Received: 20 January 2020 | Revised: 7 April 2020 | Accepted: 18 April 2020

DOI: 10.1002/JPER.20-0040

JOURNAL OF Periodontology

HUMAN RANDOMIZED CONTROLLED TRIAL

Laser-assisted regenerative surgical therapy for peri-implantitis: A randomized controlled clinical trial

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[Corrections added on 22 March 2021, after first online publication: The spelling of the third author's last name was corrected, and ORCID identifiers were added for all authors.]

Funding information
This study was supported by grants from J. Morita (Tokyo, Japan) and the Department of Periodontics and Oral Medicine Clinical Research Fund.

Abstract

Background: Different surgical approaches have been proposed to treat peri-implantitis defects with limited effectiveness and predictability. Laser has been proposed as an effective tool to assist in bacterial decontamination and modulating peri-implant tissue inflammation. The aim of this pilot clinical trial was to evaluate the adjunctive benefits of Er:YAG laser irradiation for regenerative surgical therapy of peri-implantitis-associated osseous defects.

Methods: Twenty-four patients diagnosed with peri-implantitis with a radiographic infrabony defect were randomized into two groups. Both test and control groups received the following treatment: open flap mechanical debridement, supracrestal implantoplasty, bone grafting using a mixture of human allograft with demineralized bone matrix human allograft putty, and then covered with acellular dermal matrix membrane. The only difference in the test group was the adjunctive use of Er:YAG laser to modulate and remove inflammatory tissue as well as to decontaminate the implant surface. Clinical assessments, including pocket depth (PD), clinical attachment level (CAL), and gingival index (GI) were performed by calibrated masked examiners for up to 6 months following surgery. Standardized radiographs were also taken to evaluate linear bone gain and defect bone fill. Student *t*-tests were used to analyze those clinical parameters.

Results: Both groups showed significant reductions in PD, GI, and CAL gain overtime. The test group demonstrated significantly higher PD reductions at the site level compared to the control group (2.65 ± 2.14 versus 1.85 ± 1.71 mm; test versus control, $P = 0.014$). There were no statistical differences found in CAL gain (1.90 ± 2.28 versus 1.47 ± 1.76 mm; test versus control), GI reduction (-1.14 ± 1.15 versus -1.04 ± 0.89; test versus control), radiographic linear bone gain (1.27 ± 1.14 versus 1.08 ± 1.04 mm; test versus control) or proportional defect size reduction (- 24.46 ± 19.00% versus -15.19 ± 23.56%; test versus control). There was a positive trend for test patients on PD reduction and CAL gain found in narrow infrabony

defects. Major membrane exposure negatively impaired the overall treatment outcome of CAL gain (2.47 ± 1.84 versus 1.03 ± 1.48 mm; no/minor versus major exposure, $P = 0.051$) and PD reduction in the test group (-3.63 ± 2.11 versus -1.66 ± 1.26 mm, $P = 0.049$).

Conclusion: This pilot study indicated using laser irradiation during peri-implantitis regenerative therapy may aid in better probing PD reduction. Nonetheless, a larger sample size and longer follow-up is needed to confirm if Er:YAG laser irradiation provides additional clinical benefits for peri-implantitis regenerative therapy (Clinicaltrials.gov: NCT03127228)

KEYWORDS

alveolar bone grafting, bone regeneration, clinical trial, dental implants, lasers, peri-implantitis

1 | INTRODUCTION

Peri-implantitis has been defined as "a pathological condition occurring in tissues around dental implants, characterized by inflammation in the peri-implant connective tissue and progressive loss of supporting bone beyond initial physiologic remodeling."[1] With the popularity of dental implant therapy[2] and the acknowledged growing prevalence of peri-implantitis (15% to 20%),[2,3] it is imperative to discern effective treatment modalities for the management of peri-implantitis. Treatment of peri-implantitis is still considered unpredictable[4,5] and currently there is no standard protocol available to manage this challenging problem.[6]

Surgical therapy is oftentimes recommended to manage advanced peri-implantitis defects,[6-8] as non-surgical therapy shows limited efficacy.[4,5,9] Guided bone regeneration (GBR) of the infrabony defects around peri-implantitis lesions has been documented as one of the promising treatment modalities.[7] Systematic reviews support the efficacy of reconstructive surgical therapy for peri-implantitis defects, but complete resolution of the disease or full repair of the infrabony defect remains unpredictable.[10,11] One of the main challenges during the surgical approach for regeneration therapy is the method to effectively disinfect the contaminated implant surface; specifically for rough surface implants with microthreads. Among the different devices and agents, currently there is no gold standard to properly decontaminate the implant surface.[12]

Application of lasers, especially erbium lasers, for the treatment of peri-implantitis have been investigated in-vitro and in-vivo with promising results. Erbium-doped yttrium aluminium garnet (Er:YAG) laser can exert potent bactericidal effects[13,14] without alteration of the implant surface.[15] Preclinical models demonstrated that Er:YAG laser can facilitate the re-osseointegration of the previously-contaminated implant surface.[16,17] In addition, Er:YAG laser can also exert biologic effects on peri-implant tissues, such as intraoperative hemostasis, degranulation, clot stabilization, and bio-stimulation of the wound healing when applied in the low energy level.[18-20]

Currently, clinical studies on the efficacy of lasers for treatment of peri-implantitis is still scarce.[21] Therefore, the aim of this examiner and patient double-masked randomized clinical trial was to evaluate the adjunctive benefit of using Er:YAG laser to assist in peri-implant defect debridement and implant surface decontamination prior to regenerative procedures in the treatment of peri-implant infections.

2 | MATERIALS AND METHODS

This study was performed in accordance with the Helsinki Declaration of 1975, as revised in 2013. The study protocol was reviewed and approved by the University of Michigan (U-M) Health Science Institutional Board (HUM00124386) and registered with ClinicalTrials.gov (NCT03127228). Twenty-four patients with at least one loaded dental implant with peri-implantitis were enrolled between June 2017 and May 2018 in the Graduate Periodontics Clinic at the Department of Periodontics and Oral Medicine at the U-M School of Dentistry, Ann Arbor, Michigan. All study visits were completed by November 2018.

