 10 ms) was applied 3 × for 30 s (i.e., 90 s per appointment) using a 0.4 mm thick fiber (WhiteStar, Orcos Medical AG, Küsnacht, Switzerland) under permanent sterile saline irrigation. The decontamination procedure of the implant surface with diode laser included the systematic movement of the laser tip along the submucosal implant surface in a vertical and horizontal scanning way. After 4–5 s, the laser tip was checked for blood coagulation in order to prevent heat generation. In cases of blood coagulation, the tip of the fiber was cut off with a scissor. The laser was consequently activated for 4–5 s followed by 2–3 s of standby mode.

At control implants, non-activated adjunctive diode laser was applied. The entire treatment procedure, including mechanical debridement, was performed at days 0 (= baseline), 7 and 14. Adjunctive antiseptics or adjunctive systemic/local antibiotics were not prescribed.

2.7 | Supportive peri-implant care

Supportive care consisting of oral hygiene monitoring and supramucosal prophylaxis by means of carbon fiber curettes and rubber cup with polishing paste was provided at the 3- and 6-month follow-ups. In cases of suppuration or increase in PPD by ≥2 mm after 3 and 6 months, rescue treatment was provided. This consisted of submucosal instrumentation with carbon fiber curettes, irrigation with sterile saline solution and adjunctive diode laser application 3× for 30 s (settings: 810 nm, 2.5 W, 50 Hz, 10 ms) according to the randomization table.

2.8 | Clinical and radiographic outcomes

Evaluation of the clinical parameters was performed at baseline (T0), after 3 (T1) and 6 months (T2) following completion of therapy, while the peri-implant marginal bone level changes were evaluated before treatment and the 6-month follow-up. The following clinical variables were recorded by the same blinded and calibrated examiner (A. St.) using a graduated manual periodontal probe (PCP-UNC 15; Hu-Friedy®, Chicago, IL, USA). The applied probing force ranged from 0.15 to 0.25 N.

- plaque index (PII) (O'Leary et al., 1972);
- BoP, evaluated dichotomously with either presence/absence of bleeding within 30 s following probing;
- suppuration on probing (SoP), with either presence/absence of suppuration after probing and
- peri-implant PPD, measured from the mucosal margin to the bottom of the probable pocket and evaluated at six sites per implant (i.e., disto-buccal, mid-buccal, mesio-buccal, mesio-lingual/palatal, mid-lingual/palatal, disto-lingual/palatal).

The implant-supported restorations were not removed prior to the assessment of the clinical parameters nor for delivery of treatment.

2.9 | Radiographic assessment

The radiographic assessment was performed following the methodology proposed by Schmid et al. (2020, 2021). Analog radiographs from intraoral dental films (Kodak Ultraspeed DF 58—Eastman Kodak Company, New York, USA) were scanned and digitized using Microtek TMA 1600 and Microtek ScanPotter (settings on Mac OS X: 1600 dpi, Diafilm, Format.tif). Subsequently, each radiographic image was calibrated and evaluated by means of the software ImageJ (National Institutes of Health, Bethesda, MD, USA). Based on the fact that all patients were rehabilitated with Straumann Tissue Level implants, the known distance between two implant threads (e.g., 1.25 mm) × 3 (1.25 mm × 3 = 3.75 mm) was used to calibrate the radiographs. Following identification of the mesial and distal edge of the implant shoulder, a line was drawn between these two points and used as landmark. Measurements of the mesial and distal bone levels were taken from these 2 points perpendicular to the connecting line to the first bone to-implant contact (BIC). In order to accurately identify the true radiographic linear distance IS-BIC, the height of the supracrestal machined neck (i.e., 2.8 mm for standard implants and 1.8 mm for standard plus implants) was subtracted from the measured values. All positive values were defined as bone gain while bone loss was defined by negative values. All radiographic measurements were assessed in duplicate by two blinded and calibrated examiners (J.-C.I and S.K.).

2.10 | Treatment success

Treatment success was considered a scenario with PPD ≤ 5 mm with absence of BoP or PPD ≤ 4 mm irrespective of presence/absence of BoP and no further marginal bone loss detectible between baseline and 6 months (Blanco et al., 2022; Carcuac et al., 2016). All patients whose implants did not meet the success criteria were informed and additional treatment was offered according to their needs.

