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RESEARCH

Stability of peri-implantitis surgical reconstructive therapy—a (> 2 years) follow-up of a randomized clinical trial

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Abstract

Objectives This follow-up study aimed to report the 24- and 30-month outcomes of a cohort previously enrolled in a randomized clinical trial on surgical reconstructive treatment of peri-implantitis.

Methods Twenty-four patients were diagnosed with peri-implantitis and treated with surgical reconstructive therapy with or without the adjunctive use of Er:YAG laser. Within-group and between-group comparisons were tested with mixed model with repeated measures.

Results Regarding peri-implant pocket depth (PPD) reduction (control vs. laser test group) between 6 months (− 1.85 vs. − 2.65 mm) and 30 months (− 1.84 vs. − 3.04 mm), the laser group showed statistically significant changes but not the control group. In terms of radiographic marginal bone loss (RMBL) at 6 months (− 1.1 vs. − 1.46 mm) to 24 months (− 1.96 vs. − 2.82 mm), both groups showed statistical difference compared to baseline. The six explanted implants all were featured by severe peri-implantitis and mostly with no or limited keratinized tissue (< 2 mm) at baseline and membrane exposure after surgery. Among the 15 retained cases, eight cases achieved more than 50% peri-implant bone level gain.

Conclusions Within the limitation and follow-up time frame of this trial, the outcome of the surgical reconstructive therapy sustained or improved in most of the cases. However, 25% of the implants with severe peri-implantitis failed 2 years after the surgical reconstructive therapy. The use of Er:YAG laser favors PPD reduction in the longer term up to 30 months.

Clinical relevance Longer-term follow-up on reconstructive therapy of peri-implantitis revealed sustained or improved stability in certain cases, but the survival of implants with severe peri-implantitis has its limitation, especially when there is limited keratinized tissue (< 2 mm or no KT).

Trial registration Clinical Trials Registration Number: NCT03127228 and HUM00160290.

Keywords Humans · Dental implants · Peri-implantitis · Laser therapy · Treatment outcome · Follow-up studies

Introduction

Peri-implantitis is an emerging disease that remains a major challenge for dental professionals to manage. Prevalence of peri-implantitis was reported to be around 22% [1], but there is no predictable treatment established. Overall, surgical treatment is more effective to obtain favorable results compared to non-surgical treatment [2–5]; however, long-term outcome is still under investigation. One of the primary concerns is the relapse of the disease since complete resolution of peri-implantitis to fully stabilize disease progression can be difficult to achieve. From available long-term follow-up studies, the disease recurrence rate can be as high as 60%, and many of the implants failed to survive [6, 7]. In addition to disease control, another ultimate goal is to regenerate lost bone to restore bony support on previously diseased implant surfaces via re-osseointegration. Although several retrospective case series with reconstructive therapy have been published [8, 9], prospective trials are still scarce [10, 11]. Analysis of long-term trials reported a dramatic decrease in implant survival rate after treatment of peri-implantitis over the years (3 vs.

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5 years, 99 to 86%) [12]. Therefore, there is an urgent need for standardized and more consistent reporting of long-term results from prospective clinical trials on peri-implantitis, especially on surgical reconstructive therapy.

One of the main challenges in reconstructive treatment for peri-implantitis is to decontaminate the implant surface for re-osseointegration [13]. The use of Er:YAG laser has been proposed and demonstrated as an effective tool for implant surface decontamination and thus presented as a promising adjunct for the treatment of peri-implantitis [8, 9, 14, 15]. A pilot long-term investigation from Schwarz et al. with a combined resective and regenerative approach showed limited adjunct benefit with the use of erbium laser in pocket reduction. However, the recruited cases seemed to have mild to moderate severity of peri-implantitis with limited vertical bony defect for regenerative approach (baseline averaged peri-implant probing depth (PPD): 5.1 – 5.5 mm) [10, 16, 17]. Previously, our group had conducted a randomized controlled clinical trial including more advanced peri-implantitis cases (baseline PPD: ~ 7.2 mm) investigating the adjunctive efficacy of Er:YAG laser on the reconstructive treatment for peri-implantitis [18]. The application in this clinical trial included thorough irradiation of the contaminated implant surface and low-energy attenuation of the peri-implant inflamed flap inner pocket lining surgically. Er:YAG laser was used to decontaminate implant surface first before resection procedures to avoid the spread of contaminated titanium particles. Other measures like the placement of bone wax in the bony defect and with high-powered vacuum also limit the accumulation of titanium particles in the peri-implant tissue. Copious saline irrigation was also applied in both groups. The initial 6 months result showed a significant favorable result in peri-implant pocket depth reduction in the laser test group, especially in a more contained peri-implant defect. However, 6-month follow-up is still considered a short-term assessment, and a longer-term outcome of reconstructive therapy is of great interest to the field.