2.1 | Trial design

The present study was a single center randomized controlled clinical trial in which both the patients and the examiners were masked. The overall design of the trial is shown in Figure 1. Inter-examiner reproducibility for

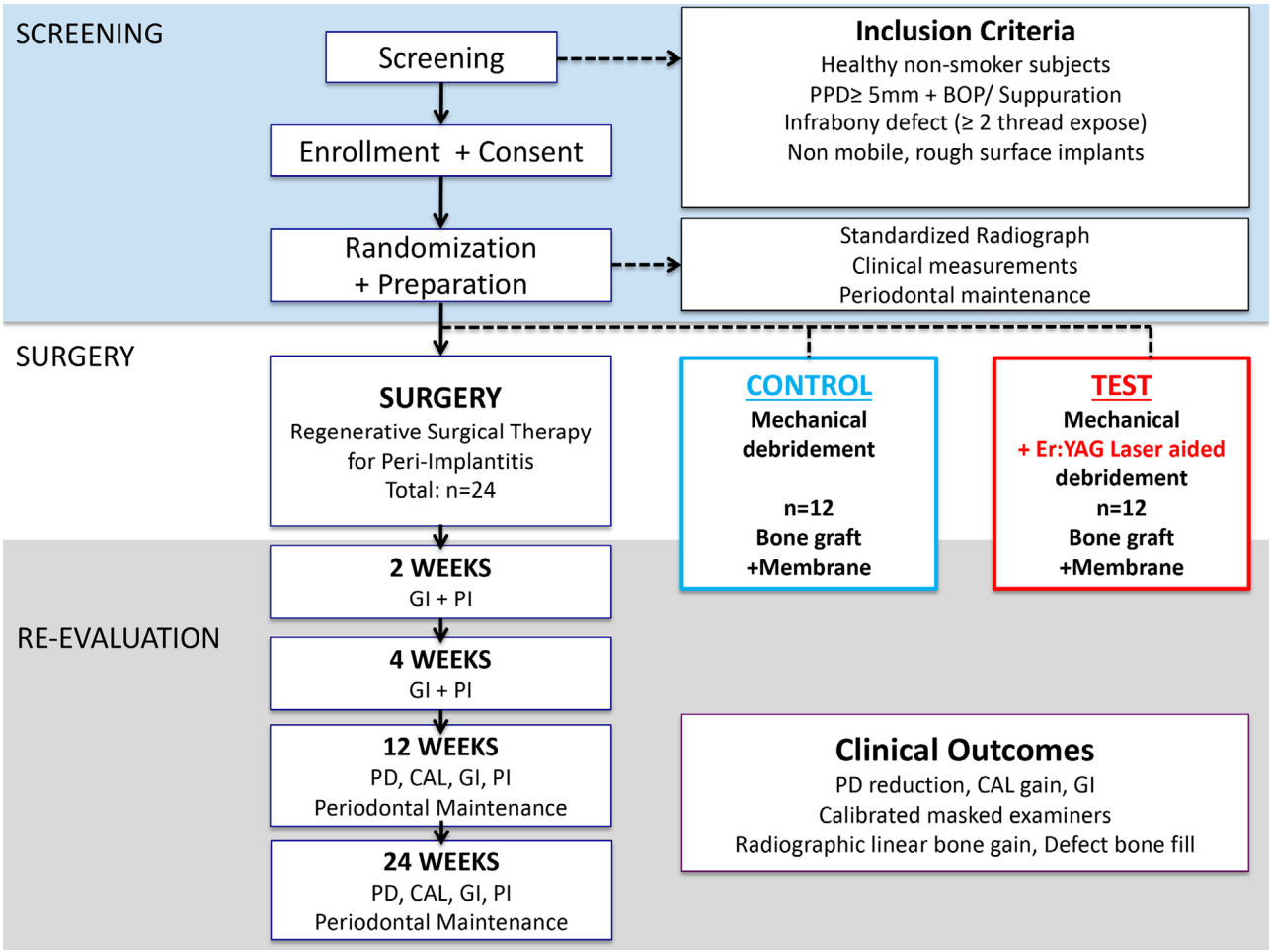

FIGURE 1 Clinical trial design and the study visits. CAL, clinical attachment level; GI, gingival index; PD, peri-implant pocket depth

the two masked examiners (MA and JK) was performed during two calibration sessions. Inter-examiner agreement was achieved with a Kappa of 0.79 (95% confidence interval (CI); 0.60 to 0.99) and a Lin's concordance correlation coefficient (CCC) of 0.79 (95% CI; 0.74 to 0.84) between MA and JK. Intra-examiner agreement was calculated with an intraclass correlation coefficient (ICC) and showed an agreement of 0.93 (95% CI; 0.89 to 0.96) for MA, and 0.84 (95% CI; 0.72 to 0.91) for JK (both 100% within 1 mm tolerance).

2.2 | Sample size determination

A prior sample size calculation was done with an estimated 0.6 mm effect size pocket depth reduction under $\alpha = 0.05$ and power = 0.8, and a minimum sample size of 20 patients (10 in each group) was required. The sample size was then finalized on a total of 24 patients to compensate an anticipated 20% of drop out.

2.3 | Patient selection

All patients referred to the Graduate Periodontics clinic for treatment of peri-implantitis were considered for recruitment. A screening study visit was designated to confirm eligibility. During the screening visits, patients were given written consent and were consecutively screened and enrolled when the following inclusion criteria was met: (1) a minimum of 1 dental implant with peri-implantitis [radiographic infrabony defect with ≥2 threads exposed or 2 mm vertical bone loss, and pocket probing depth (PD) ≥5 mm with bleeding on probing (BOP) and/or suppuration]; (2) the dental implant had to be in function for at least 6 months; (3) patient physical status ASA I or II according to the American Society of Anesthesiologists[22]; (4) only implants with rough surface were considered eligible. Exclusion criteria were: (1) use of antibiotics for > 2 weeks in the past 2 months; (2) patients taking medications known to modify bone metabolism such as bisphosphonate; (3) mobile dental implants; (4)

current smokers or patients who quit smoking < 6 months before the screening visit; (5) uncontrolled systemic diseases or conditions known to alter bone metabolism; (6) diseases or conditions known to suppress the immune system. Patients that presented with two or more dental implants eligible for the study, the dental implant with the greater infrabony defect was selected in this study.

2.4 | Study groups

Patients belonging to the control group received surgical regenerative therapy, involving mechanical debridement and GBR. Patients of the test group received adjunctive laser irradiation in addition to mechanical debridement prior to bone grafting. Control group patient also received a shame application of the laser on a wet gauze intraorally for masking purposes.

