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HUMAN RANDOMIZED CONTROLLED TRIAL

Repeated delivery of chlorhexidine chips for the treatment of periimplantitis: A multicenter, randomized, comparative clinical trial

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Abstract

Background: Periimplantitis is a challenging condition to manage and is frequently treated using non-surgical debridement. The local delivery of antimicrobial agents has demonstrated benefit in mild to moderate cases of periimplantitis. This study compared the safety and efficacy of Chlorhexidine gluconate 2.5 mg chip (CHX chips) as an adjunctive treatment to sub-gingival debridement in patients afflicted with periimplantitis.

Methods: A multicenter, randomized, single-blind, two-arm, parallel Phase-3 study was conducted. Periimplantitis patients with implant pocket depths (IPD) of 5-8 mm underwent sub-gingival implant surface debridement followed by repeated bi-weekly supra-gingival plaque removal and Chlorhexidine chips application (ChxC group) for 12 weeks, or similar therapy but without application of ChxC (control group). All patients were followed for 24 weeks. Plaque

and gingival indices were measured at every visit whereas IPD, recession, and bleeding on probing were assessed at 8, 12, 16, 24 week.

Results: A total of 290 patients were included: 146 in the ChxC group and 144 in the control. At 24 weeks, a significant reduction in IPD ($P = 0.01$) was measured in the ChxC group (1.76 ± 1.13 mm) compared with the control group (1.54 ± 1.13 mm). IPD reduction of ≥2 mm was found in 59% and 47.2% of the implants in the ChxC and control groups, respectively ($P = 0.03$). Changes in gingival recession (0.29 ± 0.68 mm versus 0.15 ± 0.55 mm, $P = 0.015$) and relative attachment gain (1.47 ± 1.32 mm and 1.39 ± 1.27 mm, $P = 0.0017$) were significantly larger in the ChxC group. Patients in the ChxC group that were < 65 years exhibited significantly better responses ($P < 0.02$); likewise, non-smokers had similarly better response ($P < 0.02$). Both protocols were well tolerated, and no severe treatment-related adverse events were recorded throughout the study.

Conclusions: Patients with periimplantitis that were treated with an intensive treatment protocol of bi-weekly supra-gingival plaque removal and local application of Chlorhexidine chips had greater mean IPD reduction and greater percentile of sites with IPD reduction of ≥2 mm as compared with bi-weekly supra-gingival plaque removal. (Clinicaltrials.gov NCT02080403).

KEYWORDS
clinical trial(s), drug delivery, implantology, infection control, local antimicrobial therapy

1 | INTRODUCTION

Treatment strategies for periimplantitis are derived from standard treatment regimens for periodontitis, but the results are generally less favorable. A Cochrane systematic review of the effectiveness of various treatment protocols for periimplantitis could not suggest which treatment modality is the most effective.[1] However, access flap surgery was found to be somewhat more effective than mechanical debridement alone. Numerous surgical procedures were tested with varying degree of predictability and success. These include open flap debridement with or without osseous re-contouring,[2] bone grafts,[3] barrier membranes,[4] enamel matrix derived,[5] growth factors,[6] or the use of progenitor cell therapy.[7]

In a survey among periodontists in the United States, 49.1% reported the use non-surgical debridement for the treatment of periimplantitis.[8] Nonetheless, a more recent meta-analysis found that this modality has a significant effect on reducing bleeding on probing but not on pocket reduction.[9]

The adjunctive local delivery of antibiotics/antiseptics into periimplant pockets were shown to enhance tissue response when compared with non-surgical debridement. In a study using minocycline microspheres for incipient periimplantitis sites, a small (0.6 mm), but significant average reduction in implants probing depth (IPD) was reported at 12 months.[10] Although in a similar study using doxycycline gel following mechanical debridement, a 1.15 mm reduction in IPD with 1.17 mm attachment level gain was reported.[11] Likewise, local delivery of tetracycline in polymeric fibers yielded marked reduction in IPD at 12 months post-op.[12]

To further enhance treatment response, an intensive protocol of Chlorhexidine chips* (ChxC) placement was tested in periimplantitis sites; in this previously reported study, marked reduction in IPD (2.19 mm) and substantial attachment level gains (2.21 mm) were reported.[13] However, the moderate sample size (30 patients with 37 to 40 implants in each group) did not allow to draw definitive conclusions.

Thus, the purpose of the present multicenter, randomized, single-blind, two-arm, parallel clinical trial was to assess in a large patient population, the adjunctive effect of multiple application of Chlorhexidine chips into the peri-implant pockets affected by periimplantitis after subgingival implant surface debridement and compare it to repeated implant surface debridement alone.

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2 | MATERIALS AND METHODS

This study (registered at ClinicalTrials.gov, number NCT02080403) was conducted in accordance with the globally accepted standards of International Clinical Harmonization Good Clinical Practice (ICH-GCP), in agreement with the revision of the Declaration of Helsinki (2008) and in compliance with the protocol and all applicable local laws, guidelines and regulations. The study was approved by the institutional ethics committee of all 10 participating medical centers before commencement (see authors affiliation in the title), files on record.

