IMPLANTOLOGY

Effect of prophylactic application of doxycycline at the implant–abutment interface on the outcomes of implant therapy: a split-mouth randomized clinical trial

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Objectives: Doxycycline hyclate is a controlled-release doxycycline polymer which can locally be applied. This study aimed to assess the effects of the prophylactic application of doxycycline hyclate at the implant–abutment interface on the short-term outcomes of implant therapy. **Method and materials:** The present split-mouth randomized clinical trial included 20 subjects who received two mandibular implants bilaterally (40 implants in total). In the test side (n = 20), doxycycline hyclate was injected at the implant–abutment interface at the time of delivery of final prosthesis. No intervention was performed for the control side (n = 20). The marginal bone level on mesial and distal implant surfaces, bleeding on probing, pocket probing depth, and incidence of peri-implant mucositis were recorded at baseline and after 3, 6, and 12 months. **Results:** Significant differences were found between the test and control sites, all favoring the test group, for marginal bone level changes at mesial and distal implant surfaces as well as for changes in pocket probing depth after 6 and 12 months. Furthermore, the numbers of implants with bleeding on probing and risk of developing peri-implant mucositis were significantly greater in the control group compared to the test group at 3-months, 6-months, and 12-months following baseline. **Conclusions:** Within the limitations of this study, it can be concluded that prophylactic application of doxycycline hyclate at the implant–abutment interface results in reduced crestal bone resorption and pocket probing depth levels. In addition, it reduces the risk of developing peri-implant mucositis.
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Key words: dental implants, doxycycline, peri-implantitis, peri-implant mucositis, randomized controlled trials, treatment outcome

Rehabilitation of dentition using implant-supported prostheses is a predictable therapeutic modality.[1,2] Although successful osseointegration can predictably be achieved,[3,4] the implant survival alone is no longer considered a success.[5] The success of implant therapy instead depends on several factors that affect the stability of implant–prosthetic complexes such as the health of peri-implant soft and hard tissues.[5]

Peri-implant mucositis and peri-implantitis are biologic complications that affect the stability of the implant–prosthetic complex.[6,7] Peri-implantitis is a plaque-associated pathologic condition affecting the tissue around dental implants.[6] It is characterized by inflammation in the peri-implant soft tissue and progressive loss of peri-implant hard tissue.[6] Peri-implant mucositis, however, is the inflammatory lesion of the peri-implant soft tissue without loss of implant-supporting hard tissue.[7] It is currently believed that peri-implantitis is preceded by peri-implant mucositis.[8] Hence, the management or prevention of peri-implant mucositis is a key preventive measure to decrease the incidence of peri-implantitis.[8-12]

Several treatment modalities have been utilized for the treatment of peri-implant mucositis including nonsurgical mechanical debridement, antimicrobial mouth rinses, and the use of systemic or local delivery of antibacterial agents.[7,9,12] These treatment approaches have shown a varying degree of success.[7] However, the available evidence on the prevention of peri-implant mucositis is very limited, if not nonexistent.[12]

Prophylactic local delivery of antimicrobial agents has been studied in the medical and dental fields.[13-16] In order to reduce the chance of postsurgical complications of orthopedic implants, prophylactic local delivery of antimicrobial agents such as antibiotic-loaded bone fillers, collagen fleeces, and various implant coatings have been utilized.[13-15] In addition, application of antibiotic coating on the surface of dental implants has been proposed to reduce the infection rates.[16] A more straightforward approach to achieve this goal can be prophylactic delivery of sustained-release antimicrobial systems at the time of dental implant placement or at the time of loading. The latter might help prevent peri-implant mucositis by maintaining a high of concentration sustained-released antibiotics in the peri-implant sulcus.

Doxycycline hyclate is a locally delivered sustained-release antimicrobial agent that can be easily delivered in peri-implant sulcus. It has been shown that 2 hours after the application, doxycycline hyclate gel can attain a concentration of 1,500 µg/mL in the gingival crevicular fluid. This value reaches 1,000 µg/mL after 18 hours and 140 µg/mL after 7 days.[17] This concentration is higher than the minimum concentration required for inhibition of periodontal pathogens.[18] It has been shown that this high concentration of doxycycline has a sustained effect for up to 6 months.[19]

Doxycycline hyclate has been utilized for treatment of periodontitis and peri-implantitis and it has shown promising outcomes.[18-20] However, to the best of the present authors' knowledge, the prophylactic application of doxycycline hyclate around implants with the goal of prevention of peri-implant mucositis and crestal bone loss has not been studied.

Therefore, the present study aimed to assess the effects of prophylactic application of doxycycline hyclate at the implant–abutment interface on the short-term outcomes of implant therapy. The null hypothesis was that prophylactic application of doxycycline hyclate would have no effect on the short-term consequences of implant treatment.