Therefore, this study was conducted to report the 24- to 30-month follow-up results from the previous randomized clinical trial on surgical reconstructive therapy for peri-implantitis.

Methods and materials

A 6-month randomized controlled clinical trial on surgical reconstructive treatment of peri-implantitis with or without Er:YAG laser irradiation [18] was conducted in the Graduate Periodontics Clinic at the Department of Periodontics and Oral Medicine at the University of Michigan (UM). The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013 and after approval by the UM human subject ethics board (HUM00124386) as well as registration with ClinicalTrials.gov (NCT03127228). The same patient cohort was invited to participate in this follow-up study and to attend additional examinations at 24, 27, and 30 months after peri-implantitis treatment. The follow-up study was approved by the Institutional Board (HUM00160290) before initiation.

Follow-up trial design and patient enrollment

For this follow-up trial, all patients in the cohort were contacted via mail followed by phone call to invite them for enrollment in this study. All participants signed an informed consent before enrolling into this study. Patients were scheduled for a 24-month (2-year) post-operative follow-up visit followed by two 3-month re-call appointments. Therefore, the final follow-up time was 30 months (2 years and 6 months) after the initial reconstructive surgical therapy. Periodontal and peri-implant maintenance was designed to be performed every 3 months within this period. Due to the interruption of clinical and research activities during the 2019 Coronavirus Disease (COVID-19) pandemic, several patients were not able to comply with the scheduled visits for 27 and 30 months. However, every patient received the 24-month examination and at least one examination between 27 and 30 months after peri-implantitis treatment.

Inclusion criteria and study groups

The inclusion and exclusion criteria for the trial have been previously reported in Wang et al. (2020) [18]. Briefly, patients with at least one dental implant diagnosed with peri-implantitis (probing depth (PD) $\geq$ 5 mm with bleeding on probing (BOP) and/or suppuration) and more than 2 mm infrabony defect were included. Both groups received surgical reconstructive therapy, including mechanical debridement and bone grafting with guided bone regeneration with particulate bone allograft. In the test group, additional Er:YAG laser (AdvErL EVO, J. MORITA MFG. CORP, Kyoto, Japan) was used for implant surface decontamination and tissue modulation. Composite graft included 3:1 ratio of allograft and demineralized bone fibers (MinerOss and Grafton, BioHorizons, Birmingham, Alabama) were used for grafting and absorbable acellular dermal matrix (Alloderm GBR, BioHorizons, Birmingham, Alabama) membrane was also adapted to cover the defect with a non-submerged approach. For more details about the surgical procedure and related methods, please refer to Wang et al. (2020) [18].

Clinical and radiographic examination

Clinical and radiographic evaluations were recorded consistently with the previously published methods [18]. PPD was measured as the linear distance in millimeters from the free mucosal margin to the probe tip during light-force probing. Recession (REC) was measured as the linear distance in millimeters from the crown-abutment margin to the free mucosal margin. Standardized intraoral periapical radiographs were obtained with the use of the same personalized occlusal registration bite previously used during the trial by Wang et al. (2020) [18]. Radiographic marginal bone loss (RMBL) was measured as the radiographic linear distance from the implant platform to the first bone-to-implant contact. All new clinical and radiographic diagnostics were performed by a single calibrated examiner (RDG) whose intra-examiner agreement [ICC (95% CI)] was 0.87 (0.62–0.96) for PPD and 0.89 (0.53–0.97) for REC. Prior to the clinical phases of this follow-up study, a calibration session reported an inter-examiner agreement [ICC (95% CI)] of 0.80 for PD (0.74–0.84; 95% CI) and 0.78 for REC (0.69–0.84; 95% CI) between RDG and the examiners of the 6-month trial.

Statistical analysis

The data were analyzed using Mixed Models to account for the repeated measures over time. The analysis followed intention to treat principle, where all randomized subjects with available data, including those with partial follow-up data, were part of the analysis and analyzed based on their assigned group. The overall plot figure of the clinical and radiographic outcomes was presented with averaged mean at each time point. Mixed models using the Full Information Maximum Likelihood (FIML) estimate were used for the comparison within each group and also comparing delta changes between two groups over the study period. Within group testing, the values at each follow-up time point versus its baseline measures were compared. Comparative data between groups associated with mixed model used mean ± standard error (SE). Statistical significance was set to be a two-sided p value < 0.05.