2.5 | Randomization

Patient were randomly assigned to the control or test group according to the last digit of the chart number. Odd numbered dental charts were assigned to the control group and even numbered dental charts were assigned to the test group. In the event that one group had > 2 consecutive patients in the same group, the following patient enrolled was automatically included in the other group.

2.6 | Clinical and radiographic measurements

Clinical parameters were recorded during the pre-surgical visit, 2 weeks, 4 weeks, 12 weeks, and 24 weeks post-operative, using the University of North Carolina (UNC) periodontal probe. Clinical examiners (MA and JK) were masked from the treatment assignment for all patients. The following clinical parameters were recorded for six sites around the dental implant. All the values were grouped together for a site-level analysis:

1. PD: measured from mucosal margin to base of the pocket.
2. Recession (REC): measured from the crown-abutment margin to the mucosal margin.
3. Clinical attachment level (CAL): measured from the crown-abutment margin to the base of the pocket.
4. Gingival index (GI) and 5) Plaque index (PI) were reported as a numeric code from 0 to 3 according to Loe (1967).[23]
5. Bleeding on probing (BOP): measured as a dichotomic presence or absence of bleeding 15 second after probing.

Using intraoral peri-apical digital sensors, a standardized radiograph was taken at pre-op and 6 months after surgery. Customized putty bite blocks were made for each patient to standardize positioning of the sensor and angle with which radiographs were taken. Liner bone gain was assessed by determining a constant specific radiographic reference for each patient (platform, or porcelain to abutment junction) using MiPACS (Medicore, Charlotte, USA). Peri-implant defect size measurements were done and superimposed with 3D Slicer software (Version 4.10.1, Bioinformatics and Computational Biology program, National Institute of Health, USA) and ImageJ software (Version 1.8.0, National Institute of Health, USA).

The primary outcomes for this study were PD and CAL. Secondary outcomes measures were GI, BOP, and PI. Additional radiographic assessment included linear radiographic bone gain and defect size changes. The peri-implant defects were assessed during the procedure and confirmed with the surgical photos taken, based on the classifications by Monje et al. (2019).[24]

Post-operative membrane exposure occurred in a variety of degrees in most of the cases. All patients presenting with post-operative membrane exposure were reviewed by two clinicians (JW and SA) and were graded as no to mild exposure, and major exposure was with exposed gap within the flap > 1.5 mm.

2.7 | Pre-surgical visit

During the pre-surgical examination, a set of photographs and one standardized peri-apical radiograph were taken and baseline clinical peri-implant measurements (PD, CAL, GI, BOP, and PI) were recorded. In addition, a full mouth prophylaxis or a periodontal maintenance was performed with peizo-instruments and stainless-steel hand scalers without subgingival debridement around the implant. The maintenance was also performed at 3-month and 6-month follow-up visits.

2.8 | Surgical procedure

The surgeons (JW and HLW) were informed of the assigned treatment group on the day of surgery. After administration of local anesthesia, open flap debridement was done for both groups. Intrasulcular incisions were performed to expose the contaminated surface. In the control group, the dental implant surface was debrided using piezoelectric and stainless-steal scalers. For the test group,

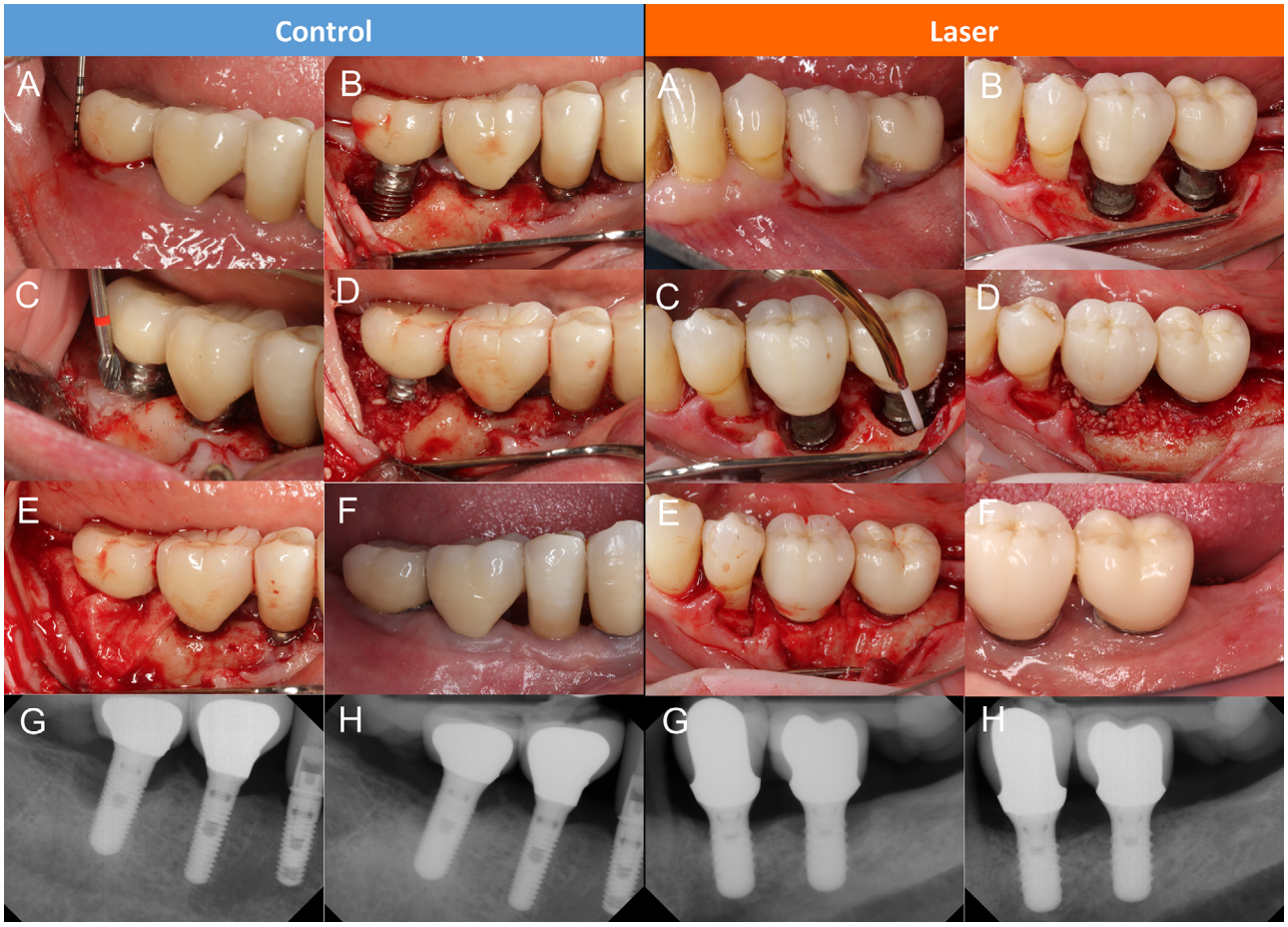

FIGURE 2 Clinical photos of the control and laser (test) groups in the clinical trial. (**A**) Peri-implantitis with suppuration and active BOP, (**B**) After debridement of peri-implant **A** defect, (**C**) During implantoplasty or laser application, (**D**) Placement of bone allografts, (**E**) Membrane adaptation, (**F**) 6 months follow-up, (**G**) Pre-op radiograph, (**H**) 6 months post-op radiograph

