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RANDOMIZED CLINICAL TRIAL

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Clinical effects of the adjunctive use of a 0.03% chlorhexidine and 0.05% cetylpyridinium chloride mouth rinse in the management of peri-implant diseases: A randomized clinical trial

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Abstract

Aim: To evaluate the efficacy of a 0.03% chlorhexidine and 0.05% cetylpyridinium chloride mouth rinse, as an adjunct to professionally and patient-administered mechanical plaque removal, in the treatment of peri-implant mucositis (PiM).

Material and Methods: Patients displaying PiM in, at least, one implant were included in this randomized, double-blinded, clinical trial. Subjects received professional prophylaxis (baseline and 6 months) and were instructed to regular oral hygiene practices and to rinse, twice daily, with the test or placebo mouth rinses, during one year. Clinical, radiographic and microbiological outcomes were evaluated at baseline, 6 and 12 months. Disease resolution was defined as absence of bleeding on probing (BOP). Data were analysed by repeated measures ANOVA, Student's t and chi-square tests.

Results: Fifty-four patients were included and 46 attended the final visit (22 in control and 24 in test group). In the test group, there was a 24.49% greater reduction in BOP at the buccal sites (95% confidence interval [3.65–45.34%]; $p = 0.002$) than in controls. About 58.3% of test implants and 50% controls showed healthy peri-implant tissues at final visit ($p > 0.05$).

Conclusions: The use of the test mouth rinse demonstrated some adjunctive benefits in the treatment of PiM. Complete disease resolution could not be achieved in every case.

KEYWORDS
chlorhexidine, dental implant, mouth rinse, peri-implant diseases, peri-implant mucositis

1 | INTRODUCTION

Long-term success of implant-supported restorations relies on the maintenance of healthy peri-implant tissues (Needleman, Chin, O'Brien, Petrie, & Donos, 2012), which depends on achieving effective preventive measurements, based on patient's self-performed oral hygiene practices and adherence to professional supportive therapy (Jepsen et al., 2015; Schwarz, Becker, & Sager, 2015). However, occurrence of peri-implant diseases is frequent, with recent systematic reviews reporting a weighted mean prevalence of

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patients affected by peri-implant mucositis and peri-implantitis of 47% and 18.5%–20%, respectively (Lee, Huang, Zhu, & Weltman, 2017; Rakic et al., 2017).

Since peri-implant mucositis, defined as the presence of inflammation in the peri-implant mucosa with or without increased probing depth (PD) and without loss of supporting bone (Lang & Berglundh, 2011), may progress to peri-implantitis, its treatment is considered the most effective measure to prevent peri-implantitis (Jepsen et al., 2015). In fact, there is evidence that the lack of regular adherence to supportive therapy significantly increases the incidence of peri-implantitis in mucositis patients (Costa et al., 2012; Monje, Wang, & Nart, 2017; Monje et al., 2016). The effective management of mucositis, however, is still a matter of controversy. Although several studies have shown that professional and patient-administered mechanical plaque control measures are effective in the control of mucositis (Porras, Anderson, Caffesse, Narendran, & Trejo, 2002; Ramberg, Lindhe, Botticelli, & Botticelli, 2009; Sreenivasan et al., 2011; Thöne-Mühling et al., 2010), other studies have reported that improved clinical outcomes can only be achieved when combining mechanical therapies with chemical biofilm control (Salvi & Ramseier, 2015).

The most frequently used adjunctive agent for chemical biofilm control around implants has been chlorhexidine (CHX). Its use, however, has been associated with undesirable side effects (tooth staining, burning feeling, soft-tissue irritation), which are dose dependent, being accentuated at concentrations above 0.1% (Smith, Moran, Addy, Doherty, & Newcombe, 1995). To prevent these side effects, without decreasing its antimicrobial activity, a reduction in the CHX concentration (Santos et al., 2004) and/or its combination with other active agents [e.g. cetylpyridinium chloride (CPC)] (Herrera et al., 2003) has been recommended. In fact, the use of mouth rinses containing low-concentration CHX (0.05%) combined with 0.05% CPC has shown efficacy in the management of gingivitis (Escribano et al., 2010; Santos et al., 2004), but its use has never been tested in the treatment of mucositis. It is, therefore, the aim of this clinical trial was to evaluate the clinical and microbiological activity of a mouth rinse containing 0.03% CHX and 0.05% CPC, as an adjunct to professional and patient-administered mechanical plaque removal, in the treatment of peri-implant mucositis.

Clinical Relevance

Scientific rationale for the study: Peri-implant mucositis (PiM) is frequent, and evidence is available for its treatment by mechanical biofilm control and adjunctive chemical antimicrobials. The use of adjunctive low-concentration chlorhexidine (CHX) mouth rinses, combined with cetylpyridinium chloride (CPC), has not been previously tested in PiM management.

Principal findings: Use of adjunctive 0.03% CHX and 0.05% CPC mouth rinse demonstrated clinical benefits in the treatment of PiM Complete disease resolution, however, could not be achieved in every case.

Practical implications: Professional and patient-administered mechanical biofilm control together with adjunctive low-dose CHX mouth rinse, could improve the clinical outcomes in patients with PiM.

2 | MATERIAL AND METHODS

2.1 | Study design

This investigation was designed as a 1-year, parallel group, double-blinded, placebo-controlled randomized clinical trial (RCT). The study was conducted between July 2015 and March 2017.