Method and materials

The present study was conducted and reported according to the CONSORT statement.[21] This clinical trial was conducted according to the principles outlined in the Declaration of Helsinki of 1975, revised in 2008 in Seoul, Korea. The protocol of this trial was approved by the Clinical Research Ethics Board of Tehran University of Medical Sciences (#92-03-69-23038). This clinical trial was also registered at www.irct.ir (IRCT20180222038827N2).

Twenty patients with at least two dental implants at the site of the first or second premolars in a partially edentulous mandible were included. All implants were bone-level with a sand-blasted, large grit, acid-etched (SLA) surface, platform switch design, and internal hexagon connection (Implantium, Dentium), 12-mm length with 3.8-mm diameter, and placed at crestal level. The patients were selected among those treated at the Dental Implant Center of School of Dentistry, Tehran University of Medical Sciences, according to the following inclusion criteria:

- presence of at least two nonrestored dental implants at sites of mandibular first or second premolars bilaterally in partially edentulous mandible
- no bleeding on probing (BOP) at implant sites
- implants must be uncovered for at least 4 weeks and placed minimum 3 months before the inclusion in the study.

The exclusion criteria were:

- poor oral hygiene (Plaque Index [PI] > 20%)
- malpositioned implants
- systemic diseases affecting the bone metabolism such as diabetes mellitus, renal disease, and osteoporosis
- smoking
- history of periodontitis
- width of attached mucosa of < 2 mm.[22,23]

All patients were informed about the procedure prior to inclusion in the study and signed informed consent forms.

Study design

This study was a split-mouth randomized controlled clinical trial that was conducted from 2018 to 2020. The patients were consecutively recruited from Dental Implant Center of School of Dentistry, Tehran University of Medical Sciences.

The test and control sides were determined by flipping a coin for each patient. The random allocation was done by a researcher who was not involved in this trial. Allocation concealment was achieved by sealed nontransparent envelopes that were opened right before the intervention by a researcher who was not involved in the study. The test implants received doxycycline hyclate (Atridox, 10% doxycycline hyclate; Zila, Tolmar) before delivery of final crown. Control sites did not receive any intervention.

Clinical and radiographic examinations were done at baseline and at 3, 6, and 12 months following the delivery of the final implant-supported prosthesis. The primary outcome vari-

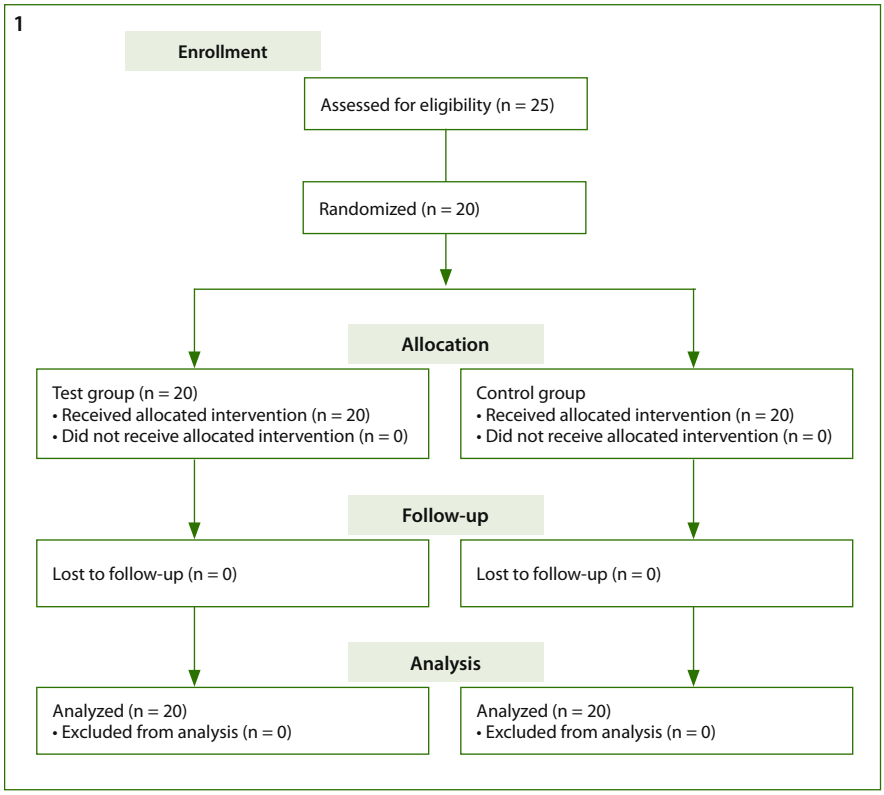


Fig 1 Consort flowchart of the present study.

able was change in pocket probing depth (PPD). The secondary outcome variables were incidence of peri-implant mucositis and BOP as well as changes in mesial and distal peri-implant bone levels. The CONSORT flowchart is presented in Fig 1.