Adult patients (≥18 years old), seeking treatment for periimplantitis were screened for this study. To be included, these implants had to be in functioning for >2 years with fixed restoration and IPD of 5 to 8 mm, bleeding and/or suppuration on probing. In addition, implants were required to display radiographic evidence of bone loss of at least 3 mm from the implant shoulder but with at least 2 mm residual bone support. Patients with a history of Chlorhexidine allergy or those who routinely use Chlorhexidine mouthwash/rinse were excluded. Likewise, a horizontal distance of less than 2 mm from its neighboring tooth/implant constituted an exclusion. Other exclusion criteria were active periodontal disease (or treated periodontitis ≤6 weeks post-op), presence of oral soft or hard tissue tumors and/or any local mechanical factors that could have acted as local etiological factors, systemic antibiotic therapy or prolonged treatment with non-steroidal anti-inflammatory drugs and/or medications known to affect hard and soft tissue conditions. Uncontroled diabetes of any type (HbA1c >7.5%), post-radiation therapy to the head and neck region and immunosuppressive therapy were also disqualifying conditions.

Following informed consent, eligible patients underwent full-mouth periodontal examination, followed by supra-gingival scaling of all teeth and implants. Baseline measurements of the diseased implants included IPD, bleeding on probing (BOP) and recession (R). At baseline, a full mouth plaque index[14] (PI) and gingival index[15] (GI) were recorded and supra-gingival plaque was removed; oral hygiene instructions, to be adhered to throughout the study, were provided. At least one but no more than two implants were selected for the study (with the deepest IPD but not exceeding 8 mm). Adjacent implants not included in the study were treated as per the investigators discretion as long as it did not affect the study inclusion/exclusion criteria (e.g. treatment with antibiotics or surgery next to a target implant included in the study. For each study implant, four sites were measured: MB, B, DB, L with one of them defined as "target site." Patients were then randomly assigned into one of the following treatment protocols: repeated supra-gingival plaque removal (control) or supra-gingival plaque removal and repeated ChxC insertion, up to two chips per pocket, depending on pocket width (experimental).

Eligible patients were assigned a randomization number at the Baseline visit (Visit 2). Each randomization number was randomly assigned to the letter A or B to reflect random assignment to either treatment with chlorhexidine chip + sub-gingival debridement or sub-gingival debridement alone, respectively. Randomization was accomplished using a computerized algorithm of random numbers generated using the SAS program before the start of the study. Randomization was stratified in balanced blocks based on smoking habits and PD measurement at the Baseline visit, with each block containing six patients (three per treatment arm). Randomization blocks were sent to sites, such that each site received four types of lists by the defined stratification factors (i.e., smokers with PD of 5 mm, smokers with PD of 6 to 8 mm, nonsmokers with PD of 5 mm, and nonsmokers with PD of 6 to 8 mm). Additional blocks were provided to the sites according to the recruitment rate. Designated study personal at each site recorded the clinical data at each visit into the CRF. A total of 100% of the clinical data that was collected and recorded was verified by the Sponsor's monitor. Each CRF had an investigator confirmation at the "Study Completion" form.

In both groups, sub-gingival debridement was performed at baseline and at the last treatment sessions (week 12). In the first 12 weeks of the study patients were seen once every 2 weeks. At each visit, the above treatment protocol was repeated and PI and GI of the target implant were recorded; oral hygiene protocol was reinforced, and soft tissue examination was performed. Patients were instructed to refrain from use of Chlorhexidine-based oral rinses throughout the study and to avoid use of toothpicks and floss for at least 24 hours after treatment. At weeks 8, 12, and 16, IPD, recession and BOP were recorded, and final measurements were recorded at 6 months. Adverse events and changes in medication regimens were recorded at each visit.

All the clinical measurements were performed by calibrated examiners (standardized among investigators at each medical center before study initiation). In short, the agreement between the examiners (inter-observed) and between the assessments of the same examiner (intra observed) was evaluated using Kappa statistics. Intra-observed reliability was determined by comparison of matched test and re-test data (first and second readings) for each examiner (where available) and was expressed as weighted Kappa coefficient with 95% confidence interval. Inter-observed reliability (internal consistency) was determined by comparing data between pairs of examiners and

was expressed as weighted Kappa coefficient with 95% confidence interval. Kappa values > 0.61, were required.

The data was analyzed using the SAS version 9.1 (or higher). All the clinical measurements were performed by calibrated examiners (standardized among investigators at each medical center before study initiation).

IPD and R measurements were taken with a standard University of North Carolina (UNC) 15-mm periodontal probe. BOP was measured (0/1) at the target implant immediately after measuring the IPD. Relative attachment level (RAL) was calculated by summing the R and IPD. Throughout the study, all examiners were blinded to the treatment the patient was receiving.

2.1 | Statistical analysis

Power calculation to determine the sample size was based on the findings of a previous phase IIa study.[13] The Primary Efficacy Endpoint was mean probing PD reduction (absolute change) for the selected target implant from baseline to 24 weeks. To detect a mean inter-group PD difference of 0.50 mm, with an alpha error of 5% and 85% power, a sample size of 123 individuals in each group was required (assuming mean PD reduction of -2.29 mm in the experimental group and mean PD reduction of -1.79 mm in the control group, with standard deviation of 1.30 mm in both groups). The Secondary efficacy endpoints included PD reduction, baseline to 6 months, for sites 6 to 8 mm at baseline; reduction in bleeding on probing (BOP) baseline to 16 and baseline to 24 weeks; and changes in PD baseline to 16 weeks (this sample size was not powered to detect differences in any of the secondary outcomes.). This was detailed in the statistical analysis plan and study protocol.