2.11 | Crevicular fluid sampling and analysis

Peri-implant crevicular fluid (PICF) samples for quantification of the host-derived biomarkers interleukin-1beta (IL-1b), IL-10 and matrix-metalloproteinase-8 (MMP-8) were collected by means of sterile paper strips (Periopaper, Oraflow Inc., Smithtown, NY, USA). PICF samples were collected from a determined site (e.g., site with the deepest PPD at the baseline examination) around each experimental unit. The implant was first isolated with cotton rolls and a saliva ejector and then, air-dried. The paper strips were placed at the entrance of the crevice and left in place for 30 s. Subsequently, the paper strips were placed into a screw top plastic vial and placed immediately into dry ice. Paper strips were stored at −80°C until assayed. Samples were eluted at 4°C overnight into 700 μl phosphate-buffered saline containing proteinase inhibitors (Sigma-Aldrich, St Louis, MO, USA), a day before analysis. After being centrifuged at 400×*g* for 4 min, the paper strips were removed and 100 μl aliquots of the supernatant were used. The concentrations of total MMP-8, IL-1β and IL-10 were determined using commercially available enzyme- linked immunosorbent assay kits (R&D Systems Europe Ltd., Abingdon, UK) according to the manufacturer's instructions. The detection levels of the kits ranged from 1 pg/site for IL-1β and IL-10 to 50 pg/site for MMP-8.

2.12 | Submucosal bacterial sampling and analysis

Following crevicular fluid sampling, biofilm sampling was performed at the same site. Sterile paper points were inserted until the bottom of the pocket. The samples were placed in separate Eppendorf tubes and forwarded to microbiological analysis. DNA was extracted using the Chelex method. Then, two multiplex-real-time qPCR runs were performed. The first run quantified *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola* and the second run *Fusobacterium nucleatum* and *Campylobacter rectus*. PCR amplifications were carried out as described recently (Jentsch et al., 2020). The results are given as bacterial counts $\log_{10}$.

2.13 | Data analysis

Sample size calculation was performed considering PPD change as the primary outcome variable. More specifically, assuming a mean of 1.0 mm PPD difference between study groups and a standard deviation in PPD of 0.9 mm in each group at the 6-month follow-up (de Tapia et al., 2019; Schwarz et al., 2010), 12 experimental subjects and 12 control subjects were needed to reject the null hypothesis with an alpha error of 0.05 and a beta error of 0.2 and a statistical power of 80%. In order to compensate for attrition over the 6-month follow-up, 15 patients/group were allocated to intervention. Each patient contributed with one dental implant only and was, therefore, considered as the statistical unit. Descriptive analysis was performed providing absolute and relative frequencies for categorical variables and mean, standard deviation, 95% confidence intervals or medians, for continuous variables. Normal distribution of the quantitative measures was checked by Shapiro–Wilk's test. Two-sample *t*-test was used to compare means of normally distributed parameters between both implant groups and paired *t*-test was used for intra-groups over time comparisons. For non-normally distributed parameters, Mann–Whitney's and Wilcoxon's tests were used respectively. All multiple post-hoc comparisons were corrected by Bonferroni's criteria. Chi-square independence, Fisher's exact test and two-sample *t*-test were used to assess the association between sociodemographic and implant characteristics by group. The assessment of the linear radiographic measurements by two examiners yielded a Cohen's kappa coefficient of 0.72 across all radiographs. The calculated inter-examiner agreement with Dahlberg's *d* test was 0.23 and 0.29 mm at mesial and distal sites, respectively and the intra-class correlation coefficient (ICC) was 0.92 and 0.90 providing a very high level of reproducibility of the performed radiographic measurements. All the tests were two-tailed and the level of significance was set at 5%. The statistical analysis was performed with a commercially available dedicated software (SPSS 15.0, Chicago, IL, USA).

3 | RESULTS

3.1 | Subject accountability

Thirty-eight patients were assessed for their eligibility prior to entering the study. Of these, 8 patients were excluded: 6 because they did not meet the inclusion criteria, while 2 were not willing to participate (Figure 1). Consequently, 30 patients with 30 implants were enrolled and randomly allocated to test or control group, respectively. The last treatment appointment took place in May 2021.