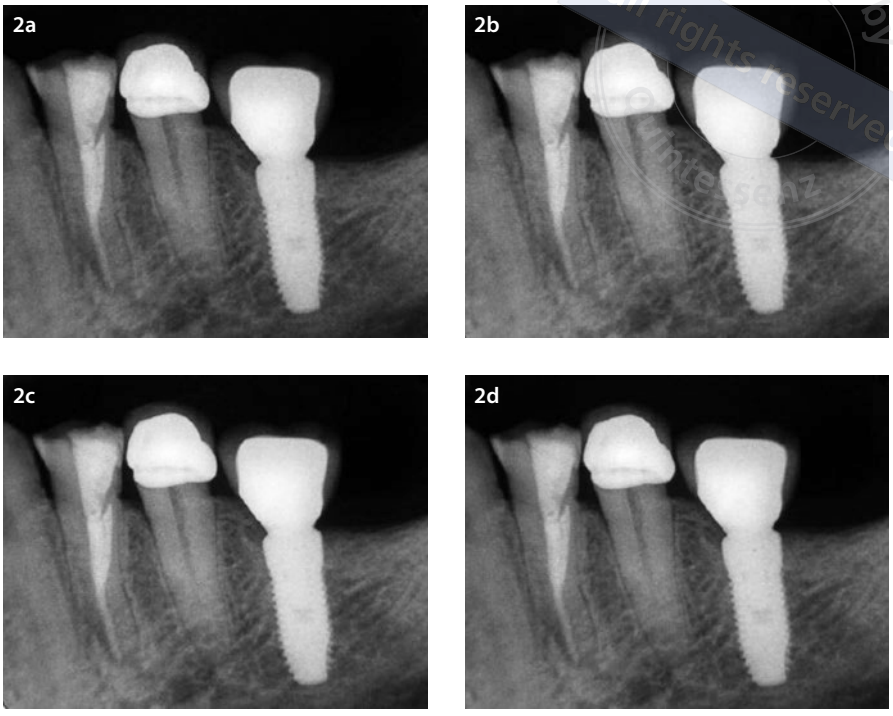
Intervention

After removal of the healing abutment, doxycycline hyclate was injected into the annulus of the implant at the implant–abutment interface. Doxycycline hyclate is supplied in two syringes. Syringes A and B should be mixed 100 times prior to injection. Doxycycline polymer was placed in the annulus space at the delivery session of prosthesis before screwing and torquing of the abutment. Delivery of doxycycline hyclate was done by an experienced prosthodontist. Control sites did not receive doxycycline hyclate.

All patients received porcelain-fused-to-metal (PFM) crowns. The abutments (Implantium, Dentium) in both groups were disinfected using chlorhexidine for 10 minutes. The abutment screw was torqued to 35 Ncm, and the PFM single crown was placed and cemented with temporary cement (Kerr). Then, periapical radiographs were obtained. Patient were seen every 3 months for recall visits. At each visit, a clinical examination was done. Afterwards, oral hygiene instructions were reinforced, and supragingival scaling was performed.

Clinical examinations

Clinical examinations were done after delivery of the final prosthesis (baseline), and at 3, 6, and 12 months later. BOP was recorded as the presence/absence of bleeding up to 30 seconds following probing at the implant sulcus. PPD was recorded from the gingival margin to the bottom of implant sulcus. All probing measurements were done at four sites around the implant with a Williams periodontal probe (Hu-Friedy). The diagnosis of mucositis was made based on presence of BOP and bone loss < 2 mm at 1 year following the prosthetic delivery.[7] All clinical examinations were done by a calibrated examiner blinded to the group allocation. Intra-examiner reliability was assessed by recording duplicate measurements of PPD and BOP from five patients at two sessions with a 48-hour interval. The Kappa for intra-examiner reliability was 0.90.



Figs 2a to 2d Periapical radiographs of an implant in the test group during the 12-month study period. *(a)* Baseline; *(b)* after 3 months; *(c)* after 6 months; and *(d)* after 12 months.

Radiographic examinations

Standardized periapical radiographs were obtained at baseline, and at 3, 6, and 12 months later (Fig 2). All radiographs were taken with the parallel technique. The distance from the fixture shoulder to the implant apex was measured on each radiograph. Then, the radiographs were standardized based on the actual length of the implant (12 mm). The point coordinates of the implant shoulder and the first bone–implant contact mesially and distally were determined. Then, peri-implant bone levels were determined by measuring the distance from the implant shoulder to the bone crest on the mesial and distal of each implant on each radiograph. These measurements were expressed in millimeters. All measurements were done using Photoshop software (Version 7.0; Adobe Systems).

