Lasers in Medical Science (2022) 37:665–674
https://doi.org/10.1007/s10103-021-03436-5

ORIGINAL ARTICLE

Erbium, chromium-doped: yttrium, scandium, gallium, garnet and diode lasers in the treatment of peri-implantitis: clinical and biochemical outcomes in a randomized-controlled clinical trial

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Received: 22 April 2021 / Accepted: 1 October 2021 / Published online: 12 October 2021

Abstract

This study aims to evaluate the effects of 940 nm diode laser and 2780 nm erbium, chromium-doped: yttrium, scandium, gallium, garnet (Er,Cr:YSGG) laser used in addition to mechanical therapy in the non-surgical treatment of peri-implantitis on clinical parameters and matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) levels in the peri-implant crevicular fluid. A total of 50 patients with peri-implantitis were randomized into three groups to receive peri-implant treatment. The control group ($n=17$) only received conventional non-surgical mechanical therapy. The trial groups [(diode group ($n=16$) and Er,Cr:YSGG group ($n=17$)] received dental laser in addition to mechanical therapy. Gingival index (GI), plaque index (PI), bleeding on probing, probing depth (PD), MMP-9, and TIMP-1 levels were assessed at baseline (T0) and at 6 months after treatment (T1). The GI, PI, and PD significantly decreased in all groups at T1, compared to T0 ($p<0.05$). The decrease in the PD was similar between the control and diode groups with Er,Cr:YSGG providing more reduction (1.16 ± 0.64 mm) than either method ($p=0.032$). A significant intra-group decrease in MMP-9 level was only observed in the Er,Cr:YSGG group ($p=0.009$). The decrease in TIMP-1 level from T0 to T1 was similar between the control and the diode groups ($p>0.05$) and it was significantly lower than the decrease in the Er,Cr:YSGG group ($p<0.05$). Addition of diode laser to non-surgical mechanical therapy does not provide any additional benefit for treatment outcomes. The Er,Cr:YSGG laser seems to be more efficient both at clinical and molecular levels. ClinicalTrials, ID: NCT04730687. Registered 13 April 2021. Retrospectively registered, https://clinicaltrials.gov/ct2/show/NCT04730687

Keywords Peri-implantitis · Laser therapy · Er,Cr:YSGG · Diode · MMP-9 · TIMP-1

Introduction

With the use of dental implants becoming widespread, an increasing trend in peri-implant diseases has occurred [1]. Peri-implant diseases are separated into two groups as peri-implant mucositis and peri-implantitis. Peri-implant mucositis is limited to soft tissues with no bone loss being observed, except for the physiological bone remodeling. Peri-implantitis is an inflammatory process involving both soft and hard tissues with a progressive bone loss beyond physiological bone remodeling [2]. While there are a number of risk factors defined as possibly causing onset and progression of peri-implantitis, the main cause has been shown to be the increased rates of periodontal pathogens by activating inflammatory cells and they secreting cytokines and enzymes that are detrimental to host cells [3].

If left untreated, peri-implant diseases may lead to a process of losing the affected implant; however, there is currently no consensus on the treatment of peri-implantitis [1]. Dental implants are covered with a micro/nano texture to stimulate bone-implant contact. When these surfaces are exposed to and contaminated with pathogens, a durable and fast-accumulating biofilm occurs [4]. Therefore, when treatment procedures are performed, it is recommended to not

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only remove the inflamed tissues, but also decontaminate the infected implant surfaces [3]. Ultrasonic instruments, plastic, carbon, and titanium curettes can be used for the mechanical treatment of peri-implant diseases. However, it has been reported that they are not fully effective in the debridement of implant surfaces in some cases [5]. Based on the currently available information, there is insufficient evidence to support any non-surgical treatment for peri-implantitis showing better results than debridement alone. Chemical antimicrobial agents and local or systemic antibiotics added to mechanical therapy have been shown to be substantially successful. However, these agents may have various side effects [6]. Recently, with the development of laser technologies, the use of dental laser for the detoxification of implant surfaces became a main topic of conversation. Dental lasers increasingly attract interest as they have anti-infective properties, are easy to use, and have hemostatic effects. Another advantage of the dental lasers is the local effect of laser beam on the pathogens; therefore, no systemic side effect is expected [5, 6].

Diode lasers stand out as they are safe when used directly on the implant surface, have soft tissue penetration, antibacterial, and biostimulating effects [7]. They detoxify the implant surfaces by killing pathogenic bacteria and deactivating bacterial endotoxins [8, 9].

Erbium lasers have also promising results in implant treatment thanks to their advantageous properties such as soft and hard tissue ablation and decontamination. Erbium, chromium-doped: yttrium, scandium, gallium, garnet (Er,Cr:YSGG) lasers have the capability to debride the micro-structured surfaces of the dental implants without causing mechanical damage thanks to their water-powered properties [5]. Its efficacy has not yet been tested in a randomized-controlled trial in the treatment of peri-implantitis.