The mixed linear model was used, with treatment as the fixed factor and patient and pocket as random effects. The model was adjusted to baseline measure, center, age, gender, and smoking status. The treatment-by-smoking interaction was found statistically significant (P-value < 0.05) and, therefore, was added to the model as covariate. Other post-hoc endpoints explored included the changes (from baseline) in recession (R) and relative attachment level (RAL). Statistical significance level for all analyses was set to 5%.

Statistically significant center effect could not be established (albeit individual centers variation); thus, all data were grouped together for statistical analyses. Data sets analyzed included the modified intent-to-treat (mITT) study sample, which included all patients who had undergone at least one sub-gingival debridement procedure (control arm) or treated with at least one ChxC (experimental arm), with no major protocol violations, and the per protocol (PP) study sample, which included all patients who completed the study with no major protocol deviations and within the following allowed inter-visit time windows: no limitation between screening (visit 1) and baseline (visit 2); among visits 3, 4, 5, 6, 7, and 8 the allowance was 14 + 7 days or 14-4 days; between visit 8 and 9, the allowance was 28 ± 7 days and between visit 9 and 10, the allowance was 56 + 28 days or 56-14 days.

3 | RESULTS

The study was conducted between August 19, 2014 (first patient in) and June 28, 2018 (last patient out). Of the 370 patients screened, 290 were found eligible and were randomized to one of the two study arms (experimental: n = 146; control: n = 144). The majority of patients (59%) were female, 84.1% were White, 4.45% of Black or African American descent, 91.4% non-Latino/Hispanic. Age ranged from 23.8 to 87.4 years, mean 62.6 ± 11.4 years (Table 1). In total, 386 implants (experimental: n = 197; control: n = 189) were treated, in 10 centers across Europe, North America, and Asia, with individual centers varying in the number of patients recruited (8 to 47) and implants treated (8 to 65). There were 235 implants in the maxilla and 151 in the mandible. Posterior implants in the molar/premolar region (322) vastly outnumbered the anterior one (64). Of these, 90.7% of the patients completed the study.

The changes in IPD baseline to 24 weeks, as measured in the mITT (n = 259 [324]) and PP (n = 193 [263]) patients [pockets], are presented in Table 2. In the mITT sample, the experimental group showed a significant pocket depth reduction of 1.76 ± 1.13 mm (median 2.0 mm), whereas a mean IPD reduction of 1.54 ± 1.13 mm (median 1.0 mm) was measured in the control group (P = 0.0128). Greater differences were noted for the PP sample, which showed a mean pocket depth reduction of 1.79 ± 1.12 mm (median 2.0 mm) following the experimental protocol compared with 1.52 ± 1.14 mm (median 1.0 mm) in the control (P = 0.0012). In the mITT sample, 59.0% of the target implants in the experimental group versus 47.2% in the control group showed IPD reduction of ≥2 mm at week 24 (P = 0.0338). In the PP population, 62.6% of the target implants in the experimental group versus 47.0% in the control group showed IPD reduction of ≥2 mm at week 24 (P = 0.0109), Table 3. Overall, target implants with greater initial IPD showed greater pocket reductions at week 24 (Table 4). More specifically, at 24 weeks, ChxC treated sites with a baseline pocket depth of 5-6 mm displayed a mean PD reduction of 1.53 ± 0.96 mm whereas 7 to 8 mm sites showed significantly greater reduction (2.23 ± 1.30 mm) which was statistically significant (P = 0.0008). Likewise,

TABLE 1 Demographic characteristics and dental status at baseline

Variable	Sub-gingival debridement + CHX chips (*N* = 146)	Sub-gingival debridement (*N* = 144)
Age, mean ± SD (range), years	62.5 ± 11.2 (25.5 – 86.9)	62.6 ± 11.6 (23.8 – 87.4)
Gender, *n* (%)		
Male	55 (37.7%)	63 (43.8%)
Female	91 (62.3%)	81 (56.3%)
Race, *n* (%)		
Asian	8 (5.5)	5 (3.5)
Black or African American	10 (6.8)	3 (2.1)
White	117 (80.1)	127 (88.2)
Other	11 (7.5)	9 (6.3)
Ethnicity, *n* (%)		
NA	1 (0.7)	1 (0.7)
Hispanic or Latino	14 (9.6)	9 (6.3)
Non-Hispanic or Latino	131 (89.7)	134 (93.1)
Smoking habits, *n* (%)		
Smokers	15 (10.3%)	14 (9.7%)
Former Smokers	51 (34.9%)	55 (38.2%)
Never Smoked	80 (54.8%)	75 (52.1%)
Dental status, mean ± SD (range)		
Number of natural teeth	19.96 ± 6.39 (0.00 – 30.00)	20.41 ± 5.65 (0.00 – 31.00)
Number of natural teeth with IPD between 4-6 mm	4.57 ± 4.14 (0.00 – 19.00)	4.78 ± 4.62 (0.00 – 21.00)
Number of natural teeth with IPD ≥ 7 mm	0.21 ± 0.60 (0.00 – 3.00)	0.17 ± 0.45 (0.00 – 3.00)
Number of implant(s)	4.21 ± 3.27 (1.00 – 15.00)	3.79 ± 3.00 (1.00 – 16.00)

Abbreviations: CHX, chlorhexidine; IPD, implant probing depth; IPD, pocket depth; SD, standard deviation.