All radiographic measurements were performed by a calibrated examiner blinded to the group allocation. Intra-examiner reproducibility was determined using two sets of radiographic measurements performed with a 1-week interval on periapical radiographs of five patients ($\kappa = 0.89$).

Statistical analysis

A power calculation was performed using Minitab software (Minitab). The sample size was estimated to provide 80% power to detect a significant difference of 1 mm in PPD between test and control sites. A minimum sample size of 18 patients would be required considering the standard deviation (SD) of 1.26[24] with a 95% confidence interval (CI) ($\alpha = .05$). Twenty patients were enrolled with a 10% probability of dropouts.

The normal distribution of the data was evaluated using Kolmogorov–Smirnov test. The implant was considered as the statistical unit. Repeated measure ANOVA was used for within-group comparison of baseline, 3-, 6-, and 12-month values for continuous parameters. The comparisons of changes in peri-implant bone levels and PPD data between the groups were done by paired *t* test at different time points. The BOP data was analyzed by the Wilcoxon signed-rank test, and the odd ratios (ORs) for risk of developing peri-implant mucositis were calculated. The statistical significance level was set at $P < .05$. Statistical analysis was conducted using SPSS Statistics software (version 22, IBM).

Table 1 Characteristics of subjects included in the study

Characteristic		Result
No. of patients		20
Sex	Female	9
	Male	11
Age (y), mean (range)		54.9 (47–63)
No. of smokers		0
No. of implants		40
Implant position	Mandibular first premolar	23
	Mandibular second premolar	17

Results

All patients completed the study period. Patients' characteristics are presented in Table 1. No implant failure or technical complications were observed during the study period. No implant was diagnosed with peri-implantitis during the study period.

At baseline, the mean mesial and distal bone levels were 1.19 ± 0.94 mm and 1.31± 1.04 mm for test sites and 0.81 ± 0.84 mm and 0.65 ± 0.59 mm for control sites, respectively. The mean PPD at baseline was 1.98 ± 0.47 mm for test sites and 1.70 ± 0.41 mm for control sites.

Table 2 presents the mean values and changes in crestal bone levels at mesial and distal implant surfaces during the study period. At 3 months, test and control sites demonstrated mean bone losses of 0.01 ± 0.10 mm and 0.13 ± 0.14 mm at mesial implant surface and 0.05 ± 0.16 mm and 0.17 ± 0.17 at distal implant surface, respectively. The difference in crestal bone level between test and control sites at the 3-month follow-up was statistically significant at the mesial implant surface ($P = .014$), but not at the distal implant surface ($P = .060$). At 6 months, control sites showed bone loss at both mesial (0.48 ± 0.66 mm) and distal (0.69 ± 0.79 mm; $P = .025$) implant surfaces compared to the baseline. On the other hand, test sites showed bone gain of 0.28 ± 0.75 mm on the mesial implant surface and 0.10 ± 0.94 mm on the distal implant surface. The differences in bone level changes between the two groups were statistically significant at both mesial ($P = .008$) and distal ($P = .025$) implant surfaces. At 12 months, the mean amount of bone loss at control sites was 0.49 ± 0.73 mm at the mesial implant surface and 0.71 ± 0.85 mm at the distal implant surface. However, at test sites, mean bone gains of 0.40 ± 0.89 mm and 0.20 ± 1.08 mm were recorded at mesial and distal implant surfaces, respectively. Statistical analysis demonstrated significant differences between test and control sites at mesial ($P = .008$) and distal ($P = .021$) implant surfaces.

Table 3 presents the mean values and changes in peri-implant probing depth. In test sites, PPD increased by 0.03 ± 0.11 mm at 3 months but decreased by 0.10 ± 0.38 mm and 0.08 ± 0.59 mm at 6 and 12 months compared to baseline, respectively. Within-group comparison demonstrated that there were no significant differences in PPD values at test sites during the study period (all $P > .05$). In the control side, PPD increased by 0.05 ± 0.15 mm, 0.28 ± 0.44 mm, and 0.43 ± 0.57 mm at 3, 6, and 12 months, respectively. The PPD values at control sites were significantly greater at 6 and 12 months compared to the baseline ($P = .014$ and $P = .004$; respectively). Comparison of changes in PPD between test and control sites demonstrated significant differences between the two groups at 6 and 12 months ($P = .021$ and $P = .025$, respectively).

