Clinical Oral Investigations
https://doi.org/10.1007/s00784-020-03474-3

ORIGINAL ARTICLE

Efficacy of a 0.03% chlorhexidine and 0.05% cetylpyridinium chloride mouth rinse in reducing inflammation around the teeth and implants: a randomized clinical trial

Juan Bollain[1] · Alberto Pulcini[1] · Ignacio Sanz-Sánchez[1] · Elena Figuero[1,2] · Bettina Alonso[1] · Mariano Sanz[1] · David Herrera[1]

Received: 30 April 2020 / Accepted: 24 July 2020

Abstract

Objectives To evaluate the efficacy of a 0.03% chlorhexidine (CHX) and 0.05% cetylpyridinium chloride (CPC) mouth rinse, as an adjunct to professional plaque removal (PPR) and mechanical hygiene, in the treatment of peri-implant mucositis (PiM) and gingivitis.

Material and methods Patients displaying PiM in, at least, one implant were included in this randomized, double-blinded, clinical trial. Subjects received PPR (at baseline and 6-month visits) and were instructed to rinse, twice daily, during 1 year with the tested mouth rinse or a placebo. Clinical and patient-reported outcomes were recorded at baseline and 6 and 12 months.

Results Fifty-four patients were included in the study and 46 attended the final visit. In the teeth and implants with inflammation, a higher reduction in BOP was observed in the test group. Statistically significant differences between groups were only observed in the lingual sites of the teeth with gingivitis (mean difference = 11.96%; 95% confidence interval [1.09; 22.83]; $p = 0.03$). Overall, compliance and satisfaction were good, even though staining were higher for the test group ($p < 0.05$).

Conclusions The combined use of mechanical debridement with a 0.03% CHX and 0.05% CPC mouth rinse may have adjunctive benefits in the management of gingivitis, and it is associated with a higher degree of staining.

Clinical relevance The control of gingivitis can be improved, after professional mechanical debridement, with toothbrushing and the supplementary use of a 0.03% CHX and 0.05% CPC mouth rinse at home.

Clinical trial registration number NCT03533166

Keywords Chlorhexidine · Mouthwashes · Gingivitis · Peri-implant mucositis

Introduction

The long-term success of the treatment of periodontal and peri-implant diseases is related to the patient's compliance in maintaining an optimal self-performed plaque control [1, 2] and attendng a proper supportive care program [3–5].

Both conditions are inflammatory diseases, caused by bacterial biofilms, that affect the soft tissues around the teeth and implants. Recent epidemiological studies have shown that the prevalence of peri-implant mucositis (PiM) ranges between 43 and 47% [6–11], 29.48% (implant level), or 46.83% (patient level), while the corresponding figures for gingivitis are higher, being the most prevalent form of periodontal disease affecting up to 90% of the world's adult population [12, 13].

Experimental studies in animals and humans have shown that the supracrestal connective tissue compartment around the teeth and dental implants has marked differences in both quantitative and qualitative in regard to the number of fibroblasts, collagen fiber orientation, and vascular supply. In spite of these structural differences, clinical studies aiming to experimentally induce PiM and gingivitis have not shown significant differences in the spread and progression of the soft

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00784-020-03474-3) contains supplementary material, which is available to authorized users.

✉ Elena Figuero
elfiguer@ucm.es

[1] ETEP (Etiology and Therapy of Periodontal and Peri-implant Diseases) Research Group, Faculty of Dentistry, University Complutense of Madrid, Madrid, Spain

[2] Department of Dental Clinical Specialties, Faculty of Dentistry, Complutense University of Madrid, Plaza de Ramón y Cajal, s/n, 28040 Madrid, Spain

Published online: 31 July 2020

tissue inflammatory changes [14]. Even though the direct causal relationship between the accumulation of biofilm on tooth and implant surfaces and the development of gingivitis and PiM has been clearly demonstrated [15, 16], there is still controversy on the differential inflammatory response, since some studies have reported a higher degree of inflammation in PiM [17], while others have reported similar outcomes [18]. Nevertheless, it is clear that, if left untreated, there is a higher risk of progression in both conditions to more advanced forms of disease, namely, peri-implantitis and periodontitis [3, 5].

The main clinical feature of gingivitis is the presence of bleeding on probing (BOP) with probing depths (PD) ≤ 3 mm [19], whereas PiM is defined as the presence of peri-implant mucosal inflammation (profuse bleeding and/or suppuration) in the absence of continuous marginal peri-implant bone loss [20]. Notwithstanding that the presence of BOP during periodontal evaluation does not represent a good predictor for periodontal breakdown, it is well established that the absence of BOP is an excellent predictor of periodontal and peri-implant tissues' stability [21, 22]. Therefore, the main goal of secondary prevention of both periodontitis and peri-implantitis is to maintain low levels of inflammation by professional care and patient plaque control [23].

With the goal to improve these preventive measures, the adjunctive use of chemical agents has been recommended to improve self-performed patient plaque control. Among these agents, chlorhexidine (CHX) has demonstrated antiplaque and antigingivitis effects when used as a mouth rinse [24, 25]. It has shown to be effective in the management of gingivitis [26, 27] and PiM [17, 28, 29]. However, several undesirable side effects have been reported such as tooth staining, burning feeling, and soft tissue irritation [30]. Those side effects can be decreased without losing clinical efficacy by reducing the concentration and/or combining them with other antimicrobials [31, 32]. There is, however, no relevant information on the relative efficacy of this adjunctive treatment when both gingivitis and PiM affect the same patient. It was, therefore, the aim of this investigation to evaluate the long-term effect of a 0.03% CHX and 0.05% CPC mouth rinse, as an adjunct to professional plaque removal (PPR), in the treatment of PiM and gingivitis.