2.2 | Study population

Study subjects were recruited among patients attending the periodontal supportive program at the Periodontal Postgraduate Clinic, University Complutense of Madrid. Consecutive patients with dental implants were screened. The inclusion criterion was the presence of, at least, one dental implant with clinical signs of peri-implant mucositis, defined as bleeding on gentle probing (BOP) and/or suppuration without progressive radiographic bone loss (after at least 1 year of functional loading). Conversely, patients were excluded if they presented with: (a) untreated or recurrent periodontitis [presence of nine or more sites with PD ≥ 5 mm and with full-mouth bleeding score (FMBS) > 25%]; (b) implants affected by peri-implantitis, (BOP and/or suppuration and progressive radiographic bone loss); (c) removable implant-retained prosthesis; (d) systemic antibiotic intake within the previous month or other chronic systemic medications that could interfere with the study outcomes; and (e) women being pregnant or breastfeeding.

Those patients fulfilling the described criteria were invited to participate in the study and, for that, they received detailed information on the purpose, benefits and possible hazards associated with this clinical trial. Those willing to participate signed an informed consent, which had been previously approved by the institutional ethic committee (C.I. 15/064, Comité de Ensayos Clínicos del Hospital Clínico de San Carlos, Madrid).

2.3 | Study visits

2.3.1 | Screening visit

Once recruited as described above, a periapical radiograph of the selected implant was taken to confirm the diagnosis of peri-implant mucositis.

2.3.2 | Baseline visit

At the selected implant (one per patient), clinical and microbiological outcomes were registered. If more than one implant in the same patient presented mucositis, the implant showing deepest PD and BOP was selected (the other implants received the same treatment

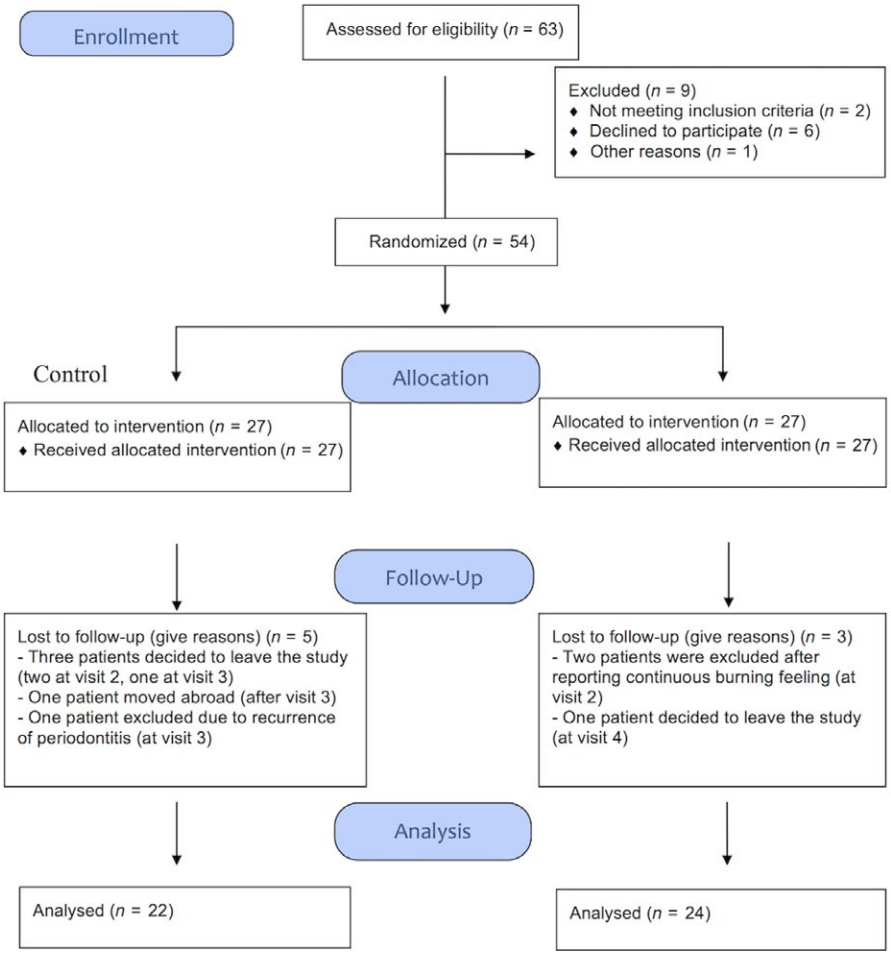

FIGURE 1 Consolidated Standards of Reporting (CONSORT) flow diagram of the study

as the selected implant). Then, these subjects received a conventional professional prophylaxis with an ultrasonic device (EMS, Nyon, Switzerland) using a plastic tip (FS-295, EMS) and powered air-polishing (Airflow®, EMS) with erythritol (Perio Plus®, EMS). All participants received standardized oral hygiene instructions with the use of a manual toothbrush (Vitis® Medio, Dentaid, Barcelona, Spain), individualized inter-dental brushes (Interprox Plus®, Dentaid) or dental floss (Vitis® Seda Dental, Dentaid), and a toothpaste containing sodium fluoride (FluorAid®, Dentaid). Moreover, they were provided with three 500 ml bottles of test or placebo mouth rinses.

2.3.3 | Follow-up visits

At 3, 6, 9 and 12 months, participants were examined for clinical outcomes, at 3 and 12 months, periapical radiographs were taken, and at 3, 6 and 12 months, microbiological samples were collected. At 6 months, participants received again a conventional professional prophylaxis and polishing.

2.3.4 | Rescue protocol

If during the study, peri-implant tissues showed an increase ≥2 mm in PD and/or overt suppuration, treatment was carried and the patient was exited from the study.