Data on the frequency of sites with and without BOP during the study are presented in Table 4. Of all, five (25.0%) implants had BOP at 3, 6, and 12 months in the test group. In the control group, 15 implants (75.0%) showed BOP at 3 months. At 6 months and 12 months, 16 implants (80.0%) and 15 implants (75.0%) had BOP, respectively. The test group had significantly fewer implants with BOP compared to the control group at 3-month ($P = .002$), 6-month ($P = .001$), and 12-month ($P = .002$) visits.

All implants with BOP were diagnosed with peri-implant mucositis. The risk of developing peri-implant mucositis reduced significantly in the test group compared to the control group at 3 months (OR 0.11; $P = .003$), 6 months (OR 0.08; $P = .001$), and 12 months (OR 0.11; $P = .003$).

Discussion

The present study assessed the effects of prophylactic application of doxycycline hyclate at the implant–abutment interface on the short-term outcomes of implant therapy. It was found that the risk of developing peri-implant mucositis was significantly reduced after prophylactic application of doxycycline hyclate. In addition, the results demonstrated that prophylactic application of doxycycline hyclate is beneficial in minimizing peri-implant bone level and peri-implant PPD changes during the first year following loading of the implants. Hence, the present study supports the application of doxycycline hyclate at the implant–abutment interface with the goal of reducing the risk of developing of peri-implant mucositis.

Bone remodeling around dental implants usually occurs after loading of a dental implant.[25] During this process, peri-im-

Table 2 Mean ± SD values and changes in MBL and DBL at each time during the study for each treatment group

	Baseline		3 months		3 months		6 months				12 months			
	MBL	DBL	MBL	Δ MBL	DBL	Δ DBL	MBL	Δ MBL	DBL	Δ DBL	MBL	Δ MBL	DBL	Δ DBL
Test (n = 20)	1.19 ± 0.94	1.31 ± 1.04	1.20 ± 0.88	−0.01 ± 0.10	1.36 ± 0.96	−0.05 ± 0.16	0.91 ± 0.52†	0.28 ± 0.75	1.22 ± 0.69	0.10 ± 0.94	0.79 ± 0.49†	0.40 ± 0.89	1.12 ± 0.69	0.20 ± 1.08
Control (n = 20)	0.81 ± 0.84	0.65 ± 0.59	0.94 ± 0.85	−0.13 ± 0.14	0.82 ± 0.55	−0.17 ± 0.17	1.30 ± 1.08†	−0.48 ± 0.66	1.34 ± 0.81†	−0.69 ± 0.79	1.30 ± 1.12†	−0.49 ± 0.73	1.36 ± 0.86†	−0.71 ± 0.85
P value	NA	NA	NA	.014*	NA	.060	NA	.008*	NA	.025*	NA	.008*	NA	.021*

Δ, change from baseline; DBL, distal bone level; MBL, mesial bone level; NA, not applicable.
*Significant difference between the two groups ($P < .05$).
†Significant difference within group compared to baseline.

Table 3 Mean ± SD values and changes in PPD at each time point during the study for each treatment group

	Baseline	3 months		6 months		12 months	
	PPD	PPD	Δ PPD	PPD	Δ PPD	PPD	Δ PPD
Test (n = 20)	1.98 ± 0.47	2.00 ± 0.46	−0.03 ± 0.11	1.88 ± 0.48	0.10 ± 0.38	1.90 ± 0.53	0.08 ± 0.59
Control (n = 20)	1.70 ± 0.41	1.75 ± 0.38	−0.05 ± 0.15	1.98 ± 0.55†	−0.28 ± 0.44	2.13 ± 0.69†	−0.43 ± 0.57
P value	NA	NA	.577	NA	.021*	NA	.025*

Δ, change from baseline; NA, not applicable; PPD, pocket probing depth.
*Significant difference between the two groups ($P < .05$).
†Significant difference within group compared to baseline.

Table 4 Number (%) of sites with and without BOP at each time point during the study for each treatment group

	3 months		6 months		12 months	
	BOP +	BOP –	BOP +	BOP –	BOP +	BOP –
Test (n = 20)	5 (25.0%)	15 (75.0%)	5 (25.0%)	15 (75.0%)	5 (25.0%)	15 (75.0%)
Control (n = 20)	15 (75.0%)	5 (25.0%)	16 (80.0%)	4 (20.0%)	15 (75.0%)	5 (25.0%)
P value	.002*		.001*		.002*	

BOP, bleeding on probing.
*Significant difference between the two groups ($P < .05$).