granulation tissue removal was also assisted by the use of Er:YAG laser* with a metal-shield tip and the first round of dental implant decontamination was done using a slow linear motion of 0.5 mm/sec vertically and horizontally crossing over of the exposed implant surface (panel setting 50 mJ/pulse, 25 pulse per second, pps). The peri-implant defect and tissue were also irradicated with lower energy and sweeping motion (panel setting 30 mJ/pulse, 20 pps, 0.5 mm/sec). The time required to disinfect each dental implant depending on the exposure rough surface was around 3-5 minutes. In the control group, the Er:YAG laser was applied on a wet gauze intraorally on the side of the dental implant, serving as placebo to mask the grouping for the patient. A bone wax was adapted and fixed in the defect to capture titanium particles and prevent from pollution of the peri-implant defect from implantoplasty. All suprabony dental implant surfaces were treated with implantoplasty procedure and the reconstructive treatment was focused on the infrabony component of the defect. After detoxification of the dental implant surface, mineralized bone allograft was applied to both groups to fill the peri-implant defects. Composite graft included 3:1 ratio of allograft and demineralized bone fibers† . After the graft material was properly placed, an absorbable acellular dermal matrix (ADM) membrane‡ was trimmed to an appropriate size and shape to completely cover the implant site and extended about 3 mm beyond the peri-implant defect. ADM was intended to increase the soft tissue thickness for soft tissue augmentation. The flap was then sutured with polytetrafluoroethylene (PTFE) sutures§ using either a simple interrupted technique or a modified horizontal mattress suture technique. Sutures were left in place for at least 14 days. A periodontal dressing** was placed on the surgical area. Clinical photos of the surgical procedures are provided in Figure 2.

* AdvErL EVO, J. MORITA MFG. CORP, Kyoto, Japan. (Laser tips: PS600T, PSM600T, and R600T)
† MinerOss and Grafton, BioHorizons, Birmingham, Alabama
‡ Alloderm GBR, BioHorizons, Birmingham, Alabama
§ Cytoplast, BioHorizons, Birmingham, Alabama
** Coe-Pak Periodontal Dressing, Patterson Dental, St. Paul, Minnesota

TABLE 1 Clinical parameters and outcomes after surgical regenerative therapy

		Baseline (BL)	3 months	6 months	Difference (BL-6m)	*P* (BL-6m)
Probing depth (mm)	Control	6.44 ± 1.07	5.04 ± 0.879	4.59 ± 0.719	1.85 ± 1.71	<0.001
	Laser	7.73 ± 1.95	6 ± 1.63	5.08 ± 1.76	2.65 ± 2.14	<0.001
	P	0.061	0.087	0.391	0.014	
Clinical attachment level (mm)	Control	6.94 ± 1.23	6.04 ± 0.93	5.47 ± 0.96	1.47 ± 1.76	<0.001
	Laser	7.43 ± 1.91	6.05 ± 1.41	5.52 ± 1.57	1.90 ± 2.28	<0.001
	P	0.468	0.978	0.918	0.252	
Plaque index	Control	0.55 ± 0.51	0.52 ± 0.54	0.34 ± 0.31	-0.20 ±0.50	0.003
	Laser	0.20 ± 0.27	0.45 ± 0.40	0.38 ± 0.32	0.18 ± 0.32	0.024
	P	0.055	0.727	0.751	0.038	
Bleeding on probing	Control	0.86 ± 0.18	0.55 ± 0.30	0.47 ± 0.39	-0.39 ± 0.55	<0.001
	Laser	0.83 ± 0.30	0.50 ± 0.34	0.52 ± 0.33	-0.31 ± 0.62	<0.001
	P	0.78	0.67	0.71	0.393	
Gingival index	Control	1.68 ± 0.61	0.72 ± 0.52	0.63 ± 0.68	-1.04 ± 0.89	0.008
	Laser	1.68 ± 0.85	0.68 ± 0.50	0.54 ± 0.49	-1.14 ± 1.15	0.003
	P	1.00	0.844	0.69	0.573	

2.9 | Postoperative care

All patients were prescribed 500 mg of amoxicillin to take 3 times a day for 10 days; if the patient was allergic to amoxicillin, azithromycin was prescribed, 2 tablets of 250mg each for the first day then 1 time per day until the fourth day. In addition, the patients were prescribed 600 mg of ibuprofen to take as needed, for pain control, and were instructed to rinse twice daily with chlorhexidine for 1 minute, 2 times per day for the first week. Patients in both groups were also advised to avoid brushing or touching the operated area for 2 weeks.

2.10 | Statistical analyses

Statistical analyses were performed using SPSS 20 (IBM, USA). The primary outcome variable was PD reduction. CAL, GI, PI, BOP, and additional radiographic assessment were secondary outcome variables. A Kolmogorov-Smirnov Test was performed and verified that the sample data are normally distributed in both groups. For clinical and radiographic parameters, paired *t*-test was performed for within group comparison at different time points and unpaired *t*-test was conducted for inter-group comparison. ANOVA was done for various local defect morphologies.

3 | RESULTS

All 24 patients completed the 6 months clinical trial and follow-up visits with no dropouts for a 100% retention rate. Of the 24 patients, there were 14 males and 10 females ranging from 50 to 82 years of age. Demographic information is listed in Table S1 (Please see it in online *Journal of Periodontology*) and it is equally distributed between the control and test group in terms of age and gender. There were more dental implants located in the premolar region in the control group compared to the test group. There was one anterior dental implant in the test group whereas there was none in control group. Peri-implant bony defect morphology was assessed and categorized following the classification proposed by Monje et al., which includes circumferential, horizontal, 2 to 3 walls defects and combined horizontal-circumferential defects.[24] Defect configuration was equally distributed between the two groups yet the test group had one in 3c, which involves both horizontal and circumferential defects (Please see Table S2 in online *Journal of Periodontology*).