2.4 | Interventions

Participants were randomly assigned into one of two treatments, using a random-block computer-generated list. Allocation concealment was assured by a study monitor who was not involved in the clinical aspects of the trial. Both researchers and patients were

TABLE 1 Socio-demographic variables at baseline for each intervention group

Variable	Group	Control (*n* = 27)	Test (*n* = 27)
Age	Mean	61.0	61.3
	SD	12.0	8.9
Smokers (>9 cig/day)	*n*	4	2
	%	14.8	7.4
Female	*n*	14	11
	%	51.9	40.7
Systemic diseases	*n*	4	6
	%	14.8	22.2
Medication	*n*	8	11
	%	29.6	40.7
High level of stress	*n*	0	3
	%	0.0	11.1

Note. cig: cigarette; *SD*: standard deviation.

blinded to the product assignment since the numbered bottles were identical. The identification codes were kept by the study monitor and not opened until the end of the study.

The test mouth rinse contained 0.03% CHX and 0.05% CPC as main active ingredients (Dentaid, Barcelona, Spain) in a patented formulation with an optimized bioavailability. The control mouth rinse lacked the active ingredients, with the same organoleptic characteristics. Each patient was instructed to use the assigned mouthwash twice per day (15 ml for 30 s) after oral hygiene practices.

2.5 | Study outcomes

2.5.1 | Clinical variables

One blinded and calibrated investigator recorded the following clinical outcomes at six sites around the selected implant, using a plastic periodontal probe (PCV12, HuFriedy, Chicago, IL, USA): (a) BOP (Jepsen et al., 2015); (b) modified plaque index (MPII) (Mombelli, Van Oosten, Schüch, & Lang, 1987); (c) PD; and (d) crown length of the implant (CLI), distance between the incisal/occlusal portion of the crown and the peri-implant mucosal margin at the mid-buccal site.

Calibration was achieved in double measurement calibration sessions, with a gold standard examiner, on six randomly selected patients within one week. The inter-examiner agreement was assessed for all clinical parameters, resulting in kappa (*k*) values of 0.78 for BOP and 0.79 for MPII, and intra-class correlation coefficients (ICC) for PD and CLI of 0.93 and 0.96, respectively.

2.5.2 | Radiographic variables

Standardized periapical radiographs using the parallel technique (Rinn® system, Dentsply, Weybridge, UK) were used to evaluate the changes in the radiographic marginal bone levels (MBL). Scanned images were measured both at the mesial and distal sites of the selected implant using as landmarks the implant shoulder and the first bone implant contact, once they were calibrated using the known implant length by means of an image analysis software (Image-J, National Institutes of Health, Maryland, USA). Two experienced investigators performed all the radiographic measurements, once appropriately calibrated (ICC = 0.99).

2.5.3 | Microbiological variables

Pooled subgingival samples were obtained from the two most inflamed accessible sites of the selected implant in each patient. Samples were taken with two consecutive sterile medium paper-points (#30, Maillefer, Ballaigues, Switzerland) that were kept in place for 10 s and then transferred into a screw-capped vial containing 1.5 ml of reduced transport fluid (RTF) (Syed & Loesche, 1972). Samples were transported to the microbiology laboratory within 2 hr, where aliquots of 0.1 ml were plated in different culture media: Dentaid_1 for detection of *Aggregatibacter actinomycetemcomitans* (Alsina, Olle, & Frias, 2001) and non-selective blood agar medium (Blood Agar Base IIs, Oxoid, Basingstoke, England), supplemented with haemine (5 mg/L), menadione (1 mg/L) and 5% of sterile horse blood, for detection of selected periodontal pathogens. After 7–14 days of anaerobic incubation, total counts and counts of representative colonies were calculated in the most suitable plates. Suspected colonies were further identified by microscopy, by studying gram-staining and enzyme activity. Counts were transformed in colony-forming units (CFU) per ml of the original sample.

2.5.4 | Sample size calculation

BOP reduction was considered the primary outcome variable and an estimation of a mean difference in the reduction in BOP was used for calculating the sample size, when differences between test and control groups were 20%, with a standard deviation (*SD*) of 20% (Ramberg et al., 2009). Using this estimation with an alpha risk of 5% and a statistical power of 90% resulted in a sample size of 44 subjects. Assuming a potential drop-out rate of 20%, 54 participants (27 per group) was determined the target for patient inclusion.

2.6 | Statistical analysis

The primary outcome variable was the change in BOP (baseline-12 months). Secondary outcomes included mean changes in MPII, PD, CLI, MBL and microbiological data. For clinical outcomes, mean and median values of clinical parameters for all sites and for buccal, lingual/palatal and proximal sites were calculated per patient. Changes between baseline and 12-month, baseline to 6-month and 6- to 12-month visits were calculated. Disease resolution was defined as the absence of BOP, and the frequency distribution of resolved sites was calculated. The microbiological variables were presented as total anaerobic counts, frequency of detection of target pathogens, counts of each studied pathogen and proportions of each pathogen within the total microbiota. Total anaerobic counts were log transformed in order to fit a normal distribution.

Data on categorical outcomes were compared by means of the Chi-square test or Fisher-exact test. Shapiro–Wilk goodness-of-fit test and box plots were used to determine the normal distribution of the quantitative variables. Differences between groups at baseline, 6- and 12-month visits and their changes were determined by the Student's t test or Mann–Whitney U tests for quantitative outcomes. In addition, clinical variables were compared with repeated measures ANOVA with post hoc Bonferroni's correction considering the visit for the intra-group comparisons, the group (test or control) for the inter-group comparisons, and the interaction between time and group. Results were considered statistically significant at $p < 0.05$. A software package (SPSS® STATISTICS 21.0, IBM, Armonk, NY, USA) was used for all data analyses.

3 | RESULTS

3.1 | Study sample

Sixty-three patients were screened with two not fulfilling the study requirements and seven declined to participate in the investigation.