Material and methods

Study design

This clinical study was designed as a 1-year, parallel group, double-blinded, placebo-controlled randomized clinical trial (RCT), which was registered (NCT03533166) and conducted between July 2015 and March 2017. Detailed information regarding study design is available in a previous scientific publication reporting the results affecting to one selected implant per patient affected by PiM [29]. In the present report, we have aimed to report the effect of both interventions on all teeth affected by gingivitis and all implants affected by PiM.

Patients attending the Postgraduate program in Periodontology at the University Complutense of Madrid (Spain) and wearing fixed implant-supported prosthesis were invited to participate if they had at least one dental implant with clinical signs of peri-implant mucositis, defined as BOP and/or suppuration without progressive radiographic bone loss (after at least 1 year of functional loading) [33]. In addition, clinical data was collected from those patients presenting at least one tooth with gingivitis, according to the most recent definition [34]. Patients were excluded if they presented with (1) untreated or recurrent periodontitis (presence of nine or more sites with PD ≥ 5 mm and with full-mouth bleeding score (FMBS) > 25%); (2) implants affected by peri-implantitis, (BOP and/or suppuration and progressive radiographic bone loss); (3) removable implant-retained prosthesis; (4) systemic antibiotic intake within the previous month or other chronic systemic medications that could interfere with the study outcomes; and (5) women being pregnant or breast-feeding. Those patients who fulfilled the inclusion/exclusion criteria were invited to participate and signed an informed consent approved by an institutional ethic committee (C.I. 15/064, Comité de Ensayos Clínicos del Hospital Clínico de San Carlos, Madrid).

Study visits

In the screening visit, a full-mouth periodontal chart was carried out and periapical radiographs from all implants were taken.

At baseline and 6-month visits, one trained operator (JB) performed a PPR. The protocol included plaque and calculus removal with an ultrasonic device (EMS®, Nyon, Switzerland), using a plastic tip (FS-295) for implants and a conventional metal tip (P1 EMS ultrasonic tip) for the teeth. Air-polishing was performed with an air-polishing device (Airflow, EMS®, Nyon, Switzerland) with erythritol (Perio Plus, EMS®, Nyon, Switzerland), using the specific nozzle (Perioflow, EMS®, Nyon, Switzerland) in implants and the handpiece on the teeth crown and root surfaces. All participants received standardized oral hygiene instructions, a new manual toothbrush (Vitis Medio, Dentaid®, Barcelona, Spain), individualized inter-dental brushes (Interprox Plus, Dentaid®, Barcelona, Spain) or dental floss (Vitis Seda Dental, Dentaid®, Barcelona, Spain), and a toothpaste containing sodium fluoride (FluorAid, Dentaid®, Barcelona, Spain).

At 6 and 12 months, participants were examined for clinical and patient-reported outcome measures (PROMs). If during the study an implant showed an increase in PD ≥ 2 mm

and/or overt suppuration, the patient was withdrawn from the study and the implant was treated with the standard of care.

Interventions

Participants were randomized using a random-block computer generated list by an independent monitor (DH). A study monitor not involved in the clinical aspects of the trial (EF) maintained allocation concealment. Examiners and patients were blinded by using similar numbered bottles. The identification codes were not revealed until the statistical analysis was performed.

Three bottles of 500 mL with either the test (0.03% CHX and 0.05% CPC) or the control mouth rinse (placebo without the active ingredients but with the same organoleptic properties) were given to the patient every 3 months. They were instructed to rinse with the assigned mouth rinse twice per day (15 mL for 30 s) after their daily mechanical plaque control.

Outcome variables

Clinical variables

One blinded calibrated investigator (AP) performed a full-mouth examination, including BOP [23], plaque index (PlI), and PD, at 6 sites around implants and the teeth, with a periodontal plastic probe PCP12 (HuFriedy®, Chicago, IL, USA) around implants, and a metal PCP15 periodontal probe (HuFriedy®, Chicago, IL, USA) around the teeth. Calibration with these outcome measurements in both teeth and implants was achieved prior to the start of the study by evaluating six random patients, resulting in kappa values of 0.78 for BOP and 0.79 for PlI, with intra-class correlation coefficients for PD of 0.93.

PROMs

A questionnaire was given to the patient to evaluate their assessment on the possible secondary effects of the assigned treatment (taste alteration, staining, burning feeling) as well as on the effects on their oral hygiene improvement at 6 and 12 months (Supplemental Material (SM), Appendix 1).

Staining

Staining of the teeth was evaluated with the use of standardized clinical photographs taken at each visit by two calibrated examiners (AP and JB) (inter-examiner agreement: 94–98%). The obtained images were scored using a modification of the Lobene index [35]. Extension (0–3) and intensity (0–3) of staining were scored both at the crown and at the root areas of the teeth in the 2nd and 5th sextants.