All the clinical parameters and treatment outcomes are presented in Table 1. Both groups were homogeneous at baseline regarding GI and sites with BOP; the average baseline PD was slightly higher in the test group and the PI was greater in the control; however, no statistically significant difference was noted between the two groups. Both groups showed significant reduction of PD at 6 months compared to baseline ($P<0.001$) with statistically higher PD reduction in favor of the test group (1.85 ± 1.71 versus 2.65 ± 2.14 mm, control versus test, $P = 0.014$). In terms of different probing sites around the dental implant, there was a higher PD reduction interproximally, but no significant difference in PD reduction between the two groups (Figure 3).

Both groups showed significant CAL gain compared to baseline ($P<0.001$) measurements. The control group

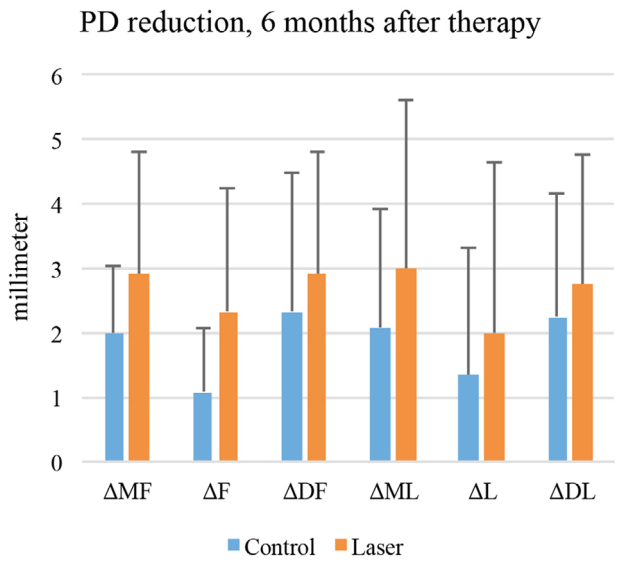

FIGURE 3 Analysis of mean probing depth (PD) reduction based on different implant site. MF = MesioFacial, F, Facial; DF, DistoFacial; ML, MesioLingual; L, Lingual; DL, DistoLingual

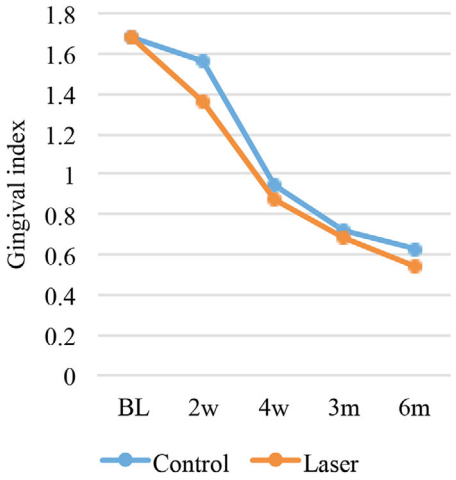

FIGURE 4 Mean gingival index reduction after therapy. BL, Baseline

showed 1.47 ± 1.76 mm CAL gain after 6 months, whereas the test group resulted 1.90 ± 2.28 mm, but the difference did not reach a statistical significance ($P = 0.252$). When analyzing at different probing sites around the implant, the mean CAL gain in the test group compared to the control group was higher at lingual sites compared to the facial sites (Lingual: 2.0 mm versus 1.5 mm; Facial: 2.1 mm versus 1.9 mm; test versus control respectively).

Regarding inflammation of peri-implant tissues, both groups showed significant BOP reduction ($P<0.001$) and GI reduction ($P<0.01$) after therapy (Table 1). Differences between groups after 6 months post-therapy were for BOP (-0.39 ± 0.55 versus -0.31 ± 0.62; control versus test) and GI (-1.04 ± 0.89 versus -1.14 ± 1.15; control versus test); however, no statistically significant difference was found at any time point (Figure 4).

Radiographic assessment data are shown in Table 2. Slightly higher mean linear bone gain was observed in the test group, but the difference failed to show statistical significance (1.08 ± 1.04 mm versus 1.27 ± 1.14 mm; control versus test, $P = 0.666$). In terms of the defect size, both groups showed reduction of the peri-implant defect. The test group showed an average of more proportional reduction in defect size compared to the control group but failed to reach statistical significance (-15.19 ± 23.56% versus -24.46% ± 19.00%; control versus test, $P = 0.300$).

Regarding the peri-implant defect morphology, only 1b and 3b defect types have > 3 patients in each group for comparison and statistical analysis. In the 1b contained infrabony defect, the test group had a much higher averaged PD reduction (1.75 ± 0.81 versus 3.75 ± 2.06; control versus test, $P = 0.085$) and CAL gain (1.83 ± 1.49 versus 2.59 ± 2.65, $P = 0548$) compared with the control group, despite no statistical significance. In the 3b defects with some horizontal bone loss, there is similar mean PD reduction (1.66 ± 1.44 versus 1.50 ± 0.60; control versus test, $P = 0.860$) but less CAL gain (1.54 ± 1.44 versus 0.66 ± 1.74, $P = 0.49$) in the test group (Please see Table S3 in online *Journal of Periodontology*)

Effect of membrane exposure on clinical outcome was assessed. Major membrane exposure was compared with no/minor membrane exposure and it seemed to have

TABLE 2 Radiographic outcomes between baseline and 6 months after therapy

		Control	Laser	*P*
Linear bone gain (mm)	Mesial	1.11 ± 1.15	1.44 ± 1.51	0.552
	Distal	1.04 ± 1.09	1.10 ± 1.29	0.552
	Average	1.08 ± 1.04	1.27 ± 1.14	0.666
Change in defect size (%)	Mesial	-8.42 ± 30.19	-25.74 ± 22.46	0.125
	Distal	-21.95 ± 20.45	-23.17 ± 22.80	0.891
	Average	-15.19 ± 23.56	- 24.46 ± 19.00	0.300

major impact on PD reduction (1.69 ± 1.33 versus 2.71 ± 1.66, $P = 0.087$) and CAL gain (1.03 ± 1.48 versus 2.47 ± 1.84, $P = 0.051$). In the test group, within those cases presented with major exposure, CAL gain of 0.66 ± 1.57 mm, whereas those with no/minor exposure showed 3.13 ± 2.31 mm. The negative influence was seen in PD reduction in the test group, as major exposure cases showed 1.66 ± 1.26 mm, and no/minor exposure cases showed 3.63 ± 2.11 mm of PD reduction, which is statistically and clinically significant ($P<0.05$) (Please see Table S4 in online *Journal of Periodontology*).