Currently, many investigators have assessed the efficiency of the dental lasers in the treatment of peri-implant diseases, although it is yet to be proven whether they have any additional contribution [10]. Several studies have focused on clinical parameters [11, 12]. However, periodontal probing and radiographs which are commonly used as diagnostic methods may provide erroneous results. These methods only indicate the pre-existing destruction rather than the present disease activity. Biomarkers are commonly used in medicine to objectively determine the disease state or the responses to a therapeutic intervention. It has been shown that peri-implant crevicular fluid (PICF) biomarkers show promising results in terms of early diagnosis and prognostic values [13]. The two main collagen-degrading enzymes in gingival crevicular fluid (GCF), matrix metalloproteinase-8 (MMP-8) and matrix metalloproteinase-9 (MMP-9), are secreted from neutrophils during disease activation and they are responsible for extracellular matrix degradation. An important inhibitor of MMPs, tissue inhibitor of metalloproteinase-1 (TIMP-1) has been reported to be released at high levels in inflamed gingiva [14, 15].

In the literature, there is a very limited number of human clinical trials investigating the effects of using dental lasers in the treatment of peri-implantitis on the treatment outcomes at clinical and molecular levels. In the present study, we aimed to examine the effects of non-surgical mechanical therapy combined with 940 nm diode laser or 2780 nm Er,Cr:YSGG laser on the clinical parameters and MMP-9 and TIMP-1 levels in PICF in patients with peri-implantitis. The null hypothesis of the trial was that the treatment results in the groups that received dental laser–assisted mechanical therapy would be similar to the group that received only mechanical therapy.

Materials and methods

Study design

This study was designed as a single-center, 6-month, double-blinded, randomized-controlled clinical trial with three parallel groups. The trial complying with the CONSORT guidelines [16] was conducted at Van Yuzuncu Yil University, Faculty of Dentistry, Department of Periodontology between 2019 and 2020. Prior to study, all participants were informed about the nature of the study and a written informed consent was obtained on the voluntary basis. The study protocol was approved by the Van Yuzuncu Yil University Clinical Trials Ethics Committee (21.11.2018/02) and conducted in accordance with the principles of the Declaration of Helsinki. The study is registered on ClinicalTrials.gov (NCT04730687).

The study sample consisted of 50 adult volunteers who have had implant treatment in our center previously and re-admitted or were referred to with peri-implant inflammation. All implants with peri-implant inflammation were the same brand implants (Implant Direct®, CA, USA) with a sandblasted, large-grit, acid-etched (SLA) surface and had a non-surgical periodontal therapy indication. All patients had cement-retained fixed ceramic bridge prosthesis supported by two or more implants. Improper restoration edges were corrected before the trial.

Eligibility criteria for participants

Eligible participants were aged 18 or older, suffering from peri-implantitis on at least one implant site. Inclusion criteria were as follows: (1) presence of inflammation including redness, edema, mucosal enlargement in the peri-implant zone, (a) with a probing depth of 4–6 mm in one or more zones, (b) bleeding on probing under mild forces (0.25 N) with or without suppuration, (c) mild peri-implantitis patients with marginal bone loss 2–3 mm [2, 17], (2) no evidence of

occlusal overload, (3) presence of implant-supported fixed bridge prosthesis in the mouth used for at least 6 months, where the prosthesis did not pose an obstacle for the assessment of clinical parameters.

Exclusion criteria were as follows: (1) tobacco use, (2) having a systemic disease which may affect treatment outcomes such as uncontrolled diabetes, metabolic bone diseases, hematological disorders, history of head and neck radiotherapy or renal disease, (3) pregnancy or lactation, (4) history of antibiotic and/or non-steroidal anti-inflammatory drug use within the last 3 months, (5) steroid and bisphosphonate use, (6) history of any kind of dental treatment within the last 3 months, (7) requirement of surgical techniques for the treatment of the peri-implantitis.

Randomization and study group allocation

The patients' data were recorded and then the patients were numbered according to the order of enrolment and randomized into three groups formed by a computer-generated table (Microsoft Excel 2007). For each patient, all areas with peri-implant diseases were treated, but only one implant site per patient was included in the study. In case of multiple zones with peri-implantitis, the implant with the highest peri-implantitis severity score that meets the inclusion criteria was chosen for the study. The control group ($n=17$) only received conventional non-surgical mechanical therapy. The trial groups received dental laser treatment (940 nm diode laser group, $n=16$ or 2780 nm Er,Cr:YSGG laser group, $n=17$) in addition to non-surgical mechanical therapy.