TABLE 1 Sociodemographic data at baseline (T0)

	Total	Test group	Control group	*p*-value
Number of patients	25	12	13	
Number of implants	25	12	13	
Age, mean ± SD	64.0 ± 12.9	67.3 ± 12.2	61.0 ± 13.2	.232 (*t*-test)
Gender				
Male, number (%)	13 (52)	6 (50)	7 (53.8)	.848 (χ^2)
Female, number (%)	12 (48)	6 (50)	6 (46.2)	
Tobacco				
Smokers ≤10 cig./day, number (%)	5 (20)	3 (25)	2 (15.4)	.645 (Fisher's exact test)
Never smokers, number (%)	20 (80)	9 (75)	11 (84.6)	
Implant position				
Maxilla, number (%)	11 (44)	5 (41.7)	6 (46.2)	.821 (χ^2)
Mandible, number (%)	14 (56)	7 (58.3)	7 (53.8)	
Screw or cemented				
Screw retained, number (%)	9 (36)	4 (33.3)	5 (38.5)	1.000 (Fisher's exact test)
Cemented, number (%)	16 (64)	8 (66.7)	8 (61.5)	

Note: *p*-values obtained from Chi-square test, Fisher's exact test and two-sample *t*-test.

TABLE 2 Mean clinical parameters measured at baseline (T0), 3 months (T1) and 6 months (T2)

	Baseline (T0)			3-month (T1)						6-month (T2)					
	Test group	Control group	*p*-value	Test group	Control group	*p*-value	Changes T1–T0 test group	Changes T1–T0 control group	*p*-value	Test group	Control group	*p*-value	Changes T2–T0 test group	Changes T2–T0 control group	*p*-value
PD	5.40 ± 0.81 (4.89–5.92)	5.29 ± 0.52 (4.98–5.61)	.694	4.28 ± 0.58 (3.91–4.65)	3.76 ± 0.69 (3.34–4.17)	.053	−1.13 ± 0.80 (−1.63 to −0.62)	−1.54 ± 0.51 (−1.85 to −1.23)	.134	4.13 ± 0.82 (3.60–4.65)	3.82 ± 0.88 (3.29–4.35)	.381	−1.28 ± 0.70 (−1.72 to −0.83)	−1.47 ± 0.68 (−1.89 to −1.06)	.484
							$p < .001$	**$p < .001$**					**$p < .001$**	**$p < .001$**	
PDd	7.00 ± 1.13 ($m = 7.0$)	7.23 ± 1.09 ($m = 7.0$)	.689	5.58 ± 0.79 ($m = 6.0$)	4.92 ± 0.86 ($m = 5.0$)	.087	−1.42 ± 1.31 ($m = -1.0$)	−2.31 ± 0.95 ($m = -2.0$)	.068	5.33 ± 1.23 ($m = 5.5$)	4.77 ± 1.24 ($m = 5.0$)	.320	−1.67 ± 1.07 ($m = -2.0$)	−2.46 ± 0.97 ($m = -3.0$)	.087
							$p = .014$	**$p = .002$**					**$p = .010$**	**$p = .002$**	
BOP	62.5 ± 30.3 (43.3–81.7)	62.8 ± 21.7 (49.7–75.9)	.976	52.8 ± 34.7 (30.7–74.8)	43.6 ± 14.5 (34.8–52.4)	.390	−9.7 ± 36.5 (−32.9 to 13.5)	−19.2 ± 21.3 (−32.1 to 6.31)	.431	47.2 ± 33.2 (26.1–68.3)	47.4 ± 27.9 (30.6–64.3)	.986	−15.3 ± 30.5 (−34.7 to 4.12)	−15.4 ± 31.5 (−34.4 to 3.67)	.993
							$p = .801$	$p = .085$					$p = .305$	$p = .262$	
BOPm	91.7 ± 28.9 ($m = 100$)	100 ± 0.0 ($m = 100$)	.728	83.3 ± 38.9 ($m = 100$)	100 ± 0.0 ($m = 100$)	.503	−8.4 ± 51.5 ($m = 0.0$)	0.0 ± 0.0 ($m = 0.0$)	.728	83.3 ± 38.9 ($m = 100$)	100 ± 0.0 ($m = 100$)	.503	−8.4 ± 51.5 ($m = 0.0$)	0.0 ± 0.0 ($m = 0.0$)	.728
							$p = 1.000$	$p = 1.000$					$p = 1.000$	$p = 1.000$	
SOP	58.3 ± 51.5 ($m = 100$)	38.5 ± 50.6 ($m = 0.0$)	.406	8.3 ± 28.9 ($m = 0.0$)	15.4 ± 37.6 ($m = 0.0$)	.769	−50.0 ± 52.2 ($m = -50.0$)	−23.1 ± 43.8 ($m = 0.0$)	.270	16.7 ± 38.9 ($m = 0.0$)	7.7 ± 27.7 ($m = 0.0$)	.728	−41.6 ± 51.5 ($m = 0.0$)	−30.8 ± 48.0 ($m = 0.0$)	.650
							$p = .028$	$p = .166$					$p = .050$	$p = .092$	
PI	8.3 ± 16.7 ($m = 0.0$)	3.8 ± 10.0 ($m = 0.0$)	.650	13.9 ± 13.9 ($m = 16.7$)	11.5 ± 19.7 ($m = 0.0$)	.437	5.6 ± 26.9 ($m = 16.7$)	7.7 ± 22.2 ($m = 0.0$)	.650	9.7 ± 13.2 ($m = 0.0$)	10.3 ± 27.7 ($m = 0.0$)	.470	1.4 ± 25.1 ($m = 0.0$)	6.5 ± 30.1 ($m = 0.0$)	.769
							$p = 1.000$	$p = .472$					$p = 1.000$	$p = 1.000$	
KM	2.33 ± 0.99 (1.70–2.96)	2.77 ± 0.99 (2.17–3.37)	.283	2.23 ± 0.79 (1.72–2.73)	2.12 ± 0.46 (1.84–2.40)	.663	−0.10 ± 0.42 (−0.37 to 0.16)	−0.65 ± 0.83 (−1.15 to −0.15)	**.048**	2.27 ± 0.91 (1.69–2.85)	2.50 ± 0.65 (2.11–2.89)	.473	−0.06 ± 0.95 (−0.67 to 0.54)	−0.27 ± 0.81 (−0.76 to 0.22)	.562
							$p = 1.000$	**$p = .005$**					$p = 1.000$	$p = .840$	