plant level changes occur, mainly in the form of bone resorption.[25] The amount of this peri-implant bone resorption depends on various factors including implant design and location of the implant–abutment interface (microcap).[25-28] Bacterial colonization has been reported in the internal cavity of two-piece dental implants,[29-31] which triggers immune responses.[27] The intensity of the immune responses depends on the immunologic profile of the patient and the type and number of periodontal pathogens.[32-34] Clinical studies on the implant–abutment connection have reported different degrees of crestal bone resorption depending the location of the microcap in implant systems that were studied.[35,36] In the present study, the average amounts of bone resorption were 0.49 ± 0.73 mm at mesial and 0.71 ± 0.85 mm at distal implant surfaces in the control group after 12 months of loading. This finding is in line with the amount of peri-implant crestal bone loss reported in studies that used the same implant system.[37,38] Lee et al[38] assessed the outcome of the implant system that was used in the present study. They reported 0.41± 0.48 mm and 0.58 ± 0.65 mm bone resorption at mesial and distal implant surfaces 1 year after loading.[38]

The results of the present study demonstrated that prophylactic application of doxycycline hyclate at the implant–abutment interface results in significant improvements in peri-implant bone level and PPD during 1-year following the loading of implants. These findings can be attributed to the antibacterial properties of doxycycline hyclate, which can affect bacterial colonization at the microgap. Doxycycline is a semi-synthetic broad-spectrum tetracycline that inhibits protein synthesis in bacteria. It has significant effects on Gram-positive, Gram-negative, and anaerobic species as well as spirochetes.[39] Concentration of doxycycline hyclate in the gingival sulcus reaches 1,500 µg/mL after 2 hours, 1,000 µg/mL after 18 hours, and 140 µg/mL after 7 days. This dosage is higher than the minimum inhibitory dose required for periodontal pathogens.[39] Hence, these antibacterial properties may minimize the inflammatory reactions that eventually result in the loss of peri-implant hard and soft tissue.

In addition to the antibacterial properties of doxycycline, other mechanisms of action of doxycycline include increase in fibronectin and subsequent increase in fibroblasts, chemotaxis, migration, and cell adhesion, which are all necessary to enhance connective tissue attachment.[40] Doxycycline also increases the adhesion of blood clots, exerts anticollagenolytic activity, prevents bone resorption, and stimulates bone metabolism and periodontal connective tissue cells.[40-42] Therefore, these functions may also have a role in improvements in the peri-implant bone level and PPD that are observed in the present study. It should be noted that although statistically significant improvements in PPD were found for the test group in the present study, the clinical magnitude of these improvements was less than 1 mm; hence, the clinical significance of these improvements remains uncertain.

In this study doxycycline hyclate was used prophylactically at the implant–abutment interface with the goal of prevention of peri-implant mucositis. The results demonstrated that BOP and the risk of developing peri-implant mucositis were significantly reduced when doxycycline hyclate was applied. To the best of present authors' knowledge, this is the first study to assess the effect of prophylactic application of doxycycline hyclate for this purpose. However, there are studies where topical doxycycline hyclate has been used to treat peri-implantitis or periodontitis.[20,43] Buchter et al[20] reported 50% reduction in BOP 4 months after nonsurgical management of implants diagnosed with peri-implantitis with local delivery of doxycycline hyclate. In addition, in patients undergoing supportive periodontal therapy, Garrett et al[43] found a significant improvement in BOP at sites treated with local application of doxycycline hyclate compared to those treated with mechanical debridement 9 months after the treatment. Therefore, the present findings are in agreement with the available evidence that indicate the application of doxycycline hyclate results in reduction in inflammation and BOP up to several months following the treatment.

One of the limitations of the present study is that the release profile of doxycycline hyclate over time and its concentration in peri-implant tissues was not evaluated. It has been shown that, when doxycycline hyclate was locally delivered in periodontal pockets, the concentration of doxycycline in gingival crevicular fluid remained more than 100 times greater than minimum inhibitory concentration (MIC) for periodontal pathogens for at least 7 days.[44] In addition, the long-term positive outcomes for local delivery of doxycycline hyclate in patients undergoing supportive periodontal therapy have been demonstrated for up to 9 months following the treatment.[43] However, in order to better understand the mechanism of action of doxycycline hyclate and its effects on peri-implant soft and hard tissues, the release profile of doxycycline hyclate in peri-implant tissue at different time intervals should be assessed in future studies. It should be also mentioned that only clinical and radiographic outcome variables were evaluated in this study, and no microbiologic or immunologic analyses were performed. Therefore, future studies are required to assess the microbiologic and immunologic parameters.

Conclusion

Within the limitations of this study, it can be concluded that prophylactic application of doxycycline hyclate at the implant–abutment interface results in reduced marginal bone level resorption and PPD levels compared to the control sites during the first year following loading of dental implants. Furthermore, the present study demonstrated that the risk of developing peri-implant mucositis reduces after prophylactic local delivery of doxycycline hyclate. Therefore, the findings of this study indicate that the prophylactic application of doxycycline hyclate is a practical approach to reduce the risk of developing peri-implant mucositis during the first year following the loading of dental implants.