To maintain the masking, forms involving the treatment method and patient information were put into identical opaque envelopes, and only the number corresponding to that patient was written on the outer side of the envelope. All sealed envelopes were delivered to another clinician who will not administer clinical treatments (NZAY). The envelopes were opened just before the treatment administration, and the two treating clinicians (DA, DiA) were informed about the treatment to be administered. Clinicians and patients were kept unaware of the trial or control group protocol throughout the trial. Statistical analyses were performed using coded group definition.

Assessment of peri-implant clinical and biochemical outcomes

An investigator (ACT) blind to the group assignment performed all clinical assessments. The investigator performed double assessments on at least 30 non-trial implants to provide intra-investigator calibration. Assessments were performed on the same patients at minimum 60-min intervals. Interclass correlation coefficient for the investigator varied from 0.89 to 0.97 and these values indicated that there is high agreement between repeated measurements. Radiographic assessment of the bone levels in mesial and distal areas was performed on panoramic radiographs using NIH ImageJ software (ImageJ, National Institutes of Health, Bethesda, MD, USA—access address: http://rsb.info.nih.gov/ij/). Plaque index (PI) [18], gingival index (GI) [19], bleeding on probing (BOP) [20], and probing depth (PD) (the distance from peri-implant margin to peri-implant pocket base) parameters were assessed in 4 regions (mesial, buccal, distal, lingual/palatinal) of each implant using a plastic probe (UNC 12 Colorvue probe, Hu-Friedy, Chicago, IL, USA), and all assessments were repeated at 6 months after treatments.

Before PICF sampling, the area was air-dried and supragingival plaque was removed. Isolation was performed using cotton rolls to avoid saliva contamination. Samples were collected using paper strips prepared specially for this purpose (PerioPaper, Oraflow, NY, USA). Paper strips were inserted into the deepest pocket until a moderate pressure is felt and kept for 30 s. Samples contaminated with blood or exudate were excluded from the trial. Three paper strips were obtained from each implant, and strips were kept at pH 7.4 in 500 µL phosphate-buffered saline (PBS) in 1.5-mL sterilized Eppendorf® tubes (SealRite 1.5 mL Microcentrifuge Tubes; Scientific Inc., Orlando, FL, USA) at − 40 °C until the laboratory step. PICF samples were collected again from the same region of the implant at 6 months after treatment. When the targeted number was reached, enzyme-linked immunosorbent assay (ELISA) method was used to assess the levels of MMP-9 and TIMP-1 in PICF according to the manufacturer's recommendations (Human Matrix Metalloproteinase-9 ELISA Kit and Human Tissue Inhibitor of Metalloproteinase-1 ELISA Kit, Bioassay Technology Laboratory, Shanghai, China). Absorbance values were read using ELISA reader at 450 nm wavelength (µQuant™ ELISA Microplate Reader, BioTek® Instruments, Inc., VT, USA).

Peri-implant treatments

Treatments were administered by two operators (DA, DiA) who were previously trained by an experienced clinician (NZAY) and calibrated.

Mechanical instrumentations were continued gently using titanium Gracey curettes (8 mm in diameter, Langer ½, item code: 7103, Kohler Medizintechnik, GmbH & Co, Ltd, Stockach, Germany) until the clinician felt that the surface is sufficiently debrided in all groups.

940 nm diode laser (Ezlase®, Biolase Technology, Inc., San Clemente, CA) was applied using an optic fiber tip with a diameter of 300 µm (E3-9 mm) placed in parallel to implant surface approx. 1 mm above the most apical part of the peri-implant pocket. During laser light emission, fiber

was moved in apico-coronal and mesial-distal direction for a total of 30 s. Laser tip was checked every 7–8 s and wiped using sterile saline to avoid a possible coagulation or temperature increase. Laser was used in continuous pulse mode, at 0.8 W power, 3 J/cm^2 energy density, and 1 mm spot diameter. Pulse width and pulse range was 20 ms.

2780 nm Er,Cr:YSGG laser (Waterlase®, Biolase Technology, Inc., San Clemente, CA) was applied in short pulse "H" mode with water cooling and by performing contactless sweeping motion for 30 s in parallel to implant surface using fiberoptic periodontal tip with a diameter of 500 μm (RFPT5-14 mm). Settings used: 1.5 W power, 30 Hz frequency, 50% water, 40% air, 140 μs pulse time, and 1 cm spot size.

The control group received the same mechanical treatment procedures without any additional laser application. Laser tip was inserted into peri-implant crevice; however, it was not activated.

After the procedures were administered in the groups, no medication was given. All patients were informed in detail about the periodontal and peri-implant diseases, dental biofilm, and prevention methods, and were taught personal hygiene practices. All patients were called back for follow-up at 1, 3, and 6 months to check the personal hygiene practices and treatment course; however, clinical assessment records and PICF samples were collected at 6 months.