TABLE 2 Pocket depth, relative attachment level, and recession at baseline and at 24 weeks (mean ± SD)

mITT population							
	Baseline		**Week 24**		**Change (Δ)**		
Clinical parameters	**Sub-gingival Debridement + CHX chips (*N* = *176*)**	**Sub-gingival Debridement (*N* = *174*)**	**Sub-gingival Debridement + CHX chips (*N* = *161*)**	**Sub-gingival Debridement (*N* = *163*)**	**Sub-gingival Debridement + CHX chips (*N* = *161*)**	**Sub-gingival Debridement (*N* = *163*)**	***P* value**
IPD (mm)	6.16 ± 1.00	6.06 ± 0.92	4.40 ± 1.25	4.52 ± 1.27	1.76 ± 1.13	1.54 ± 1.13	0.0128[a]
RAL (mm)	6.66 ± 1.31	6.32 ± 1.11	5.20 ± 1.73	4.94 ± 1.49	1.47 ± 1.32	1.39 ± 1.27	0.0017[a]
R (mm)	0.51 ± 0.99	0.26 ± 0.72	0.80 ± 1.21	0.42 ± 0.85	0.29 ± 0.68	0.15 ± 0.55	0.0150[a]
PP population							
	Baseline		**Week 24**		**Change (Δ)**		
Clinical parameters	**Sub-gingival debridement + CHX chips (*N* = *131*)**	**Sub-gingival debridement (*N* = *132*)**	**Sub-gingival debridement + CHX chips (*N* = *131*)**	**Sub-gingival debridement (*N* = *132*)**	**Sub-gingival debridement + CHX chips (*N* = *131*)**	**Sub-gingival debridement (*N* = *132*)**	***P* value**
IPD (mm)	6.13 ± 0.96	6.07 ± 0.90	4.34 ± 1.29	4.55 ± 1.24	1.79 ± 1.12	1.52 ± 1.14	0.0012[a]
RAL (mm)	6.66 ± 1.34	6.38 ± 1.14	5.13 ± 1.76	5.02 ± 1.52	1.53 ± 1.27	1.36 ± 1.32	0.0004[a]
Rec. (mm)	0.53 ± 1.00	0.31 ± 0.79	0.79 ± 1.23	0.46 ± 0.88	0.26 ± 0.60	0.15 ± 0.57	0.0162[a]

Abbreviations: IPD, implant pocket depth; mITT, modified intent-to-treat; N, number of implants; PP, per protocol; R, recession; RAL, relative attachment level.
[a]Statistically significant difference among treatment groups, in a mixed linear model that used treatment as the fixed factor and patient and pocket as random effects, and which adjusted for baseline measure, center, age, gender, smoking status, and treatment-by-smoking interaction.

TABLE 3 Frequency of implants by pocket depth decrease from baseline, at week 24

mITT population					
	Sub-gingival Debridement + CHX chips		Sub-gingival Debridement		
Reduction in IPD	*N*	Percent	*N*	Percent	*P* value
≥ 1 mm	140	87.0	137	84	0.4575
≥ 2 mm	95	59.0	77	47.2	0.0338[a]
≥ 3 mm	37	23.0	32	19.6	0.4615
≥ 4 mm	9	5.6	7	4.3	0.5905
PP population					
	Sub-gingival debridement + CHX chips		Sub-gingival debridement		
Reduction in IPD	*N*	Percent	*N*	Percent	*P* value
≥ 1 mm	113	86.3	111	84.1	0.6207
≥ 2 mm	82	62.6	62	47.0	0.0109[a]
≥ 3 mm	31	23.7	24	18.2	0.2744
≥ 4 mm	7	5.3	6	4.5	0.7653

Abbreviations: IPD: Implant pocket depth; mITT: modified intent-to-treat; N: number of implants; PP: per protocol.
[a]Statistically significant difference among treatment groups (unadjusted).
p = 0.008p = 0.008p = 0.0068p = 0.0068

TABLE 4 Pocket depth change by baseline pocket depth, at week 24

mITT population							
	Sub-gingival Debridement + CHX chips			Sub-gingival Debridement			
Baseline IPD	*N*	Mean ± SD	Median	*N*	Mean ± SD	Median	p value
5-6 mm	108	1.53 ± 0.96	2.00	112	1.39 ± 0.97	1.00	0.1185
6-7 mm	94	1.93 ± 1.04	2.00	100	1.76 ± 1.08	2.00	0.2322
7-8 mm	53	2.23 ± 1.30	2.00	51	1.84 ± 1.38	2.00	0.2605
PP population							
	Sub-gingival Debridement + CHX chips			Sub-gingival Debridement			
Baseline IPD	N	Mean ± SD	Median	N	Mean ± SD	Median	p value
5-6 mm	89	1.58 ± 0.97	2.00	88	1.33 ± 0.94	1.00	0.0153[a]
6-7 mm	78	2.00 ± 1.06	2.00	83	1.77 ± 1.10	2.00	0.1012
7-8 mm	42	2.21 ± 1.30	2.00	44	1.89 ± 1.38	2.00	0.3813