Note: Mean ± SD (95%CI) or median (m). For normally distributed parameters (PD, BOP, KM), two-sample and paired *t*-tests were used for between and within-groups comparisons respectively. For non-normally distributed parameters (PDd, BOPm, SOP, PI), Mann–Whitney's and Wilcoxon's tests were used for between and within-groups comparisons respectively. Bonferroni's corrections were applied for multiple comparisons. Bold values indicates statistically significant differences.

Abbreviations: BOP, bleeding on probing (%); BOPm, % of implants with at least 1 site with BOP; KM, keratinized mucosa (mm); PD, probing depth (mm); PDd, deepest probing depth (mm); PI, presence of plaque (%); SOP, suppuration on probing (%).

Five patients, 3 from the test group and 2 from the control group not anymore willing to take part to the study, did not attend the 6-month follow-up examination and therefore were excluded from the final analysis.

3.2 | Study participants characteristics

Baseline characteristics of the 25 participants attending the 6-month follow-up are displayed in Table 1. The mean age of the participants was 67.3 ± 12.2 and 61.0 ± 13.2 years (p = .232) for test and control group, respectively. Five patients in the test group and 3 in the control group (p = .645) were current smokers. All the included patients had a history of treated periodontitis. With respect to the implant position (i.e., maxilla vs. mandible) and type of retention of the restorations (i.e., screw vs. cemented), none of these parameters showed statistically significant differences between groups (p > .05). No rescue treatment was provided at any follow-up visit.

3.3 | Clinical outcomes

The clinical outcomes over the study period are reported in Table 2. No adverse events such as pain and swelling were reported by any patient during the whole observation period.