Statistical analysis

In the study, PD was considered main trait (characteristic) for sample size calculation. In a previous study [21], the standard deviation for PD varied between 0.38 and 0.74. Thus, standard deviation was taken as 0.56. For the 95% of confidence coefficient and approximately 80% power value, type I error is 0.05 (Z value is 1.96 for the 5% type I error), the effect size was taken by the researcher as 0.28. Based on this information, the necessary sample size was calculated by the equation "$n = Z^2 \times s^2 / d^2$." According to this equation, minimum sample size in each group was found as 15 [$n = (1.96^2 \times 0.56^2 / 0.28^2 \cong 15$]. The sample size was finalized on a total of 50 patients to compensate an anticipated drop out. The primary outcome variables were the change in PD and BOP. Secondary outcomes included mean changes in PI, GI, MMP-9, and TIMP-1 levels.

Statistical analysis was performed using the SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD) or median (min–max) for continuous variables and in number and frequency for categorical variables. Age was compared among the groups using one-way analysis of variance (ANOVA) and sex was compared using Pearson's chi-square test. Pre- (T0) and post-treatment (T1) difference for each treatment method was tested for conformity to normal distribution using the Kolmogorov–Smirnov test. The differences were determined not to conform to normal distribution, and T0-T1 differences were examined using Wilcoxon's test. Intra-group comparisons of the obtained differences for three groups were performed using the Kruskal–Wallis test. Pairwise comparisons for the parameters with significant inter-group differences were expressed by corrected p values. A p value of < 0.05 was considered statistically significant.

Results

Sample description

Fifty-eight patients who applied to the periodontology clinic with the complaint of inflammation in the peri-implant site were screened between January 2019 and February 2020. One patient with poor oral hygiene and three patients who did not meet inclusion criteria were excluded before starting the study. Fifty-four participants' initial data were recorded when they came into the program. Then, the patients were numbered according to the order of enrolment and randomized by a computer-generated table. Treatment of each patient was initiated following the initial recordings. One patient in the control group and two patients in the diode laser group, who did not attend the appointments, and one patient with poor oral hygiene in the diode laser group were excluded from the study during follow-up. Consequently, seventeen individuals were treated with conventional non-surgical mechanical therapy, sixteen individuals received 940 nm diode laser in addition to non-surgical mechanical therapy and seventeen individuals received 2780 nm Er,Cr:YSGG laser in addition to non-surgical mechanical therapy. At the end, the trial was completed with fifty patients (21 female, 29 male / mean age: 50.52 ± 9.18 years), achieving the estimated sample size and the 6-month follow-ups ended in August 2020. The study flow chart is shown in Fig. 1.

Table 1 shows the descriptive statistics for age and sex according to the groups. There was no statistically significant difference in the age and gender distribution among the groups ($p > 0.05$).

Clinical and biochemical outcomes

Table 2 shows the pre- (T0 / baseline) and post-treatment (T1 / at 6 months) values for the clinical (GI, PI, PD, BOP%) and biochemical parameters (TIMP-1 and MMP-9 levels). Within the table, results of the Wilcoxon test performed to determine the difference between these values for each group were given together with the Kruskal–Wallis test comparing difference between T0 and T1 values of each parameter