TABLE 2 Mean values for clinical outcomes at each study visit

			Baseline							6 months	
							95 CI%				
	Sites	Control/ Test	*N*	Mean	*SD*	Mean Diff.	Lower	Upper	*p*-value	*N*	Mean
PII (0–4)	All	Control	27	0.54	0.30	0.06	−0.09	0.21	0.421	24	0.30
		Test	27	0.48	0.26					24	0.26
	Buccal	Control	27	0.42	0.39	0.05	−0.14	0.24	0.595	24	0.24
		Test	27	0.37	0.28					24	0.25
	Lingual	Control	27	0.65	0.39	0.07	−0.14	0.29	0.497	24	0.36
		Test	27	0.58	0.41					24	0.26
	Proximal	Control	27	0.69	0.36	0.05	−0.14	0.23	0.615	24	0.36
		Test	27	0.64	0.31					24	0.34
BOP (%)	All	Control	27	46.30	24.17	−12.35	−26.48	1.79	0.086	24	19.58
		Test	27	58.64	27.49					24	27.08
	Buccal	Control	27	30.86	27.62	−24.69	−42.15	−7.23	**0.006**	24	18.75
		Test	27	55.56	35.81					24	27.78
	Lingual	Control	27	61.73	32.95	0.00	−17.27	17.27	1.00	24	20.83
		Test	27	61.73	30.25					24	26.39
	Proximal	Control	27	56.48	27.38	−14.82	−29.55	−0.08	**0.049**	24	20.83
		Test	27	71.30	26.59					24	30.21
PD (mm)	All	Control	27	3.38	0.60	0.02	−0.36	0.41	0.897	24	2.67
		Test	27	3.36	0.78					24	2.88
	Buccal	Control	27	3.10	0.73	−0.04	−0.49	0.42	0.871	24	2.63
		Test	27	3.14	0.93					24	2.76
	Lingual	Control	27	3.67	0.70	0.09	−0.35	0.53	0.695	24	2.71
		Test	27	3.58	0.89					24	2.99
	Proximal	Control	27	3.73	0.70	0.06	−0.36	0.48	0.758	24	2.89
		Test	27	3.67	0.83					24	3.04
CLI (mm)	Buccal	Control	27	9.45	2.19	0.82	−0.32	1.96	0.155	24	9.83
		Test	27	8.63	1.97					24	8.75

Notes. *p*-values in bold indicate statistically significant differences between study groups.
BOP: bleeding on probing; CI: confidence interval; CLI: crown length of implant; Diff.: difference; PD: probing depth; PII, plaque index; *SD*: standard deviation.

Among the 54 patients recruited, four decided to abandon the study, two were excluded after reporting a continuous intra-oral burning feeling, one moved abroad and one had to be exited due to periodontitis recurrence; thus, 46 subjects completed the final evaluation (Figure 1).

Table 1 depicts the socio-demographic variables at baseline, with no statistically significant differences between groups. The mean age was 61.15 year (*SD* = 10.12). Six patients were current smokers. One dental implant, not included in the analysis, had to be removed after displaying mobility and clear signs of loss of osseointegration. Regarding the specific characteristics of the 54 included implants, most of them were placed in posterior areas (*n* = 46; 85.2%), had cemented prosthesis (*n* = 30; 55.6%) and at least 2 mm of keratinised mucosa (*n* = 43; 79.6%), with no statistically significant differences between study groups ($p > 0.05$) (Supporting Information Table S1).

3.2 | Clinical outcomes

Clinical outcomes throughout the study are reported as mean values (Table 2) and as mean changes (Table 3). Since these outcome variables did not demonstrate a normal distribution, results are also expressed as median values (Supporting Information Table S2) and median changes (Supporting Information Table S3).

At baseline, no statistically significant differences between test and control groups were found for any clinical outcome (PD, CLI, MPI), except for mean BOP in buccal sites, which was higher in the test group [mean difference = 24.69%; 95% confidence interval (CI) (−42.15; −7.23%); $p < 0.001$].

Mean BOP percentages in the test group decreased from 58.64% (*SD* = 27.49%) at baseline to 10.42% (*SD* = 13.74%) at the 12-month visit. The corresponding values for the control group were 46.30% (*SD* = 24.17%) and 14.39% (*SD* = 18.04%), respectively. At 6

					12 months						
		95 CI%							95 CI%		
SD	Mean Diff.	Lower	Upper	*p*-value	*N*	Mean	*SD*	Mean Diff	Lower	Upper	*p*-value
0.37	0.04	−0.16	0.24	0.680	22	0.25	0.29	0.07	−0.09	0.22	0.371
0.33					24	0.18	0.22				
0.33	−0.01	−0.24	0.21	0.901	22	0.15	0.25	−0.02	−0.17	0.14	0.840
0.43					24	0.17	0.26				
0.55	0.10	−0.17	0.36	0.463	22	0.35	0.47	0.15	−0.07	0.38	0.168
0.34					24	0.19	0.26				
0.40	0.02	−0.22	0.26	0.861	22	0.30	0.32	0.04	−0.16	0.23	0.720
0.42					24	0.26	0.33				
24.40	−7.50	−22.94	7.94	0.333	22	14.39	18.04	3.98	−5.50	13.46	0.402
28.58					24	10.42	13.74				
26.61	−9.03	−27.97	9.91	0.342	22	10.61	26.00	0.88	−13.05	14.82	0.899
37.64					24	9.72	20.80				
30.79	−5.56	−23.06	11.95	0.526	22	18.18	24.62	7.07	−6.56	20.70	0.301
29.45					24	11.11	21.23				
29.18	−9.38	−27.96	9.21	0.315	22	15.91	22.55	3.41	−8.68	15.50	0.573
34.56					24	12.05	18.06				
0.52	−0.21	−0.54	0.12	0.210	22	2.57	0.57	0.07	−0.23	0.37	0.650
0.62					24	2.50	0.43				
0.67	−0.14	−0.52	0.24	0.461	22	2.50	0.79	0.11	−0.29	0.51	0.573
0.63					24	2.39	0.49				
0.58	−0.28	−0.67	0.12	0.164	22	2.64	0.61	0.03	−0.35	0.40	0.892
0.77					24	2.61	0.64				
0.59	−0.16	−0.51	0.20	0.376	22	2.78	0.53	0.08	−0.22	0.37	0.604
0.62					24	2.71	0.45				
2.07	1.08	−0.06	2.22	0.060	22	10.09	2.15	0.99	−0.20	2.19	0.101
1.86					24	9.10	1.86				

or 12 months, the differences between groups were not statistically significant (Figure 2). Between 6 and 12 months, additional BOP reductions occurred, although not statistically significant (16.67%; *SD* = 24.08% in the test versus 5.45%; *SD* = 22.74% in the control group) (Table 3).