Results

Twenty-four patients were diagnosed with peri-implantitis, treated with surgical reconstructive therapy, and successfully completed 6 months of follow-up without any implant failure [18]. Two years after treatment, all patients were contacted again and invited to participate in this follow-up trial. Three patients declined participating and dropped out from the study, two in the control group and one in the laser group. Reported reasons were long distance from study location ($n = 2$) and fear of coronavirus disease ($n = 1$). Of the 21 patients who accepted and presented at research examination, a total of six implants were lost, three in each group. Implant loss was defined as the implant missing at the time of 2-year follow-up or implant in need of removing at the 24-month examination because of symptomatic presentation. A total of 15 patients, seven patients in the control group and eight for the test (laser) group, completed this follow-up trial and retained the treated implant throughout 30 months after treatment (Fig. 1).

Between- and within-group comparisons for clinical and radiographic variables have been reported in Table 1 and Supplemental Table 1. Both groups had a significant PPD reduction at 6 months after the surgical treatment, resulting in an averaged PPD of 4.6 vs. 5.1 mm, control vs. laser group respectively. Between 24 and 30 months, while the averaged PPD continued to decrease in the laser group (4.4 to 4.3 mm), there was a small increase of the PPD in the control group but overall sustained its outcome (4.8 to 4.83 mm). In terms of the clinical attachment level (CAL), in the control group, the level improved from 6.9 to 5.5 mm at 6 months and increased to 5.8 mm at 30 months; whereas in the laser group, it changed from 7.4 to 5.5 and finally to 5.4 mm after 30 months.

Due to missing data with the lost implants and dropouts, a mixed model with repeated measures was used to account for the missing data and compare the results within and between groups. For PPD reduction, both groups had a statistically significant reduction after 6 months (− 1.85 vs. − 2.65 mm; control vs. laser, both groups p *value* < 0.001); however, at 30 months the statistical significance only existed within the laser group (− 1.84 vs. − 3.04 mm; control vs. laser; p *value* = 0.06 vs. 0.0002) (Table 1 and Fig. 2).

The RMBL decreased in both groups over time after reconstructive therapy. Both groups included severe peri-implantitis lesions yielding deep baseline infraosseous defect measures (7.3 vs. 7.7 mm; control vs. laser group). At 6- and 24-month follow-up, both groups had significant continued reduction in defect depth (2.4 vs. 3.2 mm at 24 months; control vs. laser group; p *value* = 0.003 vs. < 0.0001) yet no statistical significance between two groups. In the control group, the bone level changed from 6.2 to 4.9 mm whereas in the laser test group decreased from 6.3 to 4.5 mm. There is a statistically significant reduction in the bony defect depth in each group (− 1.96 vs. − 2.82 mm; control vs. laser); however, there is no statistical significance between two treatment groups with the mixed model analysis (Fig. 2). Considering baseline defect depth, among the 15 retained cases, eight cases achieved more than 50% peri-implant bone level gain. There is also some minor varied pattern in terms of the bone level over mesial or distal surfaces of the implant. Despite wide variation, at 24 months, both groups seemed