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References

1. Lekholm U, Grondahl K, Jemt T. Outcome of oral implant treatment in partially edentulous jaws followed 20 years in clinical function. Clin Implant Dent Relat Res 2006;8: 178–186.

2. Bassir SH, El Kholy K, Chen CY, Lee KH, Intini G. Outcome of early dental implant placement versus other dental implant placement protocols: A systematic review and meta-analysis. J Periodontol 2019;90: 493–506.

3. Derks J, Hakansson J, Wennstrom JL, Tomasi C, Larsson M, Berglundh T. Effectiveness of implant therapy analyzed in a Swedish population: early and late implant loss. J Dent Res 2015;94:44S–51S.

4. Nicolau P, Guerra F, Reis R, Krafft T, Benz K, Jackowski J. 10-year outcomes with immediate and early loaded implants with a chemically modified SLA surface. Quintessence Int 2018;50:2–12.

5. Papaspyridakos P, Chen CJ, Singh M, Weber HP, Gallucci GO. Success criteria in implant dentistry: a systematic review. J Dent Res 2012;91:242–248.

6. Schwarz F, Derks J, Monje A, Wang HL. Peri-implantitis. J Periodontol 2018; 89(Suppl 1):S267–S290.

7. Heitz-Mayfield LJA, Salvi GE. Peri-implant mucositis. J Clin Periodontol 2018;45 (Suppl 20): S237–S245.

8. Fu JH, Wang HL. Breaking the wave of peri-implantitis. Periodontol 2000 2020;84:145–160.

9. Kwon T, Wang CW, Salem DM, Levin L. Nonsurgical and surgical management of biologic complications around dental implants: Peri-implant mucositis and peri-implantitis. Quintessence Int 2020;51:810–820.

10. Kotsakis GA, Olmedo DG. Peri-implantitis is not periodontitis: Scientific discoveries shed light on microbiome-biomaterial interactions that may determine disease phenotype. Periodontol 2000 2021;86:231–240.

11. Schwarz F, Jepsen S, Obreja K, Galarraga-Vinueza ME, Ramanauskaite A. Surgical therapy of peri-implantitis. Periodontology 2000 2022;88:145–181.

12. Jepsen S, Berglundh T, Genco R, et al. Primary prevention of peri-implantitis: managing peri-implant mucositis. J Clin Periodontol 2015;42(Suppl 16):S152–S157.

13. Ostermann PA, Seligson D, Henry SL. Local antibiotic therapy for severe open fractures. A review of 1085 consecutive cases. J Bone Joint Surg Br 1995;77:93–97.

14. Metsemakers WJ, Emanuel N, Cohen O, et al. A doxycycline-loaded polymer-lipid encapsulation matrix coating for the prevention of implant-related osteomyelitis due to doxycycline-resistant methicillin-resistant *Staphylococcus aureus*. J Control Release 2015;209: 47–56.

15. Fuchs T, Stange R, Schmidmaier G, Raschke MJ. The use of gentamicin-coated nails in the tibia: preliminary results of a prospective study. Arch Orthop Trauma Surg 2011;131:1419–1425.

16. Walter MS, Frank MJ, Satué M, et al. Bioactive implant surface with electrochemically bound doxycycline promotes bone formation markers in vitro and in vivo. Dent Mater 2014;30:200–214.

17. Schenk G, Flemmig TF, Betz T, Reuther J, Klaiber B. Controlled local delivery of tetracycline HCl in the treatment of periimplant mucosal hyperplasia and mucositis. A controlled case series. Clin Oral Implants Res 1997;8:427–433.

18. Salvi GE, Mombelli A, Mayfield L, et al. Local antimicrobial therapy after initial periodontal treatment. J Clin Periodontol 2002;29:540–550.

19. Garrett S, Johnson L, Drisko CH, et al. Two multi-center studies evaluating locally delivered doxycycline hyclate, placebo control, oral hygiene, and scaling and root planing in the treatment of periodontitis. J Periodontol 1999;70:490–503.

20. Buchter A, Meyer U, Kruse-Losler B, Joos U, Kleinheinz J. Sustained release of doxycycline for the treatment of peri-implantitis: randomised controlled trial. Br J Oral Maxillofac Surg 2004;42:439–444.

21. Altman DG. Better reporting of randomised controlled trials: the CONSORT statement. BMJ 1996;313:570–571.

22. Heitz-Mayfield LJ, Salvi GE, Botticelli D, et al. Anti-infective treatment of peri-implant mucositis: a randomised controlled clinical trial. Clin Oral Implants Res 2011;22:237–241.