At buccal sites, significantly greater BOP reduction between baseline to 12 months occurred in the test, compared with the control group [mean difference = 24.49%; 95% CI (−45.34; −3.65%); $p = 0.020$)].

Statistically significant mean reductions in MPI, BOP and PD occurred between baseline to 6 months in both groups, but differences between groups were not significant. Similarly, changes between baseline and 12 months for these parameters did not significantly differ between groups (Tables 2 and 3).

The main findings of the repeated measures ANOVA model (0, 3, 6, 9 and 12 months) are summarized in Supporting Information Table S4. While the time effect was statistically significant during the whole study ($p < 0.001$), the type of treatment and the interaction between intervention and time did not significantly affect any clinical parameter. For the intra-group comparisons in BOP, whereas the control group showed only significant reductions between baseline and each follow-up visit, the test group presented an additional significant benefit from 3 to 9 months, 3 to 12 months and 9 to 12 months.

3.3 | Disease resolution

At baseline, the mean number of sites per implant presenting positive BOP was slightly greater in the test group, although this difference was not statistically significant. Both groups showed a progressive reduction in the number of sites with BOP (Supporting Information Table S5). After 12 months, 58.3% of the implants in the test group and 50% in the controls demonstrated disease resolution (Figure 3).

TABLE 3 Mean changes in clinical outcomes between study visits

			Baseline-12 months							Baseline-6 months	
							95 CI%				
	Sites	Control/ Test	*N*	Mean	*SD*	Mean Diff.	Lower	Upper	*p*-value	*N*	Mean
PII (0–4)	All	Control	22	0.28	0.34	0.02	−0.15	0.19	0.784	24	0.22
		Test	24	0.26	0.23					24	0.18
	Buccal	Control	22	0.32	0.45	0.17	−0.07	0.40	0.155	24	0.19
		Test	24	0.15	0.29					24	0.07
	Lingual	Control	22	0.24	0.45	−0.12	−0.37	0.14	0.351	24	0.24
		Test	24	0.36	0.40					24	0.29
	Proximal	Control	22	0.39	0.41	0.05	−0.16	0.27	0.619	24	0.29
		Test	24	0.33	0.30					24	0.25
BOP (%)	All	Control	22	35.61	27.36	−13.01	−28.85	2.84	0.105	24	29.72
		Test	24	48.61	25.97					24	31.94
	Buccal	Control	22	22.73	36.20	−24.49	−45.34	−3.65	**0.022**	24	15.97
		Test	24	47.22	33.93					24	29.17
	Lingual	Control	22	48.48	39.48	−1.52	−23.78	20.75	0.892	24	43.06
		Test	24	50.00	35.44					24	34.72
	Proximal	Control	22	44.32	30.79	−14.02	−31.26	3.23	0.109	24	39.58
		Test	24	58.33	27.25					24	40.63
PD (mm)	All	Control	22	0.83	0.61	−0.01	−0.47	0.45	0.976	24	0.77
		Test	24	0.84	0.90					24	0.47
	Buccal	Control	22	0.62	0.81	−0.10	−0.62	0.42	0.697	24	0.53
		Test	24	0.72	0.93					24	0.35
	Lingual	Control	22	1.05	0.71	0.09	−0.45	0.62	0.745	24	1.01
		Test	24	0.96	1.05					24	0.58
	Proximal	Control	22	0.94	0.71	0.03	−0.47	0.53	0.915	24	0.91
		Test	24	0.92	0.95					24	0.58
CLI (mm)	Buccal	Control	22	−0.45	0.65	0.18	−0.23	0.58	0.386	24	−0.31
		Test	24	−0.63	0.71					24	−0.28

Notes. *p*-values in bold indicate statistically significant differences.
BOP: bleeding on probing; CI: confidence interval; CLI: crown length of implant; Diff.: difference; PD: probing depth; PII, plaque index; *SD*: standard deviation.

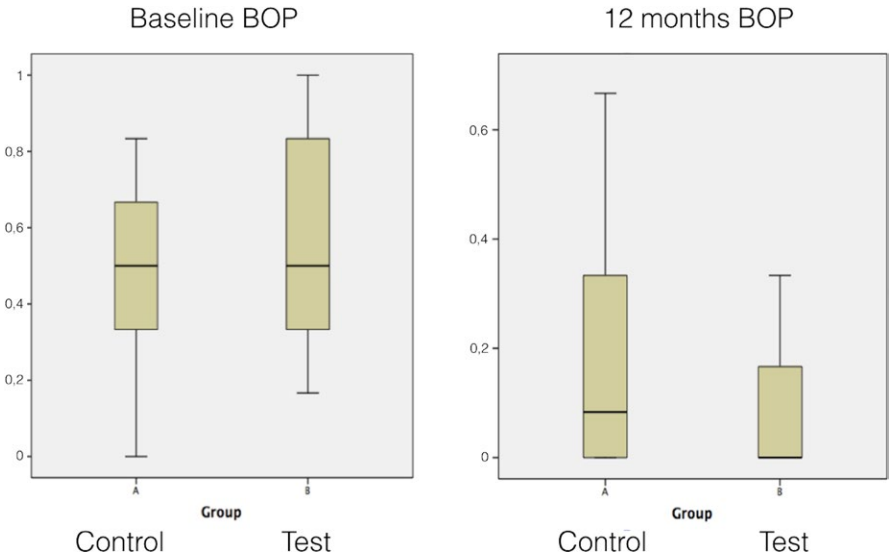

FIGURE 2 Box plots representing median and interquartile range of bleeding on probing (BOP) for implants of control and test groups at baseline and 12 months