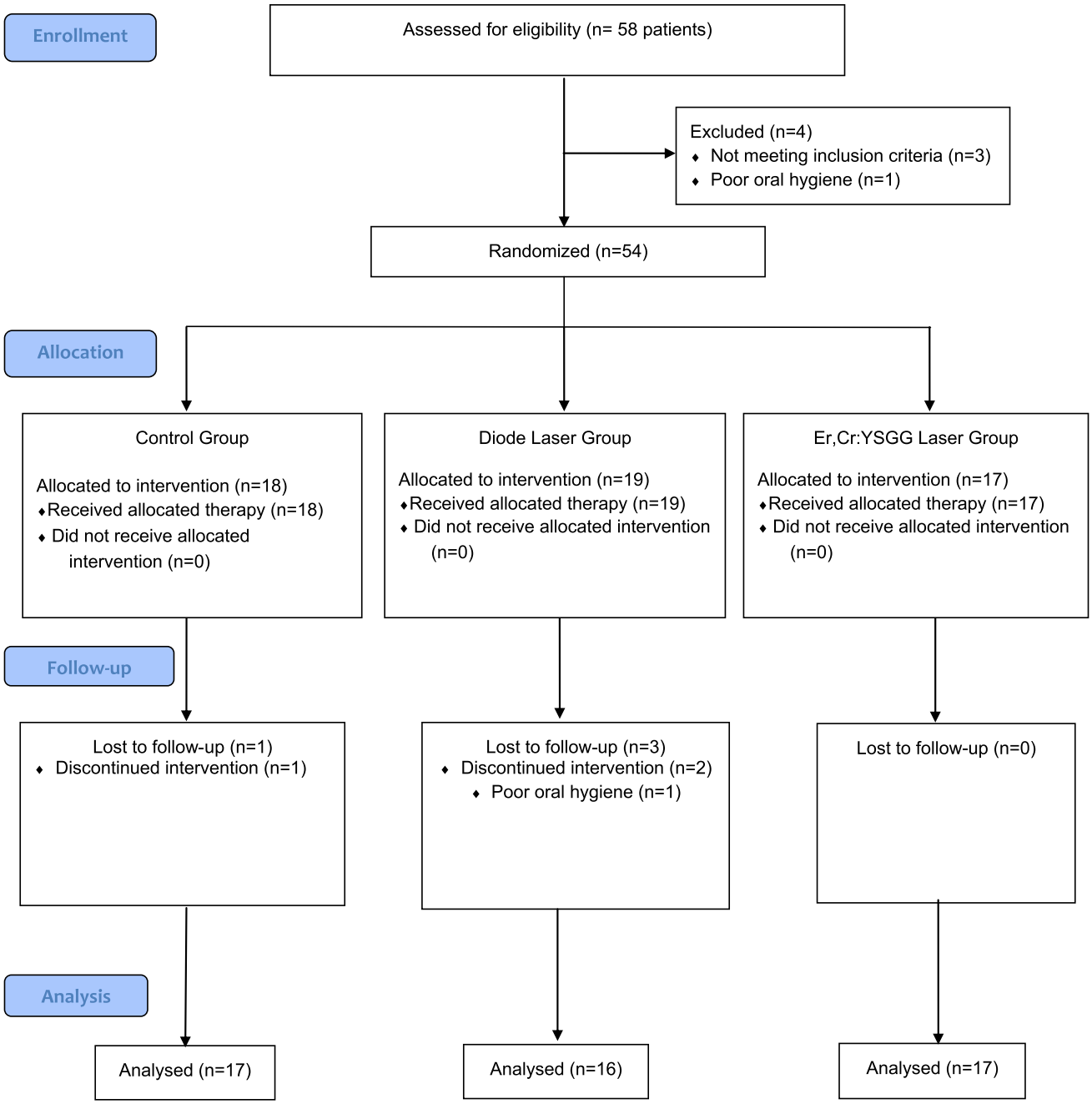

Fig. 1 CONSORT diagram showing the study layout

among the groups. There were no statistically significant differences between the groups at baseline clinical parameters. When the baseline biochemical parameters were examined, the MMP-9 level was similar between the control and the diode laser groups, and it was significantly lower than the Er,Cr:YSGG group ($p = 0.002$). The TIMP-1 levels were similar again in the control and the diode groups at the baseline, and these values were significantly higher than the TIMP-1 level of the Er,Cr:YSGG group ($p = 0.023$). Due to the differences in the baseline values of the biochemical parameters, the changes in the values before and after the treatment were taken into account when interpreting the study findings.

In terms of GI scores, the values obtained at T1 were statistically significantly lower than T0 values in all three groups. Nonetheless, the greatest decrease was observed in the Er,Cr:YSGG laser–assisted mechanical therapy group (0.56 ± 0.36). This was followed by diode laser–assisted mechanical therapy group with a value of 0.38 ± 0.45. While PI scores statistically significantly ($p < 0.05$) decreased in

Table 1 Descriptive statistics in the treatment groups

	Age, years	Gender, *n* (%)	
Groups	Mean ± SD	Female	Male
Control	50.36 ± 6.85	4 (23.50)	13 (76.5)
Diode	46.50 ± 11.34	9 (56.30)	7 (43.80)
Er,Cr:YSGG	54.71 ± 7.34	8 (47.10)	9 (52.90)
p-value	*0.148* [1]	*0.143* [2]	
Total	50.52 ± 9.18	21 (42.00)	29 (58.00)

[1]One-way analysis of variance *p*-value; [2]chi-square *p*-value; *SD* standard deviation

all three groups following the therapy, the method with the greatest decrease was again the Er,Cr:YSGG group with a decrease of 0.91 ± 0.30. The PD values also statistically significantly decreased in all groups with a *p*-value of < 0.05, and similar to the GI and PI values, the group with the greatest decrease from T0 to T1 was the Er,Cr:YSGG group with a difference of 1.16 ± 0.64 mm. When BOP percentage values were examined, T0-T1 differences and statistical significance levels of the control, diode, and Er,Cr:YSGG groups were 11.31 ± 21.58, $p = 0.068$; 26.19 ± 33.94, $p = 0.026$; and 48.81 ± 19.84, $p = 0.001$, respectively. Er,Cr:YSGG group