At T0 (i.e., baseline), all the investigated variables did not statistically significantly differ between test and control groups (p > .05). At T1 (i.e., 3 months) and T2 (i.e., 6 months), mean PPD changes both in the test and control group showed statistically significant reductions compared with baseline (T1: 1.13 mm ± 0.80, −1.54 mm ± 0.51; T2: −1.28 mm ± 0.70; −1.47 mm ± 0.68) but not between groups (p > .05).

BoP values failed to change statistically significantly both at T1 and T2 in the test and control group (T1: −9.7% ± 36.5; −19.2% ± 21.3; T2: −15.3% ± 30.5; −15.4% ± 31.5) (p > .05). Implants in the test group displayed a statistically significant reduction in SoP (50.0% ± 52.2, p = .028) after 3 months (T1). However, within (p = .650) and between (p = .728) both groups, no statistically significant differences were observed at the 6-month follow-up.

3.4 | Radiographic outcomes

At T0, no statistically significant difference (p > .05) with respect to the average mesial/distal bone levels was observed between test and control groups. At the 6-month follow-up, the mean bone level (BL) was −2.05 mm ± 0.95 in the test and −2.02 mm ± 0.59 in the control group (p = .922), respectively. The mean BL changes recorded at the deepest site of each implant (BLd) was 0.11 mm ± 0.72 in the test and 0.08 mm ± 0.30 in the control group respectively (p = .876). Details of the radiographic measurements are reported in Table 3.

TABLE 3 Mean radiological parameters measured at baseline (T0) and 6 months (T2)

	Baseline (T0)			6-month (T2)					
	Test group	Control group	p-value	Test group	Control group	p-value	Changes T2–T0 test group	Changes T2–T0 control group	p-value
BLm	−2.09 ± 1.00 (−2.72 to −1.45)	−2.04 ± 0.48 (−2.34 to −1.75)	.888	−2.05 ± 0.95 (−2.65 to −1.44)	−2.02 ± 0.59 (−2.37 to −1.66)	.922	0.04 ± 0.50 (−0.28 to 0.36) p = .721	0.03 ± 0.23 (−0.11 to 0.17) p = .800	.936
BL distal	−2.16 ± 1.13 (−2.87 to −1.44)	−2.06 ± 0.65 (−2.46 to 1.67)	.801	−2.12 ± 1.08 (−2.80 to −1.43)	−2.08 ± 0.77 (−2.54 to −1.61)	.913	0.04 ± 0.85 (−0.50 to 0.57) p = .834	−0.02 ± 0.18 (−0.13 to 0.10) p = .929	.840
BL mesial	−2.02 ± 1.21 (−2.79 to −1.25)	−2.03 ± 0.46 (−2.31 to −1.75)	.988	−1.98 ± 1.06 (−2.65 to −1.31)	−1.96 ± 0.45 (−2.23 to −1.68)	.949	0.04 ± 0.60 (−0.33 to 0.42) p = .747	0.07 ± 0.31 (−0.12 to 0.26) p = .595	.895
BLd	−2.58 ± 1.03 (−3.23 to −1.93)	−2.25 ± 0.60 (−2.62 to −1.89)	.332	−2.47 ± 0.99 (−3.10 to −1.84)	−2.18 ± 0.69 (−2.60 to −1.76)	.394	0.11 ± 0.72 (−0.35 to 0.57) p = .485	0.08 ± 0.30 (−0.10 to 0.26) p = .620	.876

Note: Mean ± SD (95%CI). All comparisons were conducted with two-sample and paired t-tests for between- and within-groups comparisons respectively. Bonferroni's corrections were applied for multiple comparisons.

Abbreviations: BLd, bone level measured at the deepest site per implant; BLm, bone level measured as an average of mesial and distal aspects.

3.5 | Treatment success

At the final 6-month evaluation, treatment success was observed in 41.7% ($n = 5$) of test and 46.2% ($n = 6$) of control patients, respectively ($p = .821$) (Table 4).

3.6 | Host-derived biomarkers outcomes

The biomarker levels of Il-1β and IL-10 did not change over time neither in the test nor in the control groups. In the test group, a decrease in the levels of MMP-8 was observed from T0 to T1 ($p = .169$) and from T0 to T2 ($p = .028$). A statistically significant difference in the biomarker levels between test and control groups was never recorded at any time point (Table 5).