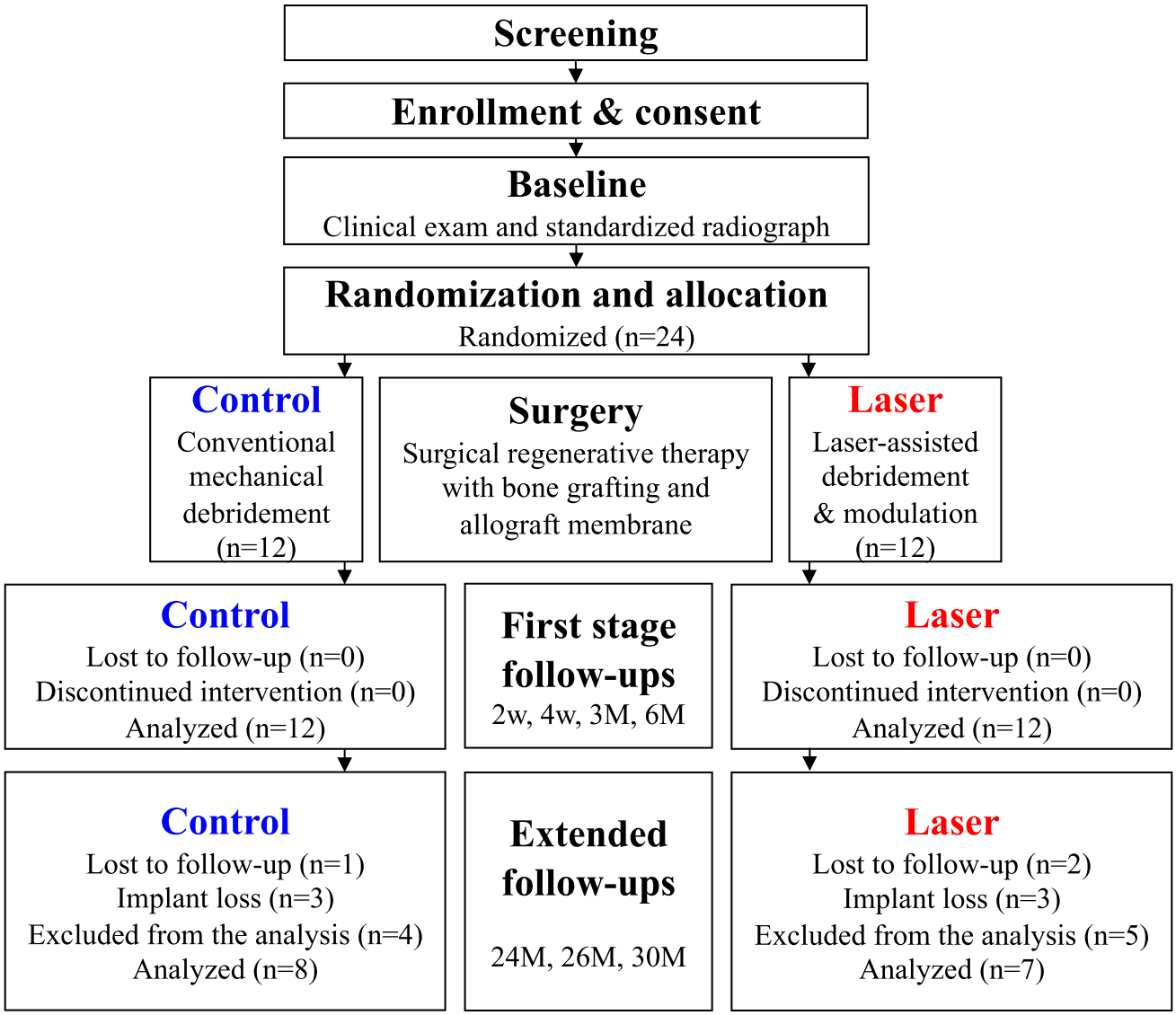


Fig. 1 CONSORT clinical trial diagram. A total of 24 patients were originally included. Six implants were removed after two and a half years (three in each group). Three patients dropped out (moved out of state, fear of COVID-19, and transportation issues), resulting in seven patients in the control group and eight in the test group at the end of this follow-up study

to reach similar bone level over the mesial site but slightly higher averaged level over the distal site of the implant in laser group (Supplemental Fig. 1). On radiographic assessment, a few cases showed continued improvement between 6 and 24 months over bone-to-implant contact with quality trabecular bone and lamina dura reconstructed. Two representative cases in the laser group restored nearly to its original marginal bone level (Fig. 3). At 6 months (yellow arrow), improvement in radiographic bone fill and linear bone gain restores the original bone loss, and after 2 years, complete restoration of the bone loss was noted with transition in bone-to-implant contact also evident (green arrow).

Within the follow-up cohort, two cases also experienced relapse of the treatment outcome. Representative cases in both groups with relapsed peri-implantitis were presented in Fig. 4. Radiographic bone fills at 6 months were lost after 2 years. Both cases presented with signs of clinical inflammation at 2-year follow-up, including bleeding tendency and minor erythematous of the peri-implant mucosa.

Discussion

This study followed up the patient cohort previously published in Wang et al. (2020) [18] up to 30 months after treatment of peri-implantitis. Notably, while all treated implants were maintained during the first 6 months, six out of 24 implants lost osseointegration or were explanted because of

Table 1 Thirty-month treatment outcome following surgical reconstructive therapy for peri-implantitis

Peri-implant	Groups	Baseline	3 months	6 months	24 months	30 months
Peri-implant probing depth (mm)	Control	6.44 ± 1.07	5.04 ± 0.88	4.59 ± 0.72	4.81 ± 2.57	4.83 ± 2.96
	Laser	7.73 ± 1.95	6.00 ± 1.63	5.08 ± 1.76	4.43 ± 1.94	4.25 ± 1.47
	ΔControl	-	− 1.40 ± 0.40***	− 1.85 ± 0.45***	− 1.65 ± 1.01	− 1.84 ± 1.00
	ΔLaser	-	− 1.74 ± 0.40***	− 2.65 ± 0.45***	− 2.84 ± 1.01**	− 3.04 ± 1.00**
	ΔDifference	-	0.33 ± 0.56	0.81 ± 0.64	1.19 ± 1.43	1.20 ± 1.41
Clinical attachment level (mm)	Control	6.94 ± 1.23	6.04 ± 0.93	5.47 ± 0.96	5.63 ± 1.70	5.80 ± 2.04
	Laser	7.43 ± 1.91	6.05 ± 1.41	5.52 ± 1.57	5.52 ± 2.13	5.44 ± 1.93
	ΔControl	-	− 1.18 ± 0.47*	− 1.65 ± 0.54**	− 1.86 ± 1.01	− 1.77 ± 0.99
	ΔLaser	-	− 1.38 ± 0.47**	− 1.90 ± .054***	− 1.75 ± 1.01	− 1.84 ± 0.99
	ΔDifference	-	0.19 ± 0.66	0.25 ± 0.76	− 0.11 ± 1.42	0.07 ± 1.40
Radiographic bony defect level (mm)	Control	7.31 ± 068	-	6.21 ± 0.68	4.90 ± 0.83	-
	Laser	7.77 ± 0.68	-	6.31 ± 0.68	4.57 ± 0.83	-
	ΔControl	-	-	− 1.10 ± 0.37**	− 1.96 ± 0.46***	-
	ΔLaser	-	-	− 1.46 ± 0.37***	− 2.82 ± 0.46****	-
	ΔDifference	-	-	0.36 ± 0.53	0.86 ± 0.64	-