Compliance

Each subject received standardized verbal and written instructions on how to use the assigned products and was asked to bring back at each visit the remaining bottles to measure the remnant volume of mouth rinse with the aid of a laboratory calibrated test tube.

Sample size calculation

Sample size calculation was based on an estimation of mean difference (MD) in the reduction of BOP between test and control groups of 20%, with a standard deviation (SD) of 20% [36], an alpha-risk of 5%, and a statistical power of 90%, resulting in a sample size of 44 subjects. Assuming a potential dropout rate of 20%, 54 participants (27 per group) were determined as the target for patient inclusion.

Statistical analysis

For clinical outcomes, implants with PiM and teeth with gingival inflammation were recorded in the baseline visit and were followed prospectively during the study. Mean values for these locations were calculated considering the patient as the statistical unit for the analysis.

The primary outcome variable was the change in BOP between baseline and 12 months. Secondary outcomes included mean values and changes in BOP, disease resolution, PlI, PD, number of teeth or implants with inflammation, staining, compliance, and PROMs. In the staining analysis, mean values of extension, intensity, and extension*intensity per patient, and then per group, were calculated for coronal and root areas, in upper and/or lower arches. PROMs were calculated as mean values for each of the nine items of the questionnaire.

Data on categorical outcomes were compared by means of the chi-square test or Fisher-exact tests. Shapiro-Wilk goodness-of-fit test was used to determine the normal distribution of the quantitative variables. Differences between groups at baseline and 6 and 12 months and their changes were determined by the Student t test or Mann-Whitney U tests for quantitative outcomes. Results were considered statistically significant at $p < 0.05$ (IBM ®SPSS® STATISTICS 24.0).

Results

Sample description

A total of 63 patients were screened, and 54 were finally included. Seven patients did not want to participate and 2 failed to fulfill the inclusion criteria. Of those 54 included patients, 46 completed the 12-month visit (Fig. 1). From the

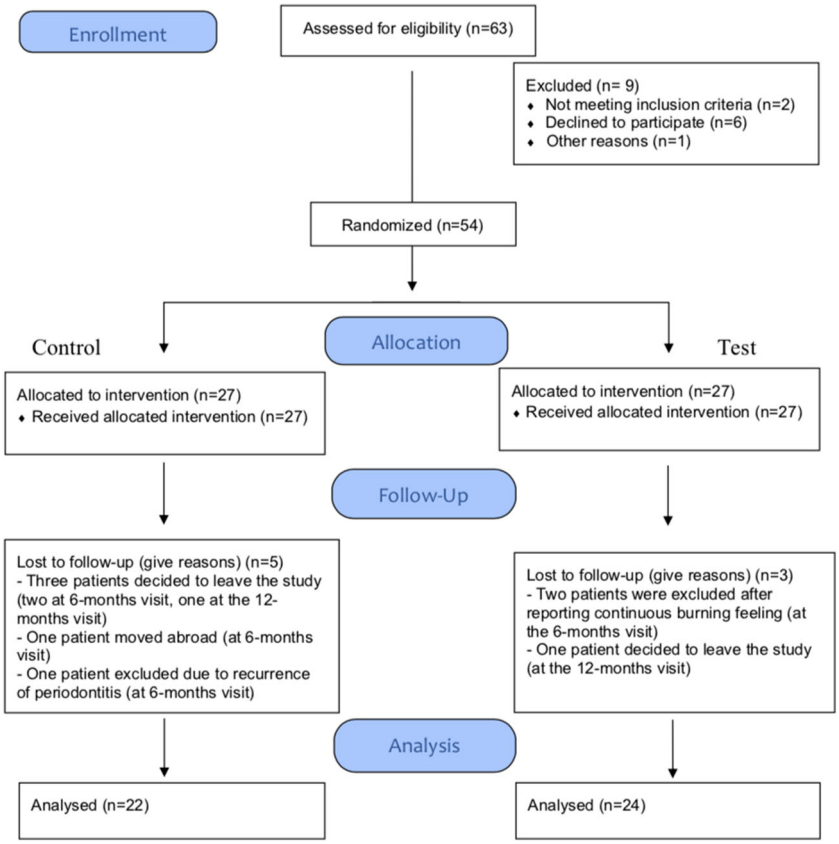

Fig. 1 Flow chart of the inclusion of the patients and the reasons for the patients leave during the study. n number of patients

8 dropouts, 2 subjects exited the study due to a burning feeling after using the mouth rinse, 4 did not return to their assigned visits, 1 was excluded due to periodontitis recurrence, and 1 left the country during the study period. Table S1 (SM) depicts the socio-demographic variables at baseline, with no statistically significant differences between groups.

Clinical outcomes

Periodontal clinical outcome variables (around the teeth)

Mean values at each study visit are reported in Table 1. At baseline, no statistically significant differences were found between test and control groups for any clinical variable in the evaluated teeth.

At the 6-month visit, the test group had statistically significant lower BOP than the control group, when combining all sites (MD = 6.21%; 95% confidence interval CI [0.81; 11.60]; p = 0.025); at buccal (MD = 5.23%; 95 CI [0.66; 11.13]; p = 0.017); and at proximal sites (MD = 10.11%; 95% CI [2.58; 17.65]; p = 0.009). Significantly lower PD were also observed when combining all sites (MD = 0.19; 95% CI [0.01; 0.37]; p = 0.037) and lingual sites (MD = 0.20; 95% CI [0.02; 0.39]; p = 0.033).