3.7 | Microbiological outcomes

A statistically significant difference in selected bacterial counts between test and control groups was not observed at any timepoint. At T1 to T0, counts of *P. gingivalis*, *T. forsythia*, *F. nucleatum* and *C. rectus* decreased in the test group and of *P. gingivalis*, *T. denticola* and *F. nucleatum* in the control group, respectively ($p < .05$). Only the counts of *F. nucleatum* were statistically significantly lower ($p = .028$) in the control group when comparing the timepoints T0 to T2 (Table 6).

4 | DISCUSSION

The aim of the present randomized controlled trial (RCT) was to assess the adjunctive effect of repeated applications of diode laser to treat peri-implantitis lesions by means of a non-surgical approach. The outcomes failed to detect any statistically significant difference in clinical, radiographic and microbiological outcomes after 6 months of follow-up. Therefore, the null hypothesis could not be rejected.

Comparable treatment outcomes were recently obtained following non-surgical mechanical therapy of peri-implantitis alone or with adjunctive diode laser application (Alpaslan Yayli et al., 2022). It should, however, be pointed out, that adjunctive diode laser with a higher wavelength (i.e., 940 nm) was applied in that study (Alpaslan Yayli et al., 2022).

Despite the recently published large body of evidence on the different treatment modalities to re-establish healthy peri-implant conditions (Bianchini et al., 2019; Monje et al., 2020; Ramanauskaite et al., 2018; A. Roccuzzo et al., 2021), only few studies investigated the non-surgical adjunctive efficacy of a diode laser to treat peri-implantitis (Lin et al., 2018). More specifically, only one RCT with a split-mouth design (Arısan et al., 2015) including 10 patients and 48 implants reported data comparable with those obtained in the present investigation. When focusing on the magnitude of PPD reduction, the 6-month results of the present study revealed a greater improvement compared with those reported by Arisan et al. (2015). A plausible explanation might be the higher baseline PPD values in the present study (i.e., 5.40 mm test and 5.29 mm control) compared with those reported by Arisan et al. (i.e., 4.71 mm test and 4.38 mm control) (Arısan et al., 2015). Indeed, a strict correlation between the magnitude of PPD reduction following peri-implantitis treatment irrespective of the intervention provided (i.e., surgical/non-surgical) and the initial PPD has been demonstrated (Monje et al., 2021).

One of the major concerns on the use of diode laser is the risk of heat development with consequent damage of the peri-implant hard and soft tissues. The results of the present study confirm those previously published by Mettraux et al. (2016). Indeed, no adverse events such as pain and swelling were reported by the patients, indicating that peri-implant tissues hotspots could be avoided.

Peri-implant bleeding after gentle probing is a clinical finding difficult to be properly interpreted (Monje et al., 2021). Several anatomic and technical factors might lead to the clinical misinterpretation of bleeding on probing as a sign of trauma to the soft tissues instead of true mucosal inflammation (Hashim et al., 2018). Consequently, it is nowadays widely accepted that the evaluation of the efficacy of the treatment of peri-implantitis should include a composite outcome (Sanz & Chapple, 2012). In the present study, 41.7% of test and 46.3% of control implants were defined as success at the 6-month follow-up. These results are consistent with those of recent publications following non-surgical treatment of peri-implantitis and reporting similar percentages of treatment success (i.e., approximately 50%) (Nart et al., 2020) thus underling the challenges faced to achieve disease resolution. Nevertheless, it has to be emphasized that the results of the present study revealed that additional surgical treatment could be avoided in approximately half of the cases by means of non-surgical therapy, irrespective of the adjunctive application of a diode laser.

TABLE 4 Treatment success

	Total	Test group	Control group	*p*-value
Number of patients	25	12	13	
Number of implants	25	12	13	
Success				
No, number (%; 95% CI)	14 (56; 34.9–75.6)	7 (58.3; 27.7–84.8)	7 (53.8; 25.1–80.9)	.821 (χ^2)
Yes, number (%; 95% CI)	11 (44; 24.4–65.1)	5 (41.7; 15.2–72.3)	6 (46.2; 19.2–74.9)	

Note: *p*-values obtained from Chi-square test. 95% CI computed with exact binomial distribution.