23. Renvert S, Roos-Jansaker AM, Claffey N. Non-surgical treatment of peri-implant mucositis and peri-implantitis: a literature review. J Clin Periodontol 2008;35:305–315.

24. Mombelli A, Feloutzis A, Bragger U, Lang NP. Treatment of peri-implantitis by local delivery of tetracycline. Clinical, microbiological and radiological results. Clin Oral Implants Res 2001;12:287–294.

25. Araujo MG, Lindhe J. Peri-implant health. J Clin Periodontol 2018;45(Suppl 20):S230–S236.

26. Cochran DL, Mau LP, Higginbottom FL, et al. Soft and hard tissue histologic dimensions around dental implants in the canine restored with smaller-diameter abutments: a paradigm shift in peri-implant biology. Int J Oral Maxillofac Implants 2013;28:494–502.

27. Dereci Ö, Mumcu E, Dereci ON, Dayan SÇ, Koşar YÇ, Fadhil SM. Effects of implant-related variables on the marginal bone loss around dental implants. Quintessence Int 2020;51:118–126.

28. Vroom MG, Sipos P, de Lange GL, et al. Effect of surface topography of screw-shaped titanium implants in humans on clinical and radiographic parameters: a 12-year prospective study. Clin Oral Implants Res 2009;20: 1231–1239.

29. Alecio ABW, Ferreira CF, Babu J, et al. Doxycycline release of dental implants with nanotube surface, coated with poly lactic-co-glycolic acid for extended pH-controlled drug delivery. J Oral Implantol 2019;45:267–273.

30. Guindy JS, Besimo CE, Besimo R, Schiel H, Meyer J. Bacterial leakage into and from prefabricated screw-retained implant-borne crowns in vitro. J Oral Rehabil 1998;25:403-408.

31. Dibart S, Warbington M, Su MF, Skobe Z. In vitro evaluation of the implant-abutment bacterial seal: the locking taper system. Int J Oral Maxillofac Implants 2005;20:732–737.

32. Darveau RP, Curtis MA. Oral biofilms revisited: A novel host tissue of bacteriological origin. Periodontol 2000 2021;86:8–13.

33. Borisy GG, Valm AM. Spatial scale in analysis of the dental plaque microbiome. Periodontol 2000 2021;86:97–112.

34. Eggert F, Levin L. Biology of teeth and implants: Host factors-pathology, regeneration, and the role of stem cells. Quintessence Int 2018;49:497–509.

35. Doring K, Eisenmann E, Stiller M. Functional and esthetic considerations for single-tooth Ankylos implant-crowns: 8 years of clinical performance. J Oral Implantol 2004;30:198–209.

36. Wennström J, Zurdo J, Karlsson S, Ekestubbe A, Gröndahl K, Lindhe J. Bone level change at implant-supported fixed partial dentures with and without cantilever extension after 5 years in function. J Clin Periodontol 2004;31:1077–1083.

37. Song DW, Lee DW, Kim CK, Park KH, Moon IS. Comparative analysis of peri-implant marginal bone loss based on microthread location: a 1-year prospective study after loading. J Periodontol 2009;80:1937–1944.

38. Lee JY, Park HJ, Kim JE, et al. A 5-year retrospective clinical study of the Dentium implants. J Adv Prosthodont 2011;3:229–235.

39. Gad HA, Kamel AO, Ezzat OM, El Dessouky HF, Sammour OA. Doxycycline hydrochloride-metronidazole solid lipid microparticles gels for treatment of periodontitis: development, in-vitro and in-vivo clinical evaluation. Expert Opin Drug Deliv 2017;14:1241–1251.

40. Frantz B, Polson A. Tissue interactions with dentin specimens after demineralization using tetracycline. J Periodontol 1988;59:714–721.

41. Trombelli L, Scabbia A, Wikesjö UM, Calura G. Fibrin glue application in conjunction with tetracycline root conditioning and coronally positioned flap procedure in the treatment of human gingival recession defects. J Clin Periodontol 1996;23:861–867.

42. Rompen EH, Goffinet GH, Nusgens B. Human periodontal ligament fibroblast behavior on chemically conditioned dentine: an in vitro study. J Periodontol 1999;70:1144–1152.

43. Garrett S, Adams DF, Bogle G, et al. The effect of locally delivered controlled-release doxycycline or scaling and root planing on periodontal maintenance patients over 9 months. J Periodontol 2000;71:22–30.

44. Stoller NH, Johnson LR, Trapnell S, Harrold CQ, Garrett S. The pharmacokinetic profile of a biodegradable controlled-elease delivery system containing doxycycline compared to systemically delivered doxycycline in gingival crevicular fluid, saliva, and serum. J Periodontol 1998;69:1085–1091.

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