Within group comparison to baseline ($p < 0.05$; ** $p < 0.01$; *** $p < 0.001$)

hopeless prognosis between 6 months and 2 years, leading to an implant failure rate that was 0% at 6 months but 25% as early as 2 years after peri-implantitis treatment.

Most survived cases exhibited improvement or sustainment in PPD, CAL, and RMBL throughout the follow-up. On the other hand, implants that failed were commonly featured by progressive deepening of PPD and unfavorable changes in RMBL, together with episodes of peri-implant abscesses. In the light of these observations, a more definitive outcome assessment after reconstructive therapy of peri-implantitis should occur at least 2 years after the treatment. The initial response from 6-month follow-up may suggest its long-term trajectory in most cases, but a few cases may have different longer-term prognosis and stability.

In this clinical trial, the overall mean PPD reduced from 7 to 4.5 mm for the 15 implants that were included after 2 years. Very similar results were documented in the case series of Yamamoto et al. (2021) [9] who reduced the average peri-implant pocket depth from 7.7 to 4.5 mm with laser-assisted peri-implantitis treatment. Similar to our cohort, Clem et al. (2019) [8] observed more favorable outcomes for probing depth reduction for implants with shallower baseline PPD as opposed to less favorable outcomes for implants with severe baseline disease presentation. In our cohort, the laser test group had a deeper PPD at baseline but concluded the study with shallower pockets after 30 months, thus documented continued improved PPD reduction throughout the study period (Table 1). Despite that, due to statistical power, no difference between groups was noted for PPD changes, nor for PPD at any timepoint between laser and control groups.

Among all the 15 retained cases, eight cases achieved more than 50% of peri-implant bone level gain and four cases about 20–50%. Among the eight good responders (radiographic bone gain > 50%), they were equally distributed in each group, but only two cases had more than 90% quality bone gain, and both were part of the laser group (Fig. 2). For four cases with moderate response (20–50% bone gain), one case was enrolled in the control group and three cases in the laser group. In a previous case series with the adjunct use of Er:YAG laser for reconstructive therapy, around half of the patients achieved more than 50% radiographic bone fill [8], and in the other case series of 12 patients, peri-implant bony defect reduced from 47 to 21% at 12 months [9]. Those are consistent with the findings from our clinical trial.

Qualitative assessment of the radiographic bone fill can be critical to evaluate the stability of the regenerated bone. One must acknowledge that radiographic bone fill is not equivalent to true regeneration; we are unable to assess the defined regenerative outcome without histology. There appear to be multiple factors that might impact the outcome, including defect morphology, prosthetic emergence profile, and most importantly, host immunologic factors [18]. The immune landscape of the peri-implantitis granulation tissue could be the driving force for disease progression. Therefore, recent cutting-edge research devoted to deconvolute the immunoscore revealed that it predicts the initial treatment outcome and defines the early re-colonization pattern of the periodontal pathogens. Some key immune cell profile and genetic features were also identified that shapes the immune landscape. This immune landscape profiling as a proof-of-principle takes the initiative to define peri-implant disease biotype for future diagnostics. In line with the host factor, one of the cases in this trial showed moderate response after 6 months but progressed aggressively between 6 and 24 months ended with loss implant. Associated with the