Abbreviations: IPD, Implant pocket depth; mITT, modified intent-to-treat; N, number of implants; PP, per protocol.
[a]Statistically significant difference among treatment groups, unadjusted [(Non-parametric Median test for independent samples were applied for analyzing of the difference in continuous changes among the treatment groups per time-point (week)].

for the control these figures were lower albeit significant (1.39 ± 0.97 versus 1.84 ± 1.38 mm, $P = 0.0383$).

The kinetics of IPD changes (Figure 1) showed a distinct pattern for each group, with the experimental group displaying a slow but steady IPD reduction after the first 8 weeks of treatment, followed by continuous linear improvements until week 24. In contrast, the control group showed a rapid initial improvement during the first 8 weeks of treatment, which slowed down thereafter.

At baseline, 100% of the sites in both groups showed BOP at the target implant site. At 24 weeks, approximately half of these sites had no signs of BOP (49.69% and 44.79% for the experimental and control groups, respectively).

Small increases in gingival recession were noted after 24 weeks (0.29 ± 0.68 mm for the experimental group compared with 0.15 ± 0.55 mm for the control group, $P = 0.015$). Relative attachment level gain was 1.47 ± 1.32 mm and 1.39 ± 1.27 mm for the experimental and control, respectively ($P = 0.0017$) (Table 2).

Both younger (<65 years) and elderly (≥65 years) individuals responded positively and in a similar manner to the experimental protocol (mean IPD reduction of 1.73 ± 1.17 mm and 1.78 ± 1.09 mm, respectively). However, when compared with the control cohort, younger individuals

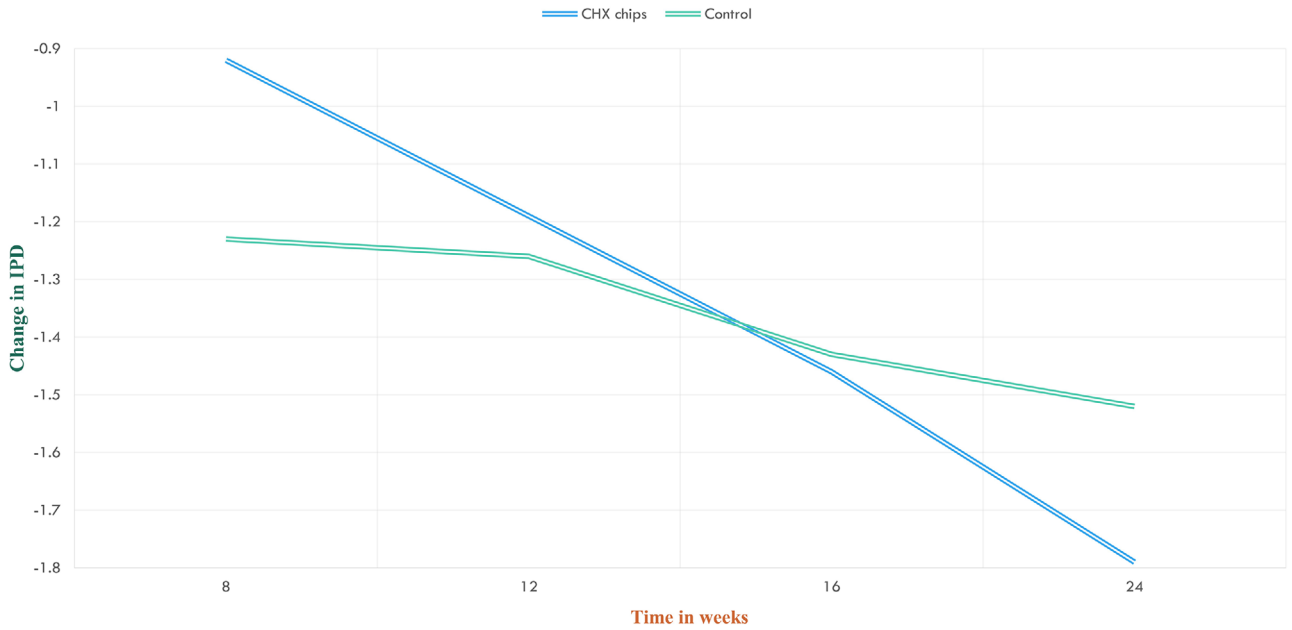

FIGURE 1 Changes in implants pocket depth compared with baseline (mITT). Please note continuous improvement throughout the 6-months in the ChxC group while initial greater improvement in the control with subsequent plateauing