TABLE 5 Levels of selected biomarkers at baseline (T0), 3 months (T1) and 6 months (T2)

	Baseline (T0)			3 months (T1)			6 months (T2)		
	Test group	Control group	*p*-value	Test group	Control group	*p*-value	Test group	Control group	*p*-value
IL-1β (pg/site)	20.78	3.63	.193	18.23	2.99	.112	15.77	8.45	1.000
p-value vs. T0	[6.56, 48.86]	[2.03, 22.86]		[6.14, 60.89]	[1.46, 10.70]		[1.61, 42.45]	[1.67, 31.49]	
				0.859	0.929		1.000	0.480	
IL-10 (pg/site)	10.32	14.07	.104	6.69	15.49	.314	11.68	14.89	.093
p-value vs. T0	[4.13, 15.91]	[11.87, 19.45]		[1.71, 15.30]	[0.00, 17.20]		[7.89, 15.60]	[12.71, 17.10]	
				0.093	0.328		0.799	0.594	
MMP-8 (ng/site)	6.79	5.10	.151	2.05	4.09	.631	2.93	10.63	.069
p-value vs. T0	[5.38, 9.71]	[2.79, 8.78]		[0.61, 11.80]	[2.79, 8.78]		[1.64, 5.22]	[2.55,12.46]	
				0.169	0.646		0.028	0.239	

Note: Median [25 percentile, 75 percentile]. All comparisons were conducted with Mann–Whitney's and Wilcoxon's tests for between and within-groups comparisons respectively. Bonferroni's corrections were applied for multiple comparisons.

Abbreviations: IL, interleukin; MMP, matrix metallo protease.

With respect to mean peri-implant marginal bone level changes, no statistically significant differences were detected in the two groups, at the 6-month follow-up examination. This might be related to the short observation period (i.e., 6 months) to detect considerable bone level changes (De Waal et al., 2021; Merli et al., 2020). On the other hand, a recent 12-month study evaluating the adjunctive use of systemic metronidazole to the non-surgical treatment of peri-implantitis reported positive results in terms of radiographic bone gain (2.33 mm vs. 1.13 mm), suggesting a correlation between antibiotics intake and the higher bone fill (Blanco et al., 2022). Nevertheless, it must be emphasized that the radiographic assessment of the present study revealed that none of the treated sites experienced progressive peri-implant marginal bone loss.

Even-though the application of diode laser leads to a prompt decrease in microbial load, it has been previously demonstrated that re-colonization of the implant surfaces occurs very fast following treatment (Dostalova & Jelinkova, 2013). Our results corroborate this finding, indicating that at the 3- and 6-month follow-up examination no relevant differences in bacterial counts were noticed between the test and the control group. A few bacterial species were selected for microbiological analysis in the present study. As shown in studies analyzing the whole microbiome relative higher amounts of *P. gingivalis*, *T. forsythia* and *F. nucleatum* are found in peri-implantitis lesions when compared with peri-implant health (Al-Ahmad et al., 2018). In addition, the effects of non-surgical therapy of peri-implantitis on bacterial counts are reported in different ways. Adjunctive systemic metronidazole reduced the counts of *P. gingivalis* and *T. forsythia* up to 6 months, whereas there was no effect without antibiotics (Blanco et al., 2022). In a study by our group, *P. gingivalis*, *F. nucleatum* and *T. forsythia* were found in decreased proportions 6 and 12 months after adjunctive application of local minocycline or photodynamic therapy (Bassetti et al., 2014). In that study, the levels of IL-1β and MMP-8 decreased only in the local antibiotics group (Bassetti et al., 2014). In the present study, no major positive effects on microbiological and host-derived parameters were observed, irrespective of adjunctive diode laser application.

Unlike the majority of the published studies for the non-surgical treatment of peri-implantitis (Blanco et al., 2022; Nart et al., 2020), where several implant types and implant surfaces were pooled and treated, this study evaluated the outcomes of submucosal mechanical instrumentation with or without diode laser application on implants with the same surface characteristics, consequently eliminating this important confounding factor. Indeed, recent data suggested a plausible link between implant surface characteristics and the chances of successfully treating peri-implantitis lesions (M. Roccuzzo et al., 2017, 2020, 2021). Nevertheless, it has to be pointed out that the generalizability of the results of the present study to implants with different micro- and macro-designs characteristics might be questionable.