4 | DISCUSSION

In this patient and examiner-masked randomized controlled clinical trial, both groups showed effective treatment outcome after 6 months. The adjunctive use of Er:YAG laser resulted in significantly greater pocket reduction in these advanced peri-implantitis lesions. The other clinical parameters and radiographic outcomes showed an average trend in favor of the use of Er:YAG laser, but no statistically significant difference between two groups was identified. Multiple confounding variables should be considered when interpreting the results of this study.

Clinical measurements of PD reduction and CAL gain were the primary outcomes of the study. PD was significantly reduced in both groups comparing to the baseline values, which showed effectiveness of both treatment modalities in reducing PD (1.85 versus 2.65 mm; control versus test group). Both groups had an average PD at 6 months below 6 mm (control: 4.59 mm, test: 5.08 mm), which can be considered a successful end-point for peri-implantitis treatment.[25] The test group showed statistically significant higher PD reduction compared to the control group, supporting the additional benefit of Er:YAG laser irradiation in regenerative treatment of peri-implantitis.

The rationale of using an Er:YAG laser could be helpful in treating peri-implantitis because of several reasons, including but not limited to: disinfecting the contaminated implant surface and bactericidal function around surrounding peri-implant tissues[13,14,26,27] without damaging the dental implant itself.[15,28] This is critical for an attempt of regeneration therapy to achieve re-osseointegration. Lasers for dental implant surface decontamination had been demonstrated to be beneficial in animal studies.[16,17] In addition, it's effect on soft tissue modulation to attenuate the hyper-inflammatory state, which is crucial in peri-implantitis compared to periodontitis lesions because it may help with ablating inflamed tissue and residual contaminated titanium particles. More in-depth mechanistic studies need to be conducted for further elucidation.

In an investigation by Schwarz et al.,[29] no statistically significant difference in PD reduction was found between Er:YAG laser group (1.7 ± 1.4 mm) compared to control group (2.4 ± 1.5 mm). It is worth mentioning that baseline average PD in Schwarz et al. was below 5.5 mm (control: 5.5 ± 1.8 mm, test: 5.1 ± 1.6 mm). Comparing these results to the present study, the baseline PD was 6 to 7 mm, which includes at least a 2 mm infrabony peri-implant defect. Additionally, Norton reported that PD reduction of laser treated implants averaged 2.7 mm (from 5.9 mm to 3.1 mm). However, no standard deviation was reported and the peri-implant PD increased after 1 year follow-up.[30] Another case series published by Clem et al. reported an average PD reduction of 2.9 mm (3.5 mm in deep sites),[31] in line with the reported results of this study.

According to present study, both modalities provided positive CAL gain compared to baseline (1.47 versus 1.90 mm; control versus test). Although the test group provided an averaged higher CAL gain than the control group, no statistical significance was found between groups. Additional site-based analysis of outcomes measures in the present study showed different patterns of CAL gain between buccal and lingual surfaces of the dental implant. The test group showed higher and consistent CAL gain on the lingual surface compared to buccal surface, although the differences did not reach statistical significance. The lingual side is usually characterized by thicker bone favoring infrabony vertical defect, which could be better irradiated with laterally-scattering laser tip and micro-explosions of Er:YAG laser.[32] The facial side of the implant could be significantly impacted by the position of the implant and membrane exposure. Given the high variability of the outcome measurements and the effective size in CAL gain, the sample size would require at least 300 to 400 patients in each group to have the power to detect statistical significance.

Many contributing factors have been identified in the literature to increase the risk of developing peri-implantitis; among most relevant, buccally-positioning of the fixture, crown emergence profile, history of periodontitis, subgingival excess cement, and tissue deficiencies.[1,33-35]

In the present study, GBR was aimed for reconstruction of soft and hard peri-implant tissues. Although previous studies used xenogenic grafts,[7,29,30,36,37] a composite allografts was used in the present study. Advantages of using allograft over xenograft is higher turnover rate, as the xenografts tend to stay intact in the long-term with slow metabolism.[38,39] In a previous in-vitro study,[17] allograft was also used and achieved a better bone-to-implant reosseointegration after laser decontamination of the implant surface. Radiographic analysis of the present study showed that although the peri-implant defect size

decreases about 15% to 25%, there was limited linear bone gain, and the difference between two groups failed to reach statistical significance. Schwarz et al.[29] did not report any quantitative analysis of radiographs. Authors described decreased translucency of the peri-implant defects using non-standardized radiographs. Norton[30] used xenogenic bone particles, which has lower bone turnover, leading to higher radio-opacity in the radiographs. Clem et al.[31] used allograft bone particles similar to present study, but provided limited information on how to assess their reported bone fill or standardization.

There were several differences in methodology in the present randomized clinical trial compared with the previous trials. Schwarz et. al.[29] only recruited cases with at least 2 mm of keratinized mucosa. Implantoplasty was performed for suprabony surfaces of the dental implants; however, based on the description in Schwarz et. al., there was no surface decontamination procedure prior to implantoplasty. Also, no isolation or protection of the peri-implant bony defect was implemented prior to implantoplasty. The risk and impact of dispersing contaminated titanium particles and dust into the surgical wound is of concern.[34] The present study utilized both bone wax as a barrier for the defect and decontamination of the surface prior to implantoplasty, to reduce the bacterial load of the titanium particles. However, the impact of titanium particles produced in this study to the treatment outcomes remain to be determined.