TABLE 5 Effect of age and smoking habits on pocket depth change at week 24 compared with baseline (post hoc evaluation)

mITT population							
	Sub-gingival debridement + CHX chips			**Sub-gingival debridement**			
Parameters	**N**	**Mean ± SD**	**Median**	**N**	**Mean ± SD**	**Median**	***P* value**
Age < 65 Years	83	1.73 ± 1.17	2.00	90	1.38 ± 1.13	1.00	0.0183[a]
Age ≥ 65 Years	78	1.78 ± 1.09	2.00	73	1.73 ± 1.11	2.00	0.6332
Non-smokers	146	1.82 ± 1.11	2.00	149	1.53 ± 1.14	1.00	0.0186[a]
Smokers	15	1.13 ± 1.19	1.00	14	1.57 ± 1.09	1.50	0.4732
PP population							
	Sub-gingival Debridement + CHX chips			**Sub-gingival Debridement**			
Parameters	**N**	**Mean ± SD**	**Median**	**N**	**Mean ± SD**	**Median**	***P* value**
Age < 65 Years	68	1.74 ± 1.18	2.00	68	1.29 ± 1.16	1.00	0.0063[a]
Age ≥ 65 Years	63	1.84 ± 1.07	2.00	64	1.75 ± 1.07	2.00	0.4643
Non-smokers	118	1.86 ± 1.09	2.00	121	1.51 ± 1.13	1.00	0.0055[a]
Smokers	13	1.08 ± 1.26	1.00	11	1.55 ± 1.21	1.00	0.5547

Abbreviations: IPD, Implant pocket depth; mITT, modified intent-to-treat; N, number of implants; PP, per protocol.
[a]Statistically significant difference among treatment groups, unadjusted [(Non-parametric Median test for independent samples were applied for analyzing of the difference in continuous changes among the treatment groups per time-point (week)].

demonstrated significantly better responses to the experimental treatment (1.73 ± 1.17 mm compared with 1.38 ± 1.13 mm; $P = 0.0183$), Table 5.

Because of the low percentage of smokers in the study population (10%), a meaningful sub-group analysis was not feasible. However, when smokers were excluded from the analysis, non-smoking patients in the experimental group showed significantly greater mean IPD reductions at week 24 (1.82 ± 1.11 mm), as compared with the control non-smokers (1.53 ± 1.14 mm), $P = 0.0186$ (Table 5).

Overall, both protocols were well tolerated and both treatment arms were only associated with mild, short-term and self-limiting adverse events (see Table S1 in online Journal of Periodontology). In total, 18 patients in the experimental group and two patients in the control group, reported mild events such as pain and discomfort. One patient in the control group presented with swelling and sinus tract on the labial aspect of the implant, which required thorough sub-gingival debridement and rinsing with antiseptics. No treatment-related severe adverse

events were reported. Twenty-seven patients were withdrawn early from the study, out of which seven patients were withdrawn because of adverse events (five in the experimental and two in the control). None of these events were found to be related to the study medication. Missing data were imputed for the primary endpoint data using the MMRM model (Mixed-effect Model for Repeated Measures) with multiple imputation, which is based on MAR (missing at random) assumption. No clinically significant changes in the dental health or concomitant medications were recorded throughout the study.

4 | DISCUSSION

In this first ever-reported large-scale, global multicenter randomized controled phase 3 study of periimplantitis, a sizable reduction in mean IPD following repeated application of ChxC was observed after 6 months (mean 1.79 mm., median 2.0 mm) which was significantly greater than control (mean 1.52 mm., median 1.0 mm). In an earlier study, using the same intensive protocol in 30 patients (40 implants), a mean 2.19 mm IPD reduction was reported at 6 months.[13] However, baseline pocket depths for that study were 6-10 mm (mean 7.60 mm) compared with 5-8 mm (mean 6.16 mm) in the present study. In a similar study of 17 patients (57 implants) using repeated local minocycline application into moderate periimplantitis pockets, a smaller (0.71 mm) IPD reduction was reported for the experimental sites.[10] More recently, in a preliminary study of similar intensive protocol and local application of Chlorhexidine and minocycline HCl, a 1.79 mm. reduction in IPD 6-12 months post-op was reported.[16] Paolantonio et al.[17] reported, in an in-vitro study, that treatment with 1% Chlorhexidine in the implant-abutment connection is required to reduce the total bacterial count in these sites. Hence, the repeated application of high concentration Chlorhexidine chips is likely to have significantly reduced the bacterial load in the periimplant pockets for an extended period of time. A systematic review and Bayesian network meta-analysis of adjunctive treatment protocols for periimplantitis reported that single and combined non-surgical modalities, including Chlorhexidine chips, yielded greater IPD reduction compared with debridement only.[18]

Implants in the control group had lesser, however, significant IPD reduction at 6 months. This phenomenon might be attributed to the repeated removal of supragingival plaque (every fortnight) performed in these sites. Treatment studies of repeated implant debridement therapy for periimplantitis have not been previously reported. In a study of repeated (monthly) scaling or oral hygiene instruction (OHI) with or without local application of 25% metronidazole gel in periodontitis sites, greater reduction was observed in PD at 12 months for the repeated OHI (2.6 mm) and scaling (3.3 mm) with no adjunctive effect for the gel application.[19] Likewise, in a clinical trial of periodontitis patients that underwent weekly supra-gingival plaque removal for 3 months, a marked reduction in overall bacterial load compatible with periodontal health was achieved at 9 months post-op.[20] Another possible explanation for this phenomenon is a strong Hawthorne effect associated with the bi-weekly visit to the dental office, coupled with the mechanical treatment. Similarly, strong Hawthorne effect was reported in orthodontic patients enrolled in a mock study compared with non-participant controls.[21] In yet another study of the predictors of placebo analgesia response in controled trials of chronic pain, the number of face-to-face visits was found to be a strong predictor of the magnitude of response.[22] A systematic review and meta-analysis of the placebo effect in ulcerative colitis studies have concluded that increase in trial duration and more interaction with healthcare providers increased the placebo effect.[23]