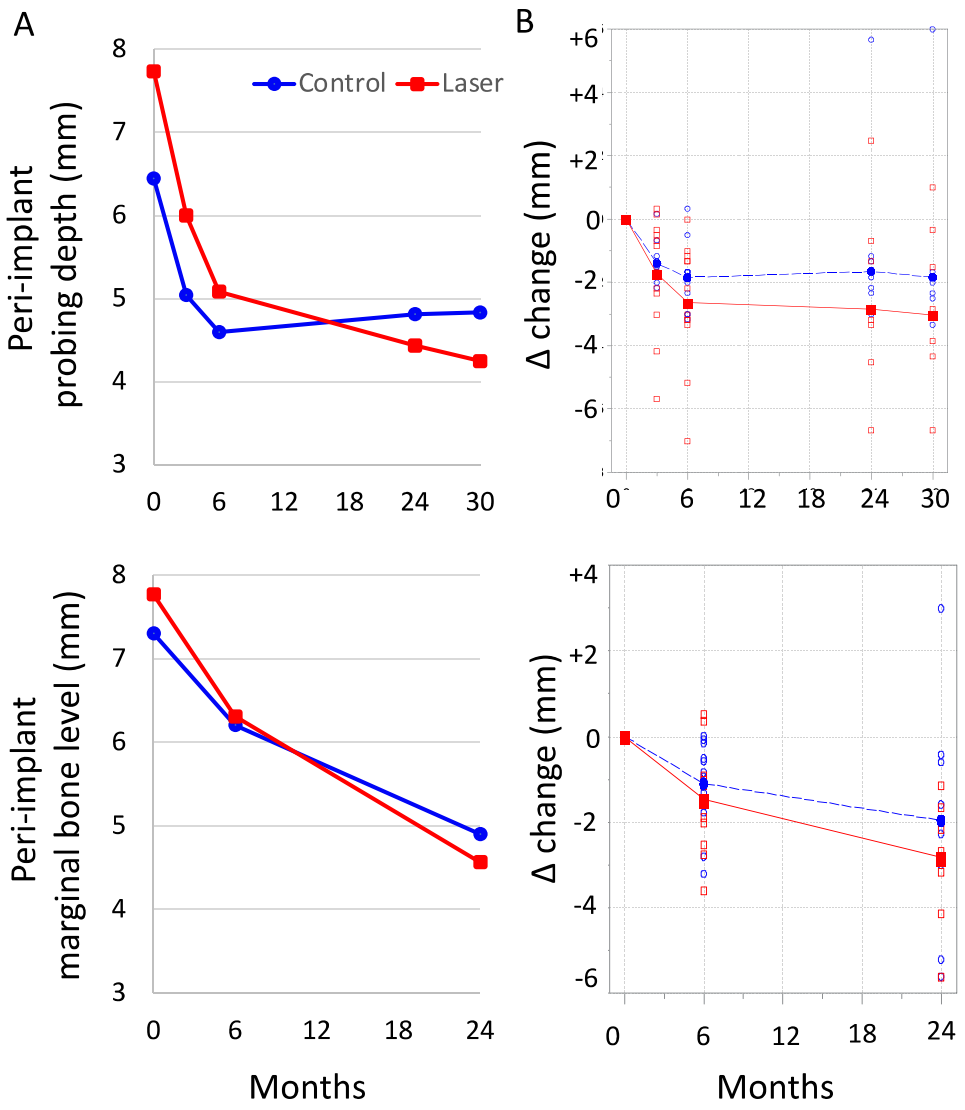


Fig. 2 Thirty-month follow-up of the treatment outcome on peri-implant probing depth reduction and radiographic marginal bone gain. **A** Averaged peri-implant probing depth and peri-implant radiographic marginal bone level. **B** Changes compared to baseline with a statistical mixed model with repeated measures to account for missing data

COVID-19 pandemic, the patient disclosed devastating job and family emergency tragedies that caused significant stress [19]. This raised the hypothesis that stress-induced compromised host response may impact peri-implant disease progression and the outcome of reconstructive therapy.

Regarding the implant loss and survival, the overall 2-year survival rate was 75%; however, for cases with baseline advanced peri-implantitis (baseline RMBL > 50%), the survival rate was 57%. Within the same institute, the survival rate in the advanced peri-implantitis cases is 60.7% (mean follow-up time is 3.5 years), and the odds ratio of implant loss is about 20 times higher compared to mild peri-implantitis cases (bone loss < 25%) [20]. Within our knowledge, the first clinical trial on the effectiveness of Erbium laser on surgical combined therapy for peri-implantitis had no reported lost implants after 2 years [17], but only four implants out of 32 had severe re-infection after 7 years despite many subjects lost to follow-up (13 subjects lost follow) [10]. This might be attributed to the initial severity of the peri-implantitis disease being mild since the probing depth average was below 5.5 mm [16]. Another long-term prospective trial investigating the use of Enamel Matrix Derivatives (EMD) on the surgical treatment of peri-implantitis had a 1-year survival rate of about 90%, but after 3 and 5 years, it dropped to 80% and 68% respectively [21]. Therefore, survival rate in advanced peri-implantitis cases still needs further investigations to refine our case selection and inform our clinical decision-making.