					6–12 months						
		95 CI%							95 CI%		
SD	Mean Diff.	Lower	Upper	*p*-value	*N*	Mean	*SD*	Mean Diff.	Lower	Upper	*p*-value
0.34	0.03	−0.15	0.22	0.705	22	0.06	0.28	−0.02	−0.19	0.16	0.550
0.29					24	0.08	0.30				
0.49	0.13	−0.14	0.39	0.346	22	0.08	0.37	−0.01	−0.23	0.22	0.946
0.42					24	0.08	0.38				
0.50	−0.06	−0.32	0.21	0.674	22	0.05	0.38	−0.02	−0.24	0.20	0.828
0.41					24	0.07	0.37				
0.41	0.04	−0.19	0.27	0.719	22	0.09	0.28	0.01	−0.22	0.23	0.946
0.38					24	0.08	0.45				
24.45	−2.22	−19.56	15.11	0.798	22	5.45	22.74	−11.21	−25.16	2.74	0.112
34.37					24	16.67	24.08				
30.09	−13.19	−34.82	8.44	0.226	22	8.33	28.05	−9.72	−28.82	9.38	0.311
43.20					24	18.06	35.41				
38.67	8.33	−13.77	30.44	0.452	22	3.03	28.93	−12.25	−29.10	4.60	0.150
37.40					24	15.28	27.77				
27.50	−1.04	−19.89	17.81	0.912	22	5.68	28.80	−12.03	−28.93	4.87	0.159
36.72					24	17.71	28.05				
0.39	0.31	−0.12	0.73	0.159	24	0.77	0.39	0.31	−0.12	0.73	0.159
0.97					24	0.47	0.97				
0.45	0.18	−0.28	0.64	0.429	24	0.53	0.45	0.18	−0.28	0.64	0.429
1.01					24	0.35	1.01				
0.59	0.43	−0.07	0.93	0.09	24	1.01	0.59	0.43	−0.07	0.93	0.090
1.06					24	0.58	1.06				
0.49	0.32	−0.14	0.78	0.166	24	0.91	0.49	0.32	−0.14	0.78	0.166
1.01					24	0.58	1.01				
0.63	0.04	−0.30	0.37	0.831	22	−0.15	0.29	−0.20	−0.41	0.02	0.070
0.54					24	−0.35	0.41				

3.4 | Radiographic outcomes

At baseline, no significant differences could be observed between test and control groups for MBL at mesial [1.48 mm (*SD* = 0.8) and 1.19 mm (*SD* = 0.88), respectively] or distal sites (1.24 mm (*SD* = 0.77) and 1.09 mm (*SD* = 0.83), respectively]. After 12 months, the test group demonstrated more mean bone loss [0.34 mm (*SD* = 0.39)] at the distal site, although these changes did not exceed the threshold of detection for a significant change from baseline. There were no implants in any group demonstrating a significant MBL.

3.5 | Microbiological variables

Table 4 and Supporting Information Table S6 depict the microbiological outcomes expressed in counts, proportions and frequency of detection of each target bacterial species at each time point.

In total bacterial counts, the control group experienced an increase after 3 and 6 months and a decrease at the end of the study ($p = 0.09$), whereas the test group demonstrated a progressive reduction ($p = 0.09$). For changes in the counts of target species, significant differences between groups occurred at 3 months, with lower counts of *Parvimonas micra* and *Campylobacter rectus* in the test group, and at 12 months, with higher counts of *Eikenella corrodens* in the control group.

No significant differences between groups were observed at any time point in regards to the frequency of detection of target species. The test group showed a significant reduction for *Tannerella forsythia* ($p = 0.038$) from baseline to 3- and 6-month visits and a slight rebound at 1-year, whereas *C. rectus* significantly increased at 6- and 12-month visits ($p = 0.001$). In the control group, there was a significant reduction for *Fusobacterium nucleatum*, then followed by an increase.

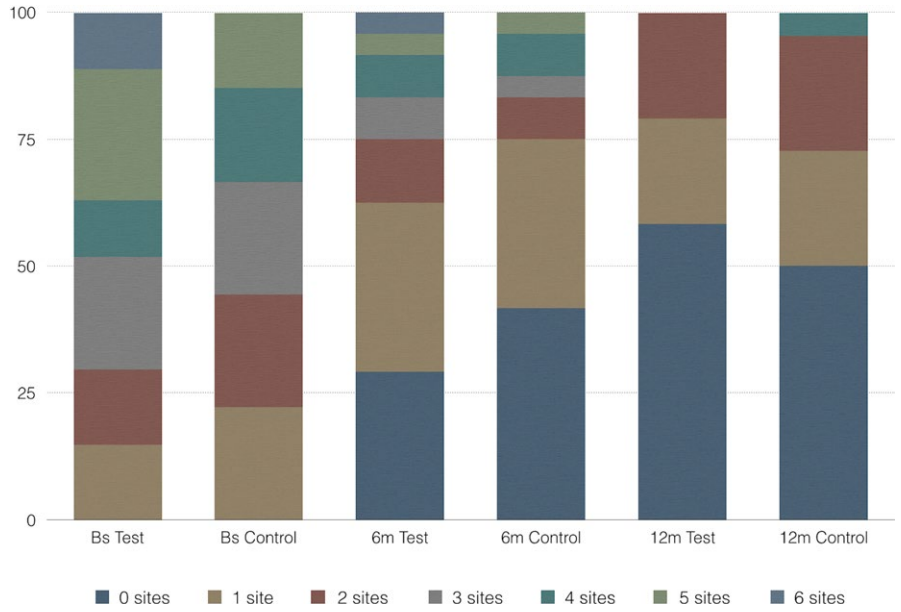

FIGURE 3 Percentage of implants in the control and test groups presenting from 0 to 6 sites positive to bleeding on probing at baseline (Bs), 6 (6 m) and 12 months (12 m)