The follow-up period designed for this study was set for 6 months. Thus, the long-term effect of this protocol cannot be evaluated. Other limitation associated with this study include the use of single rather than double blinded because of lack of placebo control; previous studies (Jeffcoat et al. 1998; Jeffcoat et al. 2000)[24,25] have shown that both modalities had similar results. The slight discomfort reported mainly in the experimental group should also be noted, however these were all transitory and minimal. Also, the cost benefit ratio is a double edge sword: on one hand the experimental arm is costlier for the patient whereas on the other hand, the greater percentiles of sites with IPD reduction of 2 mm or greater in the experimental group (62.6 versus 47%, $P = 0.01$) is likely to reduce the number of surgeries required in these implants thus improving the cost-benefit ratio (Lissovoy et al. 1999).[26]

The experimental group exhibited slow and continuous reduction in IPD through the 6-months observation period, whereas the control group showed greater initial reduction at 8 weeks with only slight improvement thereafter (Figure 1). The same phenomenon was observed in a previous phase IIa study that used the same protocol.[13] In contrast, Mombelli et al.,[12] using Tetracycline fibers for the treatment of periimplantitis reported that the bulk of this improvement in IPD occurred in the first 30 days whereas only minor further improvements occurred over the next 6 to 12 months.

Almost 2/3 of the sites treated in the experimental group displayed 2 mm or greater reduction in IPD compared with less than half of the sites in the control group ($P < 0.0338$). The sizable proportion of sites that yielded IPD reduction of 2 mm or greater, coupled with baseline IPD of 5 to 8 mm,

suggested that only few sites in the experimental group had residual IPD > 6 mm at the conclusion of the study. Similar results were previously reported.[13] A multicenter RCT on the adjunctive effect of single application of Chlorhexidine chip in reducing PD around teeth, after 12 weeks, only 30.3% of the sites exhibited PPD reduction of 2 mm or greater.[24] In summary, these findings suggest the value of repeated local delivery of ChxC to improve clinical outcomes.

Sites with deeper initial pockets demonstrated substantially greater reduction in IPD ranging from 1.53 mm for the sites of 5-6 mm around implants to 2.23 mm for the 7-8 mm sites around implants in the experimental group compared with 1.39 mm for the 5-6 mm implants to 1.84 mm for the 7 to 8 mm implants in the control, respectively. Similarly, in a previous study of mechanical debridement and local application of Chlorhexidine, sites with initial IPD ≤6 mm exhibited minimal (< 1 mm) reduction, whereas sites ≥7 mm at baseline resulted in significantly greater reduction after twelve months.[27] Also, another study using sub-gingival air polishing and povidone-iodine application into periimplantitis pockets, the group reported 1.3-1.4 mm reduction in IPD for all sites compared with 2.3 to 2.6 mm reduction in sites with initial IPD > 6 mm.[28] It is therefore reasonable to assume that sites with initial IPD of 7 to 8 mm are likely to benefit the most from this protocol with an anticipated mean reduction of ~ 2 mm. That, coupled with elimination of inflammatory signs as evident in the reduction in BOP, might reduce the need for additional surgical treatment following this protocol in such periimplantitis patients.[29,30]

In conclusion, in this large-scale multicenter RCT, periimplantitis-affected implants benefitted the most from a treatment protocol that included bi-weekly plaque removal and local application of Chlorhexidine chips. The long-term effect of this treatment modality and the exact mode of action is yet to be established.

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AUTHOR CONTRIBUTIONS

All the co-authors are PIs and co-PIs from the 10 centers that participated in the study. They were responsible for patients' recruitment, treatment and follow-up in addition to data acquisition as per protocol. Study design and drafting the manuscript was primarily the responsibility of the principle author (Eli E. Machtei) with contribution from the other PIs. All the co-authors reviewed, commented, and made revision to the draft article. A revised final version was approved for submission by all participants.

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REFERENCES

1. Esposito M, Grusovin MG, Worthington HV. Treatment of peri-implantitis: what interventions are effective? A Cochrane systematic review. *Eur J Oral Implantol*. 2012(Suppl 5):S21-S41.
2. Berglundh T, Wennström 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.
3. Renvert S, Roos-Jansåker 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.
4. Roos-Jansåker AM, Persson GR, Lindahl C, Renvert S. Surgical treatment of peri-implantitis using a bone substitute with or without a resorbable membrane: a 5-year follow-up. *J Clin Periodontol*. 2014;41:1108-1114.
5. Isehed C, Holmlund A, Renvert S, Svenson B, Johansson I, Lundberg P. Effectiveness of enamel matrix derivative on the clinical and microbiological outcomes following surgical regenerative treatment of peri-implantitis. A randomized controlled trial. *J Clin Periodontol*. 2016;43:863-873.
6. Isler SC, Soysal F, Ceyhanlı T, Bakırarar B, Unsal B. Regenerative surgical treatment of peri-implantitis using either a collagen