After 1 year, no statistically significant differences were found between groups for any clinical outcome at the teeth, although the test group had lower mean BOP values than the control group (5.50% [SD = 5.75] versus 7.98% [SD = 7.55]; p = 0.214), respectively.

Mean changes between visits are reported in Table 2. The test group presented significantly higher means of BOP reductions from baseline to 12 months on lingual sites (32.11% [SD = 18.24]), compared with the control group (20.15% [SD = 18.31]; p = 0.031). Statistically significant differences were also found in the mean changes between baseline and 6 months in BOP changes at all sites (p = 0.020), proximal (p = 0.016) and lingual (p = 0.013) sites, in favor of the test group. No statistically significant differences, in terms of mean changes in PD or PlI, were detected between any study visits, although mean reductions in PlI and PD tended to be higher in the test group.

Peri-implant clinical outcome variables (around implants)

Table 3 depicts the mean values for the clinical outcomes at each study visit for implants presenting PiM at baseline. No statistically significant differences between treatment groups were detected for any clinical outcome at any time, except for BOP in buccal sites, where the test group presented significantly higher values at baseline (p = 0.029).

When considering mean changes, no statistically significant differences were observed between groups for any of

Table 1 Mean clinical outcome variables at each study visit, for the teeth

Baseline										6 months							12 months						
		Group	*N*	Mean	SD	MD	95% CI		*p* value	*N*	Mean	SD*	MD	95% CI		*p* value	*N*	Mean	SD	MD	95% CI		*p* value
							Lower	Upper						Lower	Upper						Lower	Upper	
PII (%)	All	Control	27	47.58	30.05	−4.87	−21.47	11.73	0.559	24	33.64	20.44	4.59	−9.86	19.03	0.526	22	23.34	21.03	5.89	−4.91	16.69	0.276
		Test	27	52.45	30.75					24	29.06	28.61					24	17.45	14.11				
	Buccal	Control	27	40.00	30.59	−2.94	−20.05	14.16	0.731	24	30.81	21.88	10.28	−3.59	24.16	0.143	22	21.32	18.67	7.23	−2.59	16.88	0.138
		Test	27	42.95	32.04					24	20.53	25.73					24	14.09	13.60				
	Lingual	Control	27	55.15	32.10	−6.80	−25.27	11.68	0.464	24	36.47	23.54	−1.11	−18.78	16.57	0.900	22	25.37	26.55	4.55	−8.97	18.08	0.499
		Test	27	61.95	35.47					24	37.58	36.01					24	20.81	17.26				
	Proximal	Control	27	59.24	32.07	−6.41	−24.70	11.87	0.485	24	45.57	27.51	7.69	−10.00	25.38	0.386	22	31.45	27.84	6.71	−7.45	20.86	0.343
		Test	27	65.66	34.84					24	37.88	33.12					24	24.74	17.95				
BOP (%)	All	Control	27	27.65	9.60	−2.30	−8.33	3.72	0.447	24	13.57	10.65	6.21	0.81	11.60	0.025*	22	7.98	7.55	2.48	−1.49	6.45	0.214
		Test	27	29.95	12.30					24	7.36	7.68					24	5.50	5.75				
	Buccal	Control	27	22.72	14.74	2.72	−4.93	10.37	0.479	24	12.83	11.19	7.18	1.36	12.99	0.017*	22	4.63	6.76	1.12	−2.35	4.59	0.520
		Test	27	20.00	13.24					24	5.65	8.67					24	3.52	4.83				
	Lingual	Control	27	32.55	13.02	−7.34	−15.93	1.25	0.092	24	14.31	11.70	5.23	−0.66	11.13	0.081	22	11.34	10.27	3.84	−1.43	9.12	0.149
		Test	27	39.90	18.03					24	9.08	8.32					24	7.49	7.35				
	Proximal	Control	27	38.10	12.80	−1.26	−8.31	5.78	0.720	24	19.52	15.66	10.11	2.58	17.65	0.010*	22	10.66	10.69	3.06	−2.74	8.86	0.294
		Test	27	39.36	13.00					24	9.41	9.52					24	7.60	8.82				
PD (mm)	All	Control	27	2.63	0.26	0.18	−0.06	0.42	0.135	24	2.54	0.27	0.19	0.01	0.37	0.037*	22	2.54	0.32	0.13	−0.09	0.34	0.242
		Test	27	2.45	0.56					24	2.35	0.34					24	2.41	0.40				
	Buccal	Control	27	2.53	0.27	0.17	−0.07	0.41	0.159	24	2.46	0.32	0.18	−0.02	0.37	0.072	22	2.43	0.33	0.10	−0.12	0.32	0.372
		Test	27	2.36	0.55					24	2.29	0.35					24	2.33	0.41				
	Lingual	Control	27	2.72	0.28	0.19	−0.06	0.44	0.134	24	2.62	0.27	0.20	0.02	0.39	0.033*	22	2.64	0.35	0.16	−0.08	0.40	0.194
		Test	27	2.53	0.59					24	2.42	0.37					24	2.49	0.45				
	Proximal	Control	27	2.98	0.29	0.19	−0.08	0.45	0.165	24	2.84	0.30	0.19	−0.01	0.39	0.064	22	2.86	0.35	0.12	−0.14	0.38	0.349
		Test	27	2.80	0.62					24	2.65	0.38					24	2.74	0.49				
# of teeth with inflammation	All	Control	27	8.26	4.86	0.22	−2.19	2.63	0.854	24	3.96	3.86	−1.63	−3.55	0.30	0.096	22	2.95	3.11	−1.00	−2.54	0.55	0.201
		Test	27	8.48	3.92					24	2.33	2.66					24	1.96	2.03				