Table 2 Pre- and post-treatment values of clinical and biochemical parameters

	T0 (baseline)	T1 (post-treatment/6th months)	Difference between T0-T1	Wilcoxon test *p*-value
GI Scores				
Control	1.92 ± 0.16	1.67 ± 0.32	0.25 ± 0.37	*0.026*
Diode	1.96 ± 0.31	1.58 ± 0.45	0.38 ± 0.45	*0.012*
Er,Cr:YSGG	2.00 ± 0.00	1.44 ± 0.36	0.56 ± 0.36	*0.003*
Kruskal–Wallis *p*-value	*0.651*	*0.242*	*0.133*	
PI Scores				
Control	1.64 ± 0.74	1.00 ± 0.68	0.64 ± 0.63	*0.007*
Diode	1.90 ± 0.62	1.07 ± 0.63	0.84 ± 0.77	*0.007*
Er,Cr:YSGG	2.07 ± 0.30	1.17 ± 0.36	0.91 ± 0.30	*0.001*
Kruskal–Wallis *p*-value	*0.13*	*0.642*	*0.591*	
PD Scores / mm				
Control	4.14 ± 0.64	3.62 ± 0.71	0.53 ± 0.44[B]	*0.003*
Diode	4.14 ± 0.80	3.28 ± 1.00	0.86 ± 0.59[B]	*0.001*
Er,Cr:YSGG	4.48 ± 1.14	3.33 ± 0.93	1.16 ± 0.64[A]	*0.001*
Kruskal–Wallis *p*-value	*0.789*	*0.501*	*0.032*	
BOP Percentage				
Control	72.02 ± 23.93	60.71 ± 29.13	11.31 ± 21.58	*0.068*
Diode	88.09 ± 17.82	61.90 ± 29.37	26.19 ± 33.94	*0.026*
Er,Cr:YSGG	100.00 ± 0.00	51.19 ± 19.84	48.81 ± 19.84	*0.001*
Kruskal–Wallis *p*-value	*0.13*	*0.642*	*0.593*	
Total MMP-9 Levels ng / 30 s				
Control	658.71 ± 25.42[B]	654.61 ± 24.18[AB]	4.10 ± 32.04	*0.875*
Diode	650.29 ± 37.44[B]	611.11 ± 146.28[B]	39.19 ± 151.65	*0.176*
Er,Cr:YSGG	711.52 ± 53.16[A]	666.00 ± 20.21[A]	45.52 ± 53.13	*0.009*
Kruskal–Wallis *p*-value	*0.002*	*0.006*	*0.087*	
Total TIMP-1 Levels pg / 30 s				
Control	166.87 ± 13.46[A]	165.94 ± 15.94[A]	0.93 ± 20.47[B]	*0.379*
Diode	179.66 ± 11.03[A]	169.84 ± 11.75[A]	9.82 ± 13.97[B]	*0.022*
Er,Cr:YSGG	153.28 ± 16.43[B]	128.30 ± 23.17[B]	24.98 ± 23.43[A]	*0.008*
Kruskal–Wallis *p*-value	*0.023*	*< 0.001*	*< 0.001*	

A p value of < 0.05 was considered statistically significant.

Difference with superscript uppercase letter shows statistical difference at 0.05 levels according to pairwise comparison

GI gingival index, *PI* plaque index, *PD* probing depth, *BOP* bleeding on probing, *MMP-9* matrix metalloproteinase-9, *TIMP-1* tissue inhibitor of metalloproteinase-1, *mm* millimeter, *ng* nanogram, *s* seconds, *pg* picogram

Control group consists of the patients only receiving conventional non-surgical mechanical therapy

The diode group consists of the patients receiving diode laser–assisted non-surgical mechanical therapy

The Er,Cr:YSGG group consist of the patients receiving Er,Cr:YSGG laser–assisted non-surgical mechanical therapy group

was again the group with the greatest decrease, and the decrease in the control group was not found to be statistically significant.

The only treatment method with significant intra-group decrease in the MMP-9 level between T0 and T1 was Er,Cr:YSGG laser–assisted mechanical therapy (45.52 ± 53.13, $p = 0.009$). The group with the highest intra-group T0-T1 decrease in the TIMP-1 level was again the Er,Cr:YSGG group with a decrease of 24.98 ± 23.43 ($p = 0.008$). This was followed by the diode laser group with a decrease value of 9.82 ± 13.97 ($p = 0.022$). No statistically significant decrease was observed between T0 and T1 in the control group ($p = 0.379$).