In the present study, bone graft particles were covered by an ADM (versus absorbable collagen membrane with porcine origin)[36,37] aimed to increase soft tissue thickness. Collagen membrane is thinner and absorbs quicker than ADM, with no or limited soft tissue enhancement properties. However, ADM may have a higher tendency for exposure because of increased thickness. Some authors do not consider membrane exposure with ADM as a critical factor for the success of GBR.[40,41] Studies have showed that the use of a membrane may not be useful for a GBR procedures when treating peri-implantitis; even with use of a resorbable membrane, there is a chance of membrane exposure as well.[42,43] In the present study, the membrane exposure occurred to at different levels in each patient. Membrane exposure to the oral cavity may lead to early degradation of the ADM by salivary enzymes and bacterial colonization, which can adversely affect the regenerative potential of the membrane. Additional statistical analysis showed significant adverse effect of major exposure on PD reduction and CAL gain. It is likely that the additional benefit of the Er;YAG laser irradiation in adjunction to regenerative therapy were higher in case of flap integrity and membrane confinement after the surgery. Garcia and colleagues in 2018 reviewed the effects of membrane exposure in GBR procedures of peri-implant defects. They reported 27% difference in dehiscence reduction between sites with and without membrane exposure post-surgically.[44]

The present randomized clinical trial needs to be perceived with its limitations. The sample size was relatively small and patients were followed for a short-term of 6 months. The sub-ideal randomization system and non-surgical treatment was not performed prior to the surgery. Additionally, implant crown restorations could have been removed for improved probing assessment and primary closure for enhanced treatment outcomes. However, the practicality of not removing the crown was also considered. A larger sample size of patients, categorized based on the etiologic and contributing factors with follow-up $>$ 6 months is recommended to evaluate the efficacy of Er:YAG laser as an adjunct tool for the treatment of peri-implantitis.

5 | CONCLUSION

Within the limitations of this pilot study, the use of Er-YAG laser during peri-implantitis regenerative therapy may aid in better probing PD reduction. Managing to avoid post-operative membrane exposure would enhance clinical outcomes significantly. Nonetheless, a larger sample size and longer follow-up is needed to confirm if Er:YAG laser irradiation provides additional clinical benefits during peri-implantitis regenerative therapy.

ACKNOWLEDGMENTS

The authors thank Dr. William Giannobile (Department of Periodontics and Oral Medicine, the University of Michigan School of Dentistry) for his advice on the study design and critically reading the manuscript. This study was supported by grants from J. Morita (Tokyo, Japan) and the Department of Periodontics and Oral Medicine Clinical Research Fund. We also would like to thank the support from BioHorizons (Alabama, USA) for the biomaterials.

CONFLICT OF INTEREST

Dr. HL Wang has occasionally spoken on behalf of J. Morita and received honoraria for lectures. The other authors do not have any financial interests, either directly or indirectly, in the products or information listed in the article.

AUTHOR CONTRIBUTIONS

CWW contributed to study conception, design, performing surgeries, data analysis, drafting of the article; SA and RD contributed to manage study visits, data analysis, drafting of the article; MA and JK contributed to study coordination, data collection, and critical review of the manuscript.

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REFERENCES

1. Schwarz F, Derks J, Monje A, Wang HL. Peri-implantitis. *J Periodontol*. 2018;89 Suppl 1:S267-S290.
2. Derks J, Tomasi C. Peri-implant health and disease. A systematic review of current epidemiology. *J Clin Periodontol*. 2015;42 Suppl 16:S158-171.
3. Papathanasiou E, Finkelman M, Hanley J, Parashis AO. Prevalence, etiology and treatment of peri-Implant mucositis and peri-Implantitis: a survey of periodontists in the united states. *J Periodontol*. 2016;87:493-501.
4. Renvert S, Widen C, Persson RG. Cytokine and microbial profiles in relation to the clinical outcome following treatment of peri-implantitis. *Clin Oral Implants Res*. 2017;28:1127-1132.
5. Suarez-Lopez Del Amo F, Yu SH, Wang HL. Non-surgical therapy for peri-Implant diseases: a systematic review. *J Oral Maxillofac Res*. 2016;7:e13.
6. Berglundh T, Jepsen S, Stadlinger B, Terheyden H. Peri-implantitis and its prevention. *Clin Oral Implants Res*. 2019;30:150-155.
7. Roccuzzo M, Pittoni D, Roccuzzo A, Charrier L, Dalmasso P. Surgical treatment of peri-implantitis intrabony lesions by means of deproteinized bovine bone mineral with 10% collagen: 7-year-results. *Clin Oral Implants Res*. 2017;28:1577-1583.
8. Berglundh T, Wennstrom JL, Lindhe J. Long-term outcome of surgical treatment of peri-implantitis. A 2-11-year Retrospective Study. *Clin Oral Implants Res*. 2018;29:404-410.
9. Faggion CM, Jr., Listl S, Fruhauf N, Chang HJ, Tu YK. A systematic review and Bayesian network meta-analysis of randomized clinical trials on non-surgical treatments for peri-implantitis. *J Clin Periodontol*. 2014;41:1015-1025.
10. Chan HL, Lin GH, Suarez F, MacEachern M, Wang HL. Surgical management of peri-implantitis: a systematic review and meta-analysis of treatment outcomes. *J Periodontol*. 2014;85:1027-1041.
11. Tomasi C, Regidor E, Ortiz-Vigon A, Derks J. Efficacy of reconstructive surgical therapy at peri-implantitis-related bone defects. A systematic review and meta-analysis. *J Clin Periodontol*. 2019;46 Suppl 21:340-356.
12. Claffey N, Clarke E, Polyzois I, Renvert S. Surgical treatment of peri-implantitis. *J Clin Periodontol*. 2008;35:316-332.
13. Hauser-Gerspach I, Stubinger S, Meyer J. Bactericidal effects of different laser systems on bacteria adhered to dental implant surfaces: an in vitro study comparing zirconia with titanium. *Clin Oral Implants Res*. 2010;21:277-283.
14. Kreisler M, Kohnen W, Marinello C, et al. Bactericidal effect of the Er:YAG laser on dental implant surfaces: an in vitro study. *J Periodontol*. 2002;73:1292-1298.
15. Takagi T, Aoki A, Ichinose S, et al. Effective removal of calcified deposits on microstructured titanium fixture surfaces of dental implants with erbium lasers. *J Periodontol*. 2018;89:680-690.
16. Takasaki AA, Aoki A, Mizutani K, Kikuchi S, Oda S, Ishikawa I. Er:YAG laser therapy for peri-implant infection: a Histological Study. *Lasers Med Sci*. 2007;22:143-157.
17. Nevins M, Nevins ML, Yamamoto A, et al. Use of Er:YAG laser to decontaminate infected dental implant surface in preparation for reestablishment of bone-to-implant contact. *Int J Periodontics Restorative Dent*. 2014;34:461-466.
18. Shibli JA. Is laser the best choice for the treatment of peri-implantitis? *Photomed Laser Surg*. 2018;36:569-570.
19. Aoki A, Mizutani K, Schwarz F, et al. Periodontal and peri-implant wound healing following laser therapy. *Periodontol 2000*. 2015;68:217-269.
20. Gholami L, Asefi S, Hooshyarfard A, et al. Photobiomodulation in periodontology and Implant dentistry: part 1. *Photobiomodul Photomed Laser Surg*. 2019;37:739-765.
21. Lin GH, Suarez Lopez Del Amo F, Wang HL. Laser therapy for treatment of peri-implant mucositis and peri-implantitis: an American Academy of periodontology best evidence review. *J Periodontol*. 2018;89:766-782.
22. Hurwitz EE, Simon M, Vinta SR, et al. Adding examples to the ASA-physical status classification improves correct assignment to patients. *Anesthesiology*. 2017;126:614-622.
23. Loe H. The gingival index, the plaque index and the retention index systems. *J Periodontol*. 1967;38:Suppl:610-616.
24. Monje A, Pons R, Insua A, Nart J, Wang HL, Schwarz F. Morphology and severity of peri-implantitis bone defects. *Clin Implant Dent Relat Res*. 2019;21:635-643.
25. Berglundh T, Armitage G, Araujo MG, et al. Peri-implant diseases and conditions: consensus report of workgroup 4 of the 2017 world workshop on the classification of periodontal and peri-implant diseases and conditions. *J Clin Periodontol*. 2018;45 Suppl 20:S286-S291.
26. Tosun E, Tasar F, Strauss R, Kivanc DG, Ungor C. Comparative evaluation of antimicrobial effects of Er:YAG, diode, and CO(2) lasers on titanium discs: an Experimental Study. *J Oral Maxillofac Surg*. 2012;70:1064-1069.
27. Stubinger S, Henke J, Donath K, Deppe H. Bone regeneration after peri-implant care with the CO2 laser: a fluorescence Microscopy Study. *Int J Oral Maxillofac Implants*. 2005;20:203-210.
28. Stubinger S, Etter C, Miskiewicz M, et al. Surface alterations of polished and sandblasted and acid-etched titanium implants after Er:YAG, carbon dioxide, and diode laser irradiation. *Int J Oral Maxillofac Implants*. 2010;25:104-111.
29. Schwarz F, Sahm N, Iglhaut G, Becker J. Impact of the method of surface debridement and decontamination on the clinical outcome following combined surgical therapy of peri-implantitis: a randomized controlled Clinical Study. *J Clin Periodontol*. 2011;38:276-284.
30. Norton MR. Efficacy of Er:YAG laser in the decontamination of peri-implant disease: a one-year prospective closed cohort study. *Int J Periodontics Restorative Dent*. 2017;37:781-788.