BOP bleeding on probing, *CI* confidence interval, *PD* probing depth, *PII* plaque index, *SD* standard deviation, *MD* mean differences

*Statistically significant differences between study groups

Table 2 Mean changes in clinical outcome variables between study visits, for the teeth

			Baseline–12 months							Baseline–6 months							6–12 months						
		Group	*N*	Mean	SD	MD	95% CI		*p* value	*N*	Mean	SD	MD	95% CI		*p* value	*N*	Mean	SD	MD	95% CI		*p* value
							Lower	Upper						Lower	Upper						Lower	Upper	
PII (%)	All	Control	22	24.04	28.08	−8.58	−24.27	7.10	0.276	24	11.63	22.91	−9.40	−25.04	6.25	0.233	22	10.79	18.30	−0.81	−12.50	10.89	0.890
		Test	24	32.63	24.70					24	21.03	30.41					24	11.60	20.83				
	Buccal	Control	22	19.19	29.46	−7.79	−25.32	9.74	0.375	24	7.60	26.80	−12.94	−29.76	3.88	0.128	22	9.61	21.11	3.17	−8.54	14.89	0.588
		Test	24	26.98	29.48					24	20.54	30.94					24	6.44	18.30				
	Lingual	Control	22	28.90	31.19	−9.38	−26.67	7.91	0.280	24	15.66	25.00	−5.86	−24.96	13.25	0.540	22	11.98	21.38	−4.79	−20.34	10.76	0.538
		Test	24	38.28	26.97					24	21.52	39.21					24	16.77	29.82				
	Proximal	Control	22	27.64	32.85	−10.46	−28.66	7.75	0.253	24	11.03	26.38	−13.93	−31.40	3.54	0.115	22	14.85	25.24	1.71	−13.48	16.91	0.821
		Test	24	38.10	28.39					24	24.96	33.35					24	13.14	25.80				
BOP (%)	All	Control	22	18.71	12.11	−5.56	−12.71	1.60	0.125	24	13.66	13.94	−8.75	−16.07	−1.43	0.020*	22	5.36	6.03	3.50	0.14	6.87	0.042*
		Test	24	24.26	11.95					24	22.40	11.09					24	1.86	5.30				
	Buccal	Control	22	17.25	16.19	0.83	−7.90	9.56	0.849	24	9.90	17.48	−4.38	−13.26	4.49	0.325	22	7.65	9.06	5.52	0.85	10.18	0.021*
		Test	24	16.42	13.16					24	14.29	12.69					24	2.13	6.53				
	Lingual	Control	22	20.15	18.31	−11.96	−22.83	−1.09	0.032*	24	17.40	16.57	−13.13	−23.34	−2.92	0.013*	22	3.08	8.89	1.49	−2.93	5.90	0.500
		Test	24	32.11	18.24					24	30.52	18.52					24	1.59	5.75				
	Proximal	Control	22	25.99	16.88	−5.46	−14.49	3.57	0.229	24	17.89	19.96	−11.75	−21.22	−2.28	0.016*	22	8.53	9.64	6.73	1.87	11.59	0.008*
		Test	24	31.45	13.44					24	29.64	11.51					24	1.80	6.53				
PD (mm)	All	Control	22	0.08	0.28	0.07	−0.23	0.36	0.651	24	0.06	0.24	−0.01	−0.28	0.26	0.934	24	0.06	0.24	−0.01	−0.28	0.26	0.934
		Test	24	0.01	0.63					24	0.07	0.61					24	0.07	0.61				
	Buccal	Control	22	0.09	0.29	0.09	−0.22	0.39	0.572	24	0.04	0.23	−0.01	−0.28	0.26	0.929	24	0.04	0.23	−0.01	−0.28	0.26	0.929
		Test	24	0.00	0.65					24	0.05	0.62					24	0.05	0.62				
	Lingual	Control	22	0.07	0.31	0.05	−0.26	0.36	0.757	24	0.08	0.32	−0.01	−0.30	0.28	0.943	24	0.08	0.32	−0.01	−0.30	0.28	0.943
		Test	24	0.02	0.65					24	0.09	0.64					24	0.09	0.64				
	Proximal	Control	22	0.12	0.33	0.09	−0.26	0.43	0.616	24	0.12	0.28	0.00	−0.30	0.30	1.000	24	0.12	0.28	0.00	−0.30	0.30	1.000
		Test	24	0.04	0.73					24	0.12	0.68					24	0.12	0.68				
BOP reduction teeth	All	Control	22	−4.91	3.42	−1.30	−3.19	0.59	0.174	24	−3.92	3.15	−1.92	−3.63	−0.20	0.029	24	−0.91	1.71	0.53	−0.65	1.72	0.367
		Test	24	−6.21	2.95					24	−5.83	2.73					24	−0.38	2.24				