When the treatment methods were compared in terms of the parameters assessed at T0 and T1, no statistically significant difference was found among the groups for GI, PI, BOP percentage and MMP-9 parameters with p-values of $p = 0.133$, $p = 0.591$, $p = 0.593$, and $p = 0.087$, respectively. For the PD score, while the difference between the control and the diode group was not found to be statistically significant, the decrease observed with the Er,Cr:YSGG laser–assisted mechanical therapy method was statistically significantly higher than the decreases observed with the other two methods ($p = 0.032$). To indicate these differences, the control and the diode groups were labeled with the same letter and the Er,Cr:YSGG group was labeled with another letter in Table 2. The decrease in the TIMP-1 level from T0 to T1 among the groups was also higher in the Er,Cr:YSGG group compared to the other groups, similar to the PD parameter. The decrease in TIMP-1 levels from T0 to T1 was similar between the control and the diode groups ($p > 0.05$) and these values were significantly lower than the decrease in the Er,Cr:YSGG group ($p < 0.05$).

The null hypothesis of the trial was that the treatment results in the groups that received dental laser–assisted mechanical therapy would be similar to the group that received only mechanical therapy. Considering all the clinical and biochemical evaluations, our null hypothesis was partially accepted. Although the addition of dental laser application to mechanical therapy improved treatment outcomes, it was not significant for many parameters and Er,Cr:YSGG laser–assisted mechanical treatment method provided relatively more successful results than the other two methods.

Discussion

In this randomized-controlled trial, the effects of addition of application of two different lasers to conventional non-surgical mechanical therapy on clinical and biochemical parameters in implant sites with peri-implantitis were examined. According to our results, while all three treatment methods provided a successful recovery, no additional benefit was observed in the diode laser–assisted non-surgical mechanical therapy group in terms of treatment outcomes compared to the control group. On the other hand, addition of the Er,Cr:YSGG laser treatment to the traditional therapy resulted in significant improvement in some of the clinical and biochemical parameters than the two other methods.

The main etiological factor for the development of peri-implant diseases is the formation of a biofilm layer [3]. Complete removal of the pathogenic microorganisms in the treatment of peri-implantitis depends on both the success of the mechanical debridement and implant surface detoxification [22]. All these situations have led clinicians to search for both more effective and more comfortable treatment approaches. Recently, laser applications have gained popularity in the treatment of peri-implant diseases [23]. The use of laser applications before surgical treatment choice has been suggested to be possibly beneficial in the management of peri-implant disease [24]. However, as dental lasers have highly variable power settings, care should be taken to preserve the implant surfaces and the integrity of peri-implant tissues [22]. Wavelengths and power settings used in this trial are within the limits of safely removing the biofilm layer and the infected tissue around the implant without causing damage [25–28]. Additionally, this study was designed to assess the efficiency of both laser wavelengths by ruling out other confounding variables that may interfere with the outcome, such as chemotherapeutic agents. Various dental laser applications are being used for the treatment of peri-implant diseases; however, most studies have been performed in the in vitro setting [26, 29] or are limited to the analyses of only clinical parameters [25, 27, 30]. To the best of our knowledge, this is the first trial comparing the effects of 940 nm diode laser and 2780 nm Er,Cr:YSGG laser on the treatment of peri-implantitis in vivo by assessing both clinical and molecular parameters. The lack of controlled clinical trials examining the effects of laser applications on treatment outcomes in terms of clinical and biochemical parameters made the comparison of the reported results highly difficult. This study can provide important data for future research with this aspect.

In a trial by Lerario et al. [27], it was observed that diode laser–assisted therapy in the treatment of peri-implantitis provides more clinical improvements compared to only conventional non-surgical mechanical therapy and the necessity for randomized clinical trials was emphasized. In another study [23], 810 nm laser was applied with or without a photosensitizing dye in addition to mechanical therapy to implants with peri-implantitis, and improvement was observed in both clinical and microbiological parameters. In that study, however, there was no control group which only received mechanical debridement. In the split-mouth trial by Arısan et al. [21], the clinical, microbiological, and radiological effects of diode laser used in addition to mechanical

therapy for the treatment of peri-implantitis were examined. At the end of the study, investigators emphasized that they did not observe any positive effect of the diode laser in the treatment of peri-implantitis. Clinical and biochemical results of our trial revealed similar results to this study, as no significant difference was detected between the control group and the diode laser–assisted mechanical therapy group in terms of both clinical and biochemical parameters. Within the groups, post-treatment values were lower than the baseline values in both groups. These results show that both treatment modalities are successful in the disease treatment and provide similar improvement.