The present study has some limitations including the relatively small sample size and the short-term follow-up (i.e., 6 months). In addition, the evaluation of a larger number of bacterial species and host-derived biomarkers may have provided additional relevant

TABLE 6 Counts (Log_{10}) of selected bacteria at baseline (T0), 3 months (T1) and 6 months (T2)

	Baseline (T0)			3 months (T1)			6 months (T2)		
	Test group	Control group	*p*-value	Test group	Control group	*p*-value	Test group	Control group	*p*-value
A.a. *p*-value vs. T0	0.00 [0.00, 2.41]	0.00 [0.00, 0.00]	.497	0.00 [0.00, 2.21] 1.000	0.00 [0.00, 1.09] 0.180	.808	0.00 [0.00, 0.00] 0.180	0.00 [0.00, 0.00] 0.317	.503
P.g. *p*-value vs. T0	6.99 [5.74, 7.42]	6.04 [5.00, 6.75]	.181	5.72 [1.31, 7.20] **0.013**	5.35 [0.00, 6.23] **0.028**	.432	5.18 [0.00, 7.02] 0.051	5.57 [0.00, 6.25] 0.116	.860
T.f. *p*-value vs. T0	6.28 [5.92, 7.24]	6.12 [5.05, 6.72]	.345	5.70 [5.41, 6.80] **0.013**	4.44 [3.14, 5.34] 0.123	.057	5.53 [5.01, 6.42] 0.093	5.18 [4.38, 6.71] 0.575	.657
T.d. *p*-value vs. T0	0.00 [0.00, 4.94]	3.20 [0.00, 5.06]	.497	0.00 [0.00, 4.30] 0.463	1.97 [0.00, 3.73] **0.046**	.702	1.83 [0.00, 5.61] 0.735	0.00 [0.00, 4.95] 0.173	.710
F.n. *p*-value vs. T0	7.69 [6.82, 7.94]	7.14 [6.37, 7.56]	.079	6.90 [5.39, 7.08] **0.002**	6.39 [5.31, 6.83] **0.013**	.381	7.09 [5.50, 7.26] 0.182	6.32 [5.55, 6.68] 0.028*	.114
C.r. *p*-value vs. T0	6.10 [5.62, 6.75]	2.94 [0.00, 6.80]	.356	4.64 [0.00, 6.37] **0.017**	0.00 [0.00, 5.97] 0.068	.796	5.32 [0.00, 6.03] 0.069	3.95 [0.00, 5.86] 0.686	.815

Note: Median [25 percentile, 75 percentile]. Mann–Whitney's and Wilcoxon's tests were used for between- and within-groups comparisons respectively. Bonferroni's correction applied for multiple comparisons. Bold values indicates statistically significant differences.

Abbreviations: A.a., *Aggregatibacter actinomycetemcomitans*; C.r. *Campylobacter rectus*; F.n., *Fusobacterium nucleatum*; P.g. *Porphyromonas gingivalis*; T.d., *Treponema denticola*; T.f., *Tannerella forsythia*.

information. Furthermore, it has to be stated that the main focus of this study was set on PPD changes and that the assessment of peri-implant soft tissue margin changes (i.e., mucosal recession) was lacking, even though the presence of at least 2 mm of keratinized and attached mucosa at all treated implants sites at the latest follow-up might provide an indirect information on the quality of the peri-implant soft tissue conditions.

In conclusion, within their limits the present results have shown that the repeated adjunctive application of diode laser in conjunction with non-surgical mechanical treatment of peri-implantitis, failed to provide significant benefits compared with mechanical instrumentation alone.

AUTHOR CONTRIBUTIONS

Andrea Roccuzzo and Giovanni E. Salvi conceived the idea and led the writing; Andrea Roccuzzo performed the treatment; Sabrina Klossner, Alexandra Stähli, Jean-Claude Imber and Sigrun Eick collected, analyzed and interpreted the data and Sigrun Eick and Anton Sculean critically revised the manuscript.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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