For proportions of target species, the test group harboured less *P. micra* and *C. rectus* ($p = 0.040$) after 3 months and less *E. corrodens* ($p = 0.030$) after one year. Furthermore, the test group showed statistically significant reductions in the proportions of *Porphyromonas gingivalis* after 3 months ($p = 0.030$) and of *Prevotella intermedia*, *F. nucleatum* and *P. micra* up to 6 months ($p < 0.05$). In the control group, significant reductions were only observed for *F. nucleatum* after 6 months ($p = 0.02$).

4 | DISCUSSION

In this double-blind, placebo-controlled RCT of 1-year duration, the test group using as chemical adjunct a rinse containing 0.03% CHX and 0.05% CPC demonstrated significant higher reductions in BOP at buccal sites, when compared to the placebo group (47.2% versus 22.7%, respectively). Both groups used identical mechanical biofilm control, both professionally and self-administered. For other clinical outcomes, differences were not statistically significant, although the test group demonstrated, only quantitively, larger reductions.

Other studies have evaluated the effect of CHX mouth rinses or gels using different concentrations (0.12%, 0.2%, 0.5%) when used during short periods of time (2–4 weeks). These studies did not show a significant additional benefit in the management of mucositis, both in experimental mucositis models (Trejo et al., 2006), or in clinical trials (Heitz-Mayfield et al., 2011; Menezes, Fernandes-Costa, Neto, Calderon, & Gurgel, 2016; Thöne-Mühling et al., 2010). The present study is the first RCT assessing the long-term, adjunctive effect, of the daily use of a 0.03% CHX and 0.05% CPC mouth rinse in the management of peri-implant mucositis.

In the treatment of gingivitis, the antiplaque and plaque-inhibitory properties of CHX have been clearly demonstrated (Serrano, Escribano, Roldán, Martín, & Herrera, 2015), but when used as adjuncts around dental implants, these properties are not as clear (Salvi & Ramseier, 2015; Schwarz et al., 2015). In fact, the results of the present study, did not demonstrate statistically significant differences between groups for most of the tested clinical parameters. One possible explanation for these could be the reported limited reliability of periodontal probing to assess peri-implant health (Coli, Christiaens, Sennerby, & Bruyn, 2017), since these measurements may be significantly affected by gender (Farina, Filippi, Brazzioli, Tomasi, & Trombelli, 2017), probing force (Gerber, Tan, Balmer, Salvi, & Lang, 2009) or the existence of an inappropriate access to insert periodontal probe (Serino, Turri, & Lang, 2013). Furthermore, different from periodontal tissues, peri-implant tissue response seems to be influenced by many factors, besides biofilm accumulation (Renvert & Polyzois, 2015), such as the presence of residual cement, absence of keratinised mucosa or type of abutment material or prosthetic, which may limit the access to oral hygiene control (Jepsen et al., 2015; Sanz-Martín, Sanz-Sánchez, Carrillo de Albornoz, Figuero, & Sanz, 2018). These aspects may help to explain the variability in the results, with higher standard deviations in all the evaluated parameters when compared with gingivitis, what makes the detection of significant benefits by the use of adjunctive antiplaque agents more difficult in the management of mucositis.

Similarly, the reported microbiological outcomes demonstrated that the test group using the antimicrobial rinse demonstrated statistically significant reductions in *P. gingivalis*, *P. micra* and *P. intermedia*, although only achieved on a short-term basis. This limited antimicrobial efficacy may be attributable to differences in the nature of the biofilm between dental and implant surfaces, which may influence the capability of antimicrobial agents around dental implants. *In vitro* studies have shown significant differences in

TABLE 4 (a) Frequency of detection (Freq.), in percentage, of target periodontal pathogens. (b) Total anaerobic counts and counts of target periodontal pathogens, in log of colony-forming units (CFU) per ml

		Baseline			6 months			12 months		
	Group	*n*	Freq. (%)	*p*-value	*n*	Freq. (%)	*p*-value	*n*	Freq. (%)	*p*-value
(a)										
P. gingivalis	Control	20	74.10	0.50	11	47.80	0.33	16	80.00	0.30
	Test	19	70.40		14	58.30		15	68.20	
P. intermedia	Control	24	88.90	0.15	17	73.90	0.21	15	75.00	0.57
	Test	20	74.10		14	58.30		16	72.70	
T. forsythia	Control	11	40.70	0.61	2	8.70	0.68	5	25.00	0.57
	Test	11	40.70		2	8.30		6	27.30	
P. micra	Control	9	33.30	0.50	1	4.30	0.32	4	20.00	0.57
	Test	10	37.00		3	12.50		5	22.70	
C. rectus	Control	5	18.50	0.50	2	8.70	0.68	4	20.00	0.30
	Test	4	14.80		2	8.30		7	31.80	
F. nucleatum	Control	25	92.60	0.70	13	56.50	0.15	18	90.00	0.55
	Test	25	92.60		18	75.00		19	86.40	
Capnocytophaga spp.	Control	3	11.10	0.50	1	4.30	0.49	3	15.00	0.45
	Test	2	7.40		0	0.00		2	9.10	
E. corrodens	Control	4	14.80	0.18	5	21.70	0.33	6	30.00	0.07
	Test	1	3.70		3	12.50		0	0.00	