In other trials [31, 32], the Er:YAG and the Er,Cr:YSGG lasers were observed to have highly effective properties on the elimination of biofilm and the decontamination of implant surface. In a recent in vitro study [26], the interaction of the Er,Cr:YSGG laser with the bacterial adhesion and fibroblast viability was examined, and laser treatment reduced the adhesion of *Porphyromonas gingivalis* and increased the fibroblast viability and osteoblast differentiation. In a case series by Al-Falaki et al. [25], 28 implants with peri-implantitis in 11 patients were treated using Er,Cr:YSGG, and highly significant results were obtained in clinical parameters, mainly in the form of a decrease in the pocket depth; however, this case series did not include a control group which only received mechanical debridement. In our study, there was a significant decrease between pre- and post-treatment values of all the clinical parameters, except for BOP in all three groups. The decrease in the PD value was significantly greater in the Er,Cr:YSGG group than the other two groups with BOP scores, showing significant intragroup decreases in the laser groups. Another aspect of our trial that stands out compared to the aforementioned study is the fact that molecular assessments were performed in addition to the analyses of clinical parameters. The Er,Cr:YSGG group was the only group which provided significant intragroup decreases in all clinical and biochemical parameters from T0 to T1. As a result of these assessments, it is concluded that the Er,Cr:YSGG laser group provides more positive contributions to the treatment outcomes.

In our trial, the MMP-9 and the TIMP-1 levels in PICF were examined as biochemical markers. When their levels were analyzed, all post-treatment values were lower than the pre-treatment values. For the TIMP-1 levels, the decrease obtained in the Er,Cr:YSGG group was statistically significantly different than the other two groups. Matrix metalloproteinases are primarily responsible for the tissue transformation both at physiological and pathological settings [33]. The balance between the local catabolic (MMP) and anti-catabolic (TIMP) activities determines the tissue degeneration and remodeling [34]. In our study, the decreases between the baseline and post-treatment (month 6) values in the biomarker levels were associated with the roles of these parameters in the course of peri-implantitis. Although the TIMP-1 level showed increases from the pre-treatment values parallel to the MMP-9 level as a defense mechanism against infection, it may not compensate for the upregulation of the MMP-9 level and peri-implantitis may develop, as it occurred in this study. There are studies in the literature showing that these two parameters have a tendency to increase together [35–37] or vice versa [38] in periodontal/peri-implant disease setting. Advanced peri-implantitis cases were not included in our trial. In the case of advanced peri-implant disease, it is foreseen that significant differences would occur in these biomarkers. Considering there are no foreseeable and effective therapeutic interventions for the treatment of peri-implantitis, scientific evidence on the host response around the dental implants might be important in the future to provide a wider preventive and/or therapeutic window for this disease. The determination of the biomarkers providing a quantitative measurement of the response to peri-implantitis treatment stands out at this point [14, 39].

Consequently, based on the clinical and biochemical examinations, our null hypothesis was partially confirmed. In the areas with peri-implantitis, while the addition of dental laser to conventional mechanical therapy improves the treatment outcomes, the differences were not significant for many of the parameters. The positive effects of the Er,Cr:YSGG laser–assisted treatment were relatively greater compared to the other groups.

One of the limitations of our trial was the fact that the treatment outcomes were assessed at 6 months and not followed up at long term; therefore, care should be exercised when the results are interpreted. The parameters possibly affecting the treatment outcomes, the width of the keratinized tissue, and peri-implant mucosa biotype were not examined. Planning more comprehensive trials with split-mouth design examining all of these parameters and eliminating the individual differences might be beneficial.

Conclusion

In conclusion, within the limits of this trial, all three treatment methods provided a successful improvement in the treatment of peri-implantitis. Similar treatment outcomes were obtained in the mechanical therapy–alone group and the diode laser–assisted mechanical therapy. Based on these findings, we suggest that using the Er,Cr:YSGG laser as an aid in the non-surgical management of the peri-implantitis appears to be more effective than the other two methods that we have used, both at clinical and molecular levels in most of the cases. Nonetheless, further studies are warranted to confirm these findings.

Acknowledgements We would like to thank the Director of the Scientific Research Projects of Van Yuzuncu Yil University for their valuable support for the conduct of the study (Project No: TSA-2019-8343).

Author contribution Categories of the authors' contribution are as follows: study concept and design (Nazli Zeynep Alpaslan Yayli), data acquisition (Ahmet Cemil Talmac, Damla Akbal, Dicle Altindal), data analysis (Nazli Zeynep Alpaslan Yayli, Serap Keskin Tunc), drafting of the work (Nazli Zeynep Alpaslan Yayli, Ahmet Cemil Talmac, Serap Keskin Tunc), writing the first draft (Nazli Zeynep Alpaslan Yayli), critical revision (Abdullah Seckin Ertugrul), supervision and editing (Nazli Zeynep Alpaslan Yayli, Abdullah Seckin Ertugrul). All authors read and approved the final manuscript.

Funding This study was funded by the authors and by Van Yuzuncu Yil University, Van, Turkey with the Project No: TSA-2019–8343.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (Van Yuzuncu Yil University Clinical Trials Ethics Committee with the Approval No: 21.11.2018/02). The study is registered on ClinicalTrials.gov (NCT04730687).

Consent to participate Prior to the study, all participants were informed about the nature of the study and a written informed consent was obtained on the voluntary basis.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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

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