31. Clem D, Gunsolley JC. Peri-implantitis treatment using Er:YAG laser and bone grafting. a prospective consecutive case series evaluation: 1 year posttherapy. *Int J Periodontics Restorative Dent*. 2019;39: 479-489.
32. Yamamoto A, Tanabe T. Treatment of peri-implantitis around TiUnite-surface implants using Er:YAG laser microexplosions. *Int J Periodontics Restorative Dent*. 2013;33:21-30.
33. Katafuchi M, Weinstein BF, Leroux BG, Chen YW, Daubert DM. Restoration contour is a risk indicator for peri-implantitis: a cross-sectional radiographic analysis. *J Clin Periodontol*. 2018;45:225-232.
34. Wilson TG, Jr. The positive relationship between excess cement and peri-implant disease: a prospective clinical endoscopic study. *J Periodontol*. 2009;80:1388-1392.
35. Monje A, Aranda L, Diaz KT, et al. Impact of maintenance therapy for the prevention of peri-implant diseases: a systematic review and meta-analysis. *J Dent Res*. 2016;95:372-379.
36. Mercado F, Hamlet S, Ivanovski S. Regenerative surgical therapy for peri-implantitis using deproteinized bovine bone mineral with 10% collagen, enamel matrix derivative and Doxycycline-A prospective 3-year cohort study. *Clin Oral Implants Res*. 2018;29:583-591.
37. Renvert S, Roos-Jansaker AM, Persson GR. Surgical treatment of peri-implantitis lesions with or without the use of a bone substitute-a randomized clinical trial. *J Clin Periodontol*. 2018;45:1266-1274.
38. Lee D-W, Pi S-H, Lee S-K, Kim E-C. Comparative histomorphometric analysis of extraction sockets healing implanted with bovine xenografts, irradiated cancellous allografts, and solvent-dehydrated allografts in humans. *Int J Oral Maxillofac Implants*. 2009;24:609-615.
39. Jensen SS, Broggini N, Hjørting-Hansen E, Schenk R, Buser D. Bone healing and graft resorption of autograft, anorganic bovine bone and β-tricalcium phosphate. A histologic and histomorphometric study in the mandibles of minipigs. *Clin Oral implants Res*. 2006;17:237-243.
40. Fowler EB, Breault LG, Rebitski G. Ridge preservation utilizing an acellular dermal allograft and demineralized freeze-dried bone allograft: part II. Immediate endosseous implant placement. *J Periodontol*. 2000;71:1360-1364.
41. Park SH, Lee Kw, Oh TJ, Misch CE, Shotwell J, Wang HL. Effect of absorbable membranes on sandwich bone augmentation. *Clinical Oral Implants Res*. 2008;19:32-41.
42. Klinge B, Meyle J, Working G. Peri-implant tissue destruction. The third EAO Consensus Conference 2012. *Clin Oral Implants Res*. 2012;23 Suppl 6:108-110.
43. Heitz-Mayfield LJ, Needleman I, Salvi GE, Pjetursson BE. Consensus statements and clinical recommendations for prevention and management of biologic and technical implant complications. *Int J Oral Maxillofac Implants*. 2014;29 Suppl:346-350.
44. Garcia J, Dodge A, Luepke P, Wang HL, Kapila Y, Lin GH. Effect of membrane exposure on guided bone regeneration: a systematic review and meta-analysis. *Clin Oral Implants Res*. 2018;29:328-338.

SUPPORTING INFORMATION

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

How to cite this article: Wang CW, Ashnagar S, Di Gianfilippo R, Arnett M, Kinney J, Wang HL. Laser-assisted regenerative surgical therapy for peri-implantitis: A randomized controlled clinical trial. *J Periodontol*. 2021;92:378–388. https://doi.org/10.1002/JPER.20-0040