		Baseline				6 months				12 months				
	Group	*N*	Mean	*SD*	*p*-value	*N*	Mean	*SD*	*p*-value	*N*	Mean	*SD*	*p*-value	*p*-value INTRA_G
(b)														
Total count	Control	27	5.78	0.89	0.141	23	6.09	0.92	0.444	20	5.51	0.87	0.237	0.091
	Test	27	5.47	0.96		25	5.94	0.83		22	5.17	0.94		0.089
Pg	Control	27	4.16	1.82	0.700	23	3.12	2.22	0.493	20	3.65	1.71	0.666	0.355
	Test	27	3.89	2.04		25	3.28	2.02		22	3.25	1.88		0.385
Pi	Control	27	3.68	1.57	0.263	23	3.28	1.77	0.108	20	3.06	1.55	0.859	0.345
	Test	27	3,39	1.73		25	2.63	1.68		22	2.97	1.59		0.323
Tf	Control	27	2.34	1.89	0.763	23	1.27	0.95	0.912	20	1.66	1.43	0.883	0.298
	Test	27	2.37	1.72		25	1.19	0.76		22	1.80	1.43		0.063
Pm	Control	27	1.85	1.79	0.919	23	1.06	0.47	0.291	20	1.64	1.66	0.888	0.537
	Test	27	1.67	1.35		25	1.38	1.11		22	1.74	1.61		0.071
Cr	Control	27	1.47	1.21	0.558	23	1.19	1.03	0.895	20	1.22	0.75	0.241	0.604
	Test	27	0.95	0.00		25	1.15	0.65		22	1.84	1.39		0.001
Fn	Control	27	3.79	1.19	0.539	23	2.61	1.79	0.355	20	3.28	1.22	0.950	0.149
	Test	27	3.71	1.20		25	3.21	1.47		22	3.19	1.18		0.197
Cap	Control	27	1.27	0.96	0.692	23	0.95	0.00	0.307	20	1.55	1.44	0.474	0.343
	Test	27	1.24	0.94		25	0.95	0.00		22	1.15	0.67		0.194
Ec	Control	27	1.38	1.02	0.144	23	1.44	1.16	0.354	20	1.84	1.44	0.006	0.183
	Test	27	1.04	0.40		25	1.35	1.01		22	0,95	0.00		0.252

Notes. Cap: Capnocytophaga spp.; *Cr: Campylobacter rectus; Ec: Eikenella corrodens; Fn: Fusobacterium nucleatum;* INTRA_G: intra-group; *Pg: Porphyromonas gingivalis; Pi: Prevotella intermedia; Pm: Parvimonas micra; SD*: standard deviation; *Tf: Tannerella forsythia.*

biofilm thickness and on three-dimensional structure, when comparing biofilms formed on titanium or on hydroxyapatite (Sánchez et al., 2014).

Complete resolution of peri-implant mucositis has been defined as no site with BOP around a dental implant with a previous diagnosis of mucositis (Sanz & Chapple, 2012). Although this outcome has been demonstrated in pre-clinical (Ericsson et al., 1995) and human studies (Pontoriero et al., 1994; Salvi, Aglietta, Eick, Sculean, & Ramseier, 2012), hence defining peri-implant mucositis as a reversible lesion, long-term clinical studies have shown that this end-point may be difficult to achieve (Schwarz et al., 2015). In the present RCT, complete resolution occurred in 50% of the implants in the control group and 58% in the test group. The goal of treating mucositis should also be to prevent the development of peri-implantitis (Jepsen et al., 2015) and this outcome was achieved in all subjects participating in this clinical trial, since no patient showed progression to peri-implantitis. It may be argued, however, that the follow-up (one year) was not long enough to allow a clear result on effective prevention. Moreover, the strict mechanical plaque control observed in both treatment groups and the professionally administered plaque removal rendered at baseline and 6 months may have shadowed the possible differential impact of the adjunctive chemical therapy used in the test group. A recent systematic review (Monje et al., 2016) has demonstrated the importance of strict plaque control and maintenance protocols in the prevention of peri-implantitis.

Although this RCT was performed with strict quality assurance measures, we should acknowledge some limitations, which may have influenced the reported results. One may be the significantly higher BOP value detected at baseline at the buccal and proximal sites in the test group, which although occurring by chance, should have disappeared with an increased sample size. Another limiting factor may be the lack of standardization in the prosthetic design of the implant-supported restorations, what may have influenced the clinical outcomes to the differences to access for plaque control or for the reach of the rinse. Along the lines of the prosthetic restoration, it would have been desirable to study the influence of the abutment material, since it may have had an impact on biofilm accumulation (Sanz-Martín et al., 2018; Sanz-Sánchez, Sanz-Martín, Carrillo de Albornoz, Figuero, & Sanz, 2018). However, taking into consideration that many of the implants included in the study were not placed in our clinic, it was very difficult to have access to this information. These differences should be accounted for by randomization, but due to the limited samples size, this effect may be significant. It can also be speculated that a one-year follow-up may be a limited period to analyse the impact of adjunctive chemical agents; however, a longer follow-up could jeopardize the compliance of the patient with the use of the product.

In conclusion, the use of a 0.03% CHX and 0.05% CPC mouth rinse demonstrated some adjunctive benefits (BOP reduction) in the treatment of peri-implant mucositis. Complete disease resolution could not be achieved in every case.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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SUPPORTING INFORMATION

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

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