BOP bleeding on probing, *CI* confidence interval, *PD* probing depth, *PII* plaque index, *SD* standard deviation, *MD* mean differences

*Statistically significant differences between study groups

Table 3 Clinical outcome variables at each study visit, for implants with peri-implant mucositis

Baseline										6 months							12 months						
		Group	*N*	Mean	SD	MD	95% CI		*p* value	*N*	Mean	SD	MD	95% CI		*p* value	*N*	Mean	SD	MD	95% CI		*p* value
							Lower	Upper						Lower	Upper						Lower	Upper	
PII (%)	All	Control	27	51.18	24.57	−4.86	−21.28	11.56	0.555	24	30.40	21.85	1.07	−14.83	16.98	0.893	22	26.98	23.29	5.66	−8.13	19.45	0.413
		Test	27	56.04	34.69					24	29.33	31.95					24	21.33	23.08				
	Buccal	Control	27	42.85	31.30	−2.40	−20.98	16.17	0.796	24	24.46	23.59	1.37	−15.91	18.64	0.874	22	17.88	19.17	−1.99	−16.91	12.94	0.790
		Test	27	45.26	36.53					24	23.09	34.80					24	19.86	29.47				
	Lingual	Control	27	59.50	33.34	−7.32	−26.83	12.19	0.455	24	36.34	29.47	0.78	−17.68	19.24	0.933	22	36.09	36.61	13.30	−4.57	31.17	0.139
		Test	27	66.82	37.96					24	35.56	33.91					24	22.79	19.55				
	Proximal	Control	27	62.61	28.29	−7.92	−25.88	10.04	0.380	24	38.18	25.45	1.26	−16.75	19.28	0.888	22	33.40	25.57	6.05	−9.41	21.51	0.435
		Test	27	70.53	36.91					24	36.92	35.71					24	27.35	26.38				
BOP (%)	All	Control	27	38.42	15.30	−7.43	−17.17	2.31	0.132	24	18.00	16.25	−5.71	−16.91	5.48	0.310	22	13.17	13.09	−0.21	−8.43	8.02	0.960
		Test	27	45.85	20.05					24	23.72	21.88					24	13.38	14.47				
	Buccal	Control	27	31.34	19.17	−13.36	−25.27	−1.44	0.029*	24	15.05	17.09	−7.83	−20.06	4.40	0.204	22	8.84	15.46	−4.94	−15.14	5.26	0.335
		Test	27	44.70	24.17					24	22.87	24.37					24	13.77	18.56				
	Lingual	Control	27	45.49	22.94	−1.50	−14.84	11.84	0.822	24	21.03	19.33	−3.43	−16.51	9.66	0.600	22	17.51	17.78	4.53	−5.98	15.03	0.390
		Test	27	46.99	25.83					24	24.46	25.31					24	12.99	17.54				
	Proximal	Control	27	46.76	15.04	−10.21	−20.58	0.16	0.053	24	19.55	21.28	−6.60	−20.60	7.40	0.347	22	15.41	15.94	0.24	−9.77	10.25	0.962
		Test	27	56.98	22.24					24	26.15	26.60					24	15.17	17.61				
PD (mm)	All	Control	27	3.13	0.37	0.03	−0.27	0.32	0.853	24	2.51	0.38	−0.13	−0.37	0.11	0.289	22	2.35	0.32	−0.04	−0.23	0.15	0.700
		Test	27	3.10	0.68					24	2.64	0.44					24	2.39	0.32				
	Buccal	Control	27	2.89	0.47	−0.08	−0.42	0.26	0.642	24	2.46	0.49	−0.10	−0.37	0.17	0.465	22	2.29	0.43	−0.03	−0.26	0.21	0.805
		Test	27	2.97	0.73					24	2.55	0.44					24	2.32	0.36				
	Lingual	Control	27	3.36	0.40	0.13	−0.20	0.47	0.427	24	2.56	0.35	−0.16	−0.42	0.11	0.237	22	2.41	0.32	−0.04	−0.25	0.17	0.671
		Test	27	3.23	0.77					24	2.72	0.53					24	2.46	0.38				
	Proximal	Control	27	3.46	0.50	0.06	−0.29	0.40	0.746	24	2.72	0.47	−0.09	−0.37	0.18	0.493	22	2.58	0.34	−0.01	−0.22	0.19	0.909
		Test	27	3.41	0.75					24	2.81	0.48					24	2.59	0.35				
# of implants with inflammation	All	Control	27	3.22	1.89	−0.07	−1.07	0.92	0.882	24	1.54	1.28	0.50	−0.37	1.37	0.253	22	1.41	1.47	0.22	−0.70	1.13	0.638
		Test	27	3.15	1.75					24	2.04	1.68					24	1.63	1.61				

BOP bleeding on probing, *CI* confidence interval, *PD* probing depth, *PII* plaque index, *SD* standard deviation, *MD* mean differences

*Statistically significant differences between study groups

the studied variables, except for plaque reduction at the lingual sites, with higher reductions in the test group, when compared with the control group, from baseline to 12 months (42.66% [SD = 32.67] versus 18.25% [SD = 36.54]; $p = 0.021$) (Table 4).