In our trial, all failed implant loss cases had compromised healing from major membrane exposure except two cases: one of which had a fractured fixture and the other suspected loss of integration from mechanical overload. All implants received significant occlusal load and displayed limited keratinized tissue at the baseline (Supplemental Table 2). In our previous published study[20], prognostic factors not only included baseline bone level, but also history of periodontitis and maintenance compliance. Since the patients in this trial were

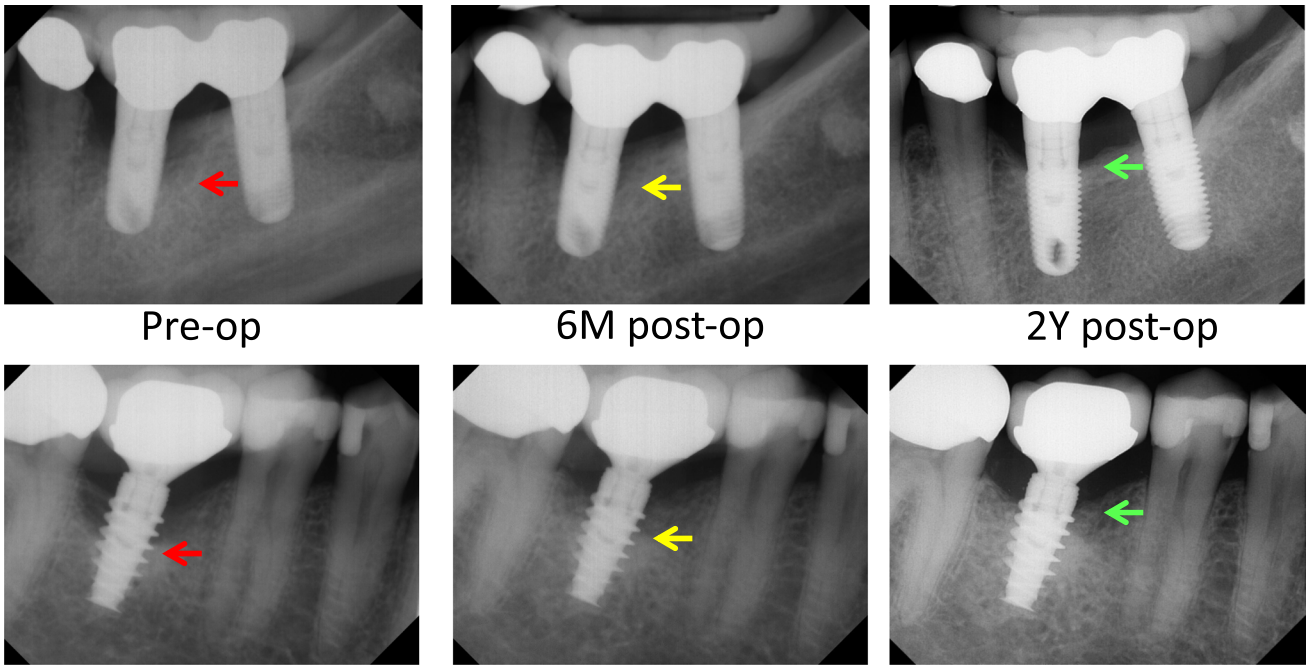


Fig. 3 Representative case and radiographic qualitative assessment supporting re-establishment of osseointegration over previously diseased implant surface after laser-assisted reconstructive therapy of peri-implantitis