membrane or concentrated growth factor: a 12-month randomized clinical trial. *Clin Implant Dent Relat Res*. 2018;20:703-712.
7. Machtei EE, Kim DM, Karimbux N, Zigdon-Giladi H. The use of endothelial progenitor cells combined with barrier membrane for the reconstruction of peri-implant osseous defects: an animal experimental study. *J Clin Periodontol*. 2016;43:289-297.
8. 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.
9. Ramanauskaite A, Daugela P, Juodzbalys G. Treatment of peri-implantitis: meta-analysis of findings in a systematic literature review and novel protocol proposal. *Quintessence Int*. 2016;47:379-393.
10. Renvert S, Lessem J, Dahlén G, Renvert H, Lindahl C. Mechanical and repeated antimicrobial therapy using a local drug delivery system in the treatment of peri-implantitis: a randomized clinical trial. *J Periodontol*. 2008;79:836-844.
11. Büchter A, Meyer U, Kruse-Lösler 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.
12. Mombelli A, Feloutzis A, Brägger 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.
13. Machtei EE, Frankenthal S, Levi G, et al. Treatment of peri-implantitis using multiple applications of Chlorhexidine chips: a double-blind, randomized multi-centre clinical trial. *J Clin Periodontol*. 2012;39:1198-1205.
14. O'Leary TJ, Drake RB, Naylor JE. The plaque control record. *J Periodontol*. 1972;43:38.
15. Löe H. The gingival index, the plaque index and the retention index systems. *J Periodontol*. 1967;38:610-616.
16. Heo S, Kim HJ, Joo JY, Lee J, Kim SJ, Choi J. Simplified nonsurgical treatment of peri-implantitis using Chlorhexidine and minocycline hydrochloride. *J Periodontal Implant Sci*. 2018;48:326-333.
17. Paolantonio M, Perinetti G, D'Ercole S, et al. Internal decontamination of dental implants: an in vivo randomized microbiologic 6-month trial on the effects of a Chlorhexidine gel. *J Periodontol*. 2008;79:1419-1425.
18. Faggion CM Jr, Listl S, Frühauf 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.
19. Zee KY, Lee DH, Corbet EF. Repeated oral hygiene instructions alone, or in combination with metronidazole dental gel with or without subgingival scaling in adult periodontitis patients: a one-year clinical study. *J Int Acad Periodontol*. 2006;8:125-135.
20. Ximénez-Fyvie LA, Haffajee AD, Som S, Thompson M, Torresyap G, Socransky SS. The effect of repeated professional supragingival plaque removal on the composition of the supra- and subgingival microbiota. *J Clin Periodontol*. 2000;27:637-647.
21. Feil PH, Grauer JS, Gadbury-Amyot CC, Kula K, McCunniff MD. Intentional use of the Hawthorne effect to improve oral hygiene compliance in orthodontic patients. *J Dent Educ*. 2002;66:1129-1135.
22. Vase L, Vollert J, Finnerup NB, et al. Predictors of the placebo analgesia response in randomized controlled trials of chronic pain: a meta-analysis of the individual data from nine industrially sponsored trials. *Pain*. 2015;156:1795-1802.
23. Jairath V, Zou G, Parker CE, et al. Systematic review and meta-analysis: placebo rates in induction and maintenance trials of ulcerative colitis. *J Crohns Colitis*. 2016;10:607-618.
24. Jeffcoat MK, Bray KS, Ciancio SG, et al. Adjunctive use of a subgingival controlled-release Chlorhexidine chip reduces probing depth and improves attachment level compared with scaling and root planning alone. *J Periodontol*. 1998;69:989-997.
25. Jeffcoat MK, Palcanis KG, Weatherford TW, Reese M, Geurs NC, Flashner M. Use of a biodegradable chlorhexidine chip in the treatment of adult periodontitis: clinical and radiographic findings. *J Periodontol*. 2000;71:256-262.
26. De Lissovoy G, Rentz AM, Dukes EM, et al. The cost-effectiveness of a new chlorhexidine delivery system in the treatment of adult periodontitis. *J Am Dent Assoc*. 1999;130:855-862.
27. John G, Sahm N, Becker J, Schwarz F. Nonsurgical treatment of peri-implantitis using an air-abrasive device or mechanical debridement and local application of chlorhexidine. Twelve-month follow-up of a prospective, randomized, controlled clinical study. *Clin Oral Investig*. 2015;19:1807-1814.
28. Stein JM, Hammächer C, Michael SS. Combination of ultrasonic decontamination, soft tissue curettage, and submucosal air polishing with povidone-iodine application for non-surgical therapy of peri-implantitis: 12 Month clinical outcomes. *J Periodontol*. 2018;89:139-147.
29. Caton JG, Armitage G, Berglundh T, et al. A new classification scheme for periodontal and peri-implant diseases and conditions – Introduction and key changes from the 1999 classification. *J Periodontol*. 2018;89(Suppl 1):S1-S8.
30. 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 Periodontol*. 2018;89(Suppl 1):S313-S318.

SUPPORTING INFORMATION

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

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