Disease resolution

Mean values of the number of teeth or implants with inflammation are presented in Tables 1, 2, 3, and 4. Although a higher reduction in the number of teeth with inflammation (compared to implants) was observed, none of the treatment groups, either on the teeth or on implants, was able to obtain a complete disease resolution at the end of the study.

Staining assessment

A statistically significant higher stain accumulation was observed in the test group at each study visit ($p < 0.001$), in terms of extension, intensity, and extension*intensity, both in the coronal and root areas (Table 5).

Patient compliance and PROMs

At 6 months, both groups demonstrated a similar degree of compliance, as measured by the remaining liquid in the returned bottles. Compliance decreased from the 6- to the 12-month visits, in both treatment groups, being the patients in the control group significantly less compliant ($p = 0.049$) (Table S2, SM).

PROMs, assessed by means of a questionnaire, did not reveal any statistically significant difference between treatment groups in terms of taste disturbance, burning feeling, and mucosal alteration (Table S3, SM). However, patients in the test group referred significant higher levels of staining on the teeth or tongue due to the use of the mouth rinse at the 6- ($p = 0.000$) and 12-month ($p = 0.009$) visits.

Discussion

This double-blind, placebo-controlled RCT, of 1-year duration, demonstrated that a mouth rinse containing a low dose of CHX (0.03%) combined with 0.05% CPC, when used as an adjunct to PMPR and self-performed biofilm control, was associated to less BOP and a greater BOP reduction in teeth with gingivitis. However, the impact of the same tested intervention on the peri-implant tissues in sites with PiM did not show statistically significant differences in any of the parameters tested, except for plaque reduction at the lingual sites.

It is important to emphasize that most patients using implant-supported prosthetic restorations are partially edentulous, hence having both teeth and dental implants at risk of both gingivitis and PiM. Therefore, the present RCT, designed to assess the adjunctive benefit in the management of both PiM and gingivitis when using daily a 0.03% CHX and 0.05% CPC mouth rinse, over a period of 12 months has clear practical implications. Only one study has previously analyzed the effect of a protocol combining PPR with an adjunctive biofilm control approach (photodynamic therapy) in the management of PiM and gingivitis [37]. Similarly to our findings, they reported a higher percentage of BOP around implants as compared with the teeth (42% vs 22%), confirming that irrespectively of the adjunctive method used, it is more difficult to control inflammation around dental implants than around the teeth.

The findings reported in regard to the efficacy of the tested intervention in PiM sites were similar to those reported in the previous publication from the same study sample, where only the most affected site per subject was evaluated [29]. Both studies failed to report any significant added benefit, either in clinical or microbiological parameters, when a low dose chlorhexidine was combined with 0.05% CPC as an adjunct to oral hygiene measures. The lesser impact of the tested mouth rinse around implants, versus around the teeth, in most the clinical outcomes measured, could be explained by different factors. One could be the questionable reliability of peri-implant soft tissue clinical parameters [38]. It is well documented that the current methods to assess peri-implant health or disease may be influenced by probing forces [39], the existence of an appropriate access to insert the periodontal probe [40], and the structural differences between the peri-implant versus periodontal supracrestal tissues [41]. As a matter of fact, the probability of false positive BOP around implants is high and a single site (around an implant) positive to BOP may not represent a true sign of pathology [6]. Other factors, such as residual PD, absence of keratinised mucosa, implant position, the abutment material, or the difficulties in access to oral hygiene due to the design of the prosthesis, have been associated with higher levels of inflammation in peri-implant tissues [23, 42]. It is, therefore, conceivable that the resulting differences in efficacy between PiM and gingivitis sites may be due not only to the tested interventions, but rather to these other factors intrinsic to the peri-implant environment, which probably require a deeper understanding. In order to prevent the onset of PiM, actions should be applied by both the clinician and the patient. The clinician needs to adequately place the implants and design the implant-supported prostheses [42] to facilitate the access for appropriate patient's plaque control. The patient must be motivated and trained to perform a correct daily mechanical and, sometimes, chemical biofilm control [23], together with the regular attendance to the supportive implant care [4].

Conversely, the results of the tested intervention on gingivitis sites, with significant reductions in BOP, for up to 6 months, and significantly higher BOP reductions from

Table 4 Mean changes in clinical outcome variables between study visits, for implants with peri-implant mucositis