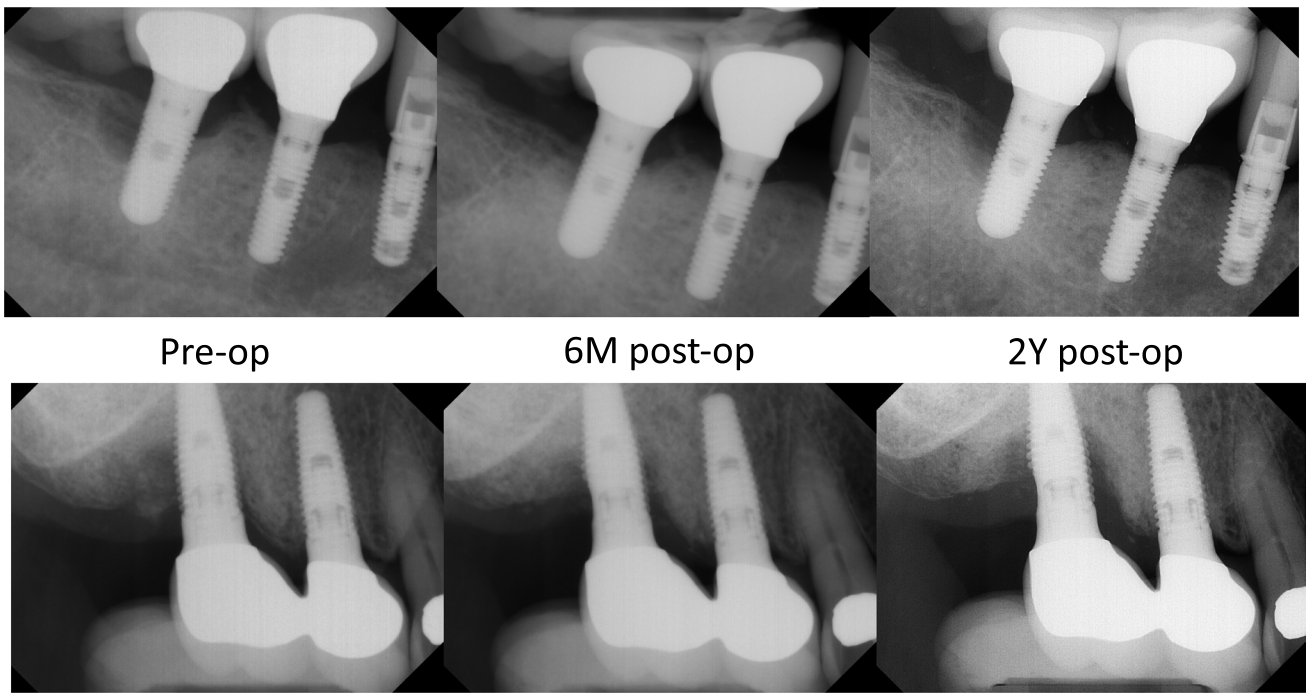


Fig. 4 Relapsed peri-implantitis cases after reconstructive therapy. The top panel case was enrolled in the control group, while the bottom panel case was enrolled in the test group

mostly referred from outside private practices, maintenance program between 6 and 24 months took place in the referring office. Additionally, due to the impact of coronavirus disease (COVID-19) pandemic, several patients also missed maintenance appointments within the time frame (24–30 months) of the clinical trial resulting in protocol deviations. Due to the limited sample size, several factors such as maintenance, plaque control, and implant location were unable to be investigated in this trial. Of note, the averaged plaque index was higher (PI = 0.7–1.1) after 2 years compared to pre-treatment level (PI = 0.2–0.6). It was suspected as a result of a poor maintenance program and the impact from COVID-19 pandemic [22]. Indeed, having a proper maintenance program can have significant impact on the outcome of peri-implantitis treatment [12]. Despite worsened plaque control around the implant, BOP and gingival index (GI) did not seem to aggravate in this clinical trial. It is now learned that BOP is not a reliable predictor for peri-implantitis and GI is not an ideal measure for peri-implant disease [23–25]. Future studies should utilize a more sensitive peri-implant mucosal bleeding index or molecular biomarkers to track the status of the peri-implant tissue. In addition, our study adopted non-submerged protocol for the treatment of peri-implant infraosseous defect; this may also explain less than ideal regenerative outcomes reported in this study. Future studies should also evaluate submerged reconstructive treatment protocol in its regenerative effect as well as the adjunctive effect of Er:YAG laser under close wound healing environment.

The current trial lost the sample size power to determine definitive results on the long-term adjunctive effects of laser-assisted reconstructive therapy compared to mechanical debridement due to loss of implants and follow-ups. However, a within group comparative trend favors the use of Er:YAG laser. Most failed cases shared some characteristics, including severe bone loss, major membrane exposure, distal-ended implant, and limited keratinized tissue; future investigations are needed to establish clinical prognostic factors. Future study designs should recruit larger cohorts with advanced peri-implantitis to compensate for long-term drop-outs and survival rates.

Conclusion

Within the limitation of this study, most maintained implants showed continued improvement or sustained its clinical and radiographic outcome; however, 25% of the implants failed after 2 years, especially implants with more than half of the bone loss. The use of Er:YAG laser favors PPD reduction in the longer term up to 30 months. Future long-term clinical trials should have larger sample sizes to further investigate different risk factors and how to manage this complex multifactorial peri-implant disease.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00784-023-05457-6.

Author contribution CWW contributed to study conception, design, performing surgeries, data analysis, drafting of the article. RD contributed to manage study visits, data analysis, drafting of the article. AO contributed to project administration and manage study visits. NK contributed to data analysis. SWF contributed to critical review of the manuscript. HLW contributed to study conception, performing surgeries, and critical review of the article.

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Data Availability The demographic information of the extracted implants were included in the supplemental table and other data is available upon request, but the results up to 6 months follow-up was published previously and the data was stated available together with the transcriptomics information [18].

Declarations

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.

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