			Baseline–12 months							Baseline–6 months							6–12 months						
		Group	*N*	Mean	SD	MD	95% CI		*p* value	*N*	Mean	SD	MD	95% CI		*p* value	*N*	Mean	SD	MD	95% CI		*p* value
							Lower	Upper						Lower	Upper						Lower	Upper	
PII (%)	All	Control	22	20.49	28.72	−11.51	−28.22	5.20	0.172	24	18.21	30.69	−5.79	−24.30	12.72	0.532	22	4.16	15.78	−3.84	−14.44	6.76	0.469
		Test	24	31.99	27.52					24	23.99	32.98					24	8.00	19.51				
	Buccal	Control	22	22.72	30.10	1.39	−16.39	19.17	0.875	24	17.38	43.42	−0.72	−23.57	22.14	0.950	22	6.79	17.07	3.56	−8.95	16.07	0.569
		Test	24	21.33	29.69					24	18.10	34.78					24	3.23	24.08				
	Lingual	Control	22	18.25	36.54	−24.41	−44.98	−3.84	0.021*	24	19.03	36.50	−10.86	−32.46	10.74	0.317	22	1.53	27.58	−11.24	−26.45	3.97	0.144
		Test	24	42.66	32.67					24	29.89	37.83					24	12.77	23.59				
	Proximal	Control	22	25.26	33.78	−14.23	−32.88	4.41	0.131	24	21.49	35.45	−8.44	−29.58	12.71	0.426	22	6.36	18.43	−3.21	−16.54	10.13	0.630
		Test	24	39.50	28.94					24	29.93	37.32					24	9.57	25.53				
BOP (%)	All	Control	22	26.21	21.70	−5.04	−16.40	6.32	0.376	24	20.41	20.11	−0.50	−12.64	11.64	0.934	22	4.95	19.18	−5.39	−15.51	4.74	0.290
		Test	24	31.25	16.36					24	20.92	21.64					24	10.33	14.78				
	Buccal	Control	22	22.68	23.50	−8.28	−21.37	4.82	0.210	24	17.08	19.73	−4.77	−17.82	8.28	0.466	22	7.07	18.64	−2.03	−12.77	8.71	0.705
		Test	24	30.96	20.57					24	21.86	24.90					24	9.10	17.50				
	Lingual	Control	22	29.73	29.26	−1.81	−17.05	13.43	0.812	24	23.67	31.77	3.59	−13.25	20.44	0.670	22	2.90	26.30	−8.57	−22.25	5.11	0.214
		Test	24	31.54	21.77					24	20.08	25.91					24	11.47	19.50				
	Proximal	Control	22	31.47	22.99	−8.08	−19.88	3.72	0.175	24	26.90	21.08	−1.68	−14.88	11.53	0.800	22	4.78	26.29	−6.20	−19.15	6.76	0.340
		Test	24	39.55	16.45					24	28.57	24.26					24	10.97	16.61				
PD (mm)	All	Control	22	0.74	0.32	0.08	−0.25	0.41	0.637	24	0.61	0.28	0.20	−0.14	0.54	0.243	24	0.61	0.28	0.20	−0.14	0.54	0.243
		Test	24	0.66	0.70					24	0.41	0.77					24	0.41	0.77				
	Buccal	Control	22	0.59	0.41	−0.01	−0.37	0.34	0.948	24	0.45	0.35	0.08	−0.28	0.45	0.655	24	0.45	0.35	0.08	−0.28	0.45	0.655
		Test	24	0.60	0.73					24	0.37	0.82					24	0.37	0.82				
	Lingual	Control	22	0.88	0.43	0.17	−0.21	0.54	0.376	24	0.77	0.38	0.31	−0.05	0.68	0.089	24	0.77	0.38	0.31	−0.05	0.68	0.089
		Test	24	0.71	0.77					24	0.45	0.80					24	0.45	0.80				
	Proximal	Control	22	0.82	0.41	0.08	−0.28	0.45	0.657	24	0.74	0.36	0.22	−0.16	0.59	0.246	24	0.74	0.36	0.22	−0.16	0.59	0.246
		Test	24	0.74	0.75					24	0.52	0.83					24	0.52	0.83				
BOP reduction implants	All	Control	22	−1.77	1.69	−0.02	−0.91	0.87	0.966	24	−1.54	1.53	0.17	−0.66	1.00	0.688	24	−0.14	1.32	−0.28	−0.97	0.41	0.414
		Test	24	−1.79	1.28					24	−1.38	1.31					24	−0.42	0.97				

BOP bleeding on probing, *CI* confidence interval, *PD* probing depth, *PII* plaque index, *SD* standard deviation, *MD* mean differences

*Statistically significant differences between study groups

Table 5 Mean values for staining (extension and intensity) at each study visit

				Baseline				6 months				12 months			
			Group	*N*	Mean	SD	*p* value	*N*	Mean	SD	*p* value	*N*	Mean	SD	*p* value
Extension	Coronal	All	Control	27	0.19	0.30	0.051	24	0.24	0.35	0.000*	22	0.22	0.26	0.000*
			Test	27	0.46	0.52		24	1.09	0.67		24	1.06	0.65	
		2nd sextant	Control	26	0.18	0.34	0.110	23	0.20	0.42	0.000*	21	0.18	0.32	0.000*
			Test	27	0.40	0.50		24	1.07	0.79		24	1.08	0.76	
		5th sextant	Control	27	0.20	0.40	0.054	24	0.28	0.38	0.001*	22	0.26	0.37	0.002*
			Test	27	0.52	0.67		24	1.14	0.89		24	1.07	0.91	
	Radicular	All	Control	23	0.52	0.54	0.054	20	0.65	0.57	0.000*	20	0.64	0.60	0.000*
			Test	23	0.92	0.75		20	2.00	0.84		20	1.94	0.84	
		2nd sextant	Control	19	0.38	0.48	0.442	16	0.40	0.48	0.011*	16	0.34	0.47	0.024*
			Test	14	0.55	0.66		11	1.47	1.18		13	1.25	1.18	
		5th sextant	Control	18	0.70	0.65	0.147	17	0.91	0.66	0.000*	17	0.92	0.74	0.000*
			Test	22	1.07	0.86		20	2.13	0.90		20	2.15	0.85	
Intensity	Coronal	All	Control	27	0.19	0.31	0.083	24	0.23	0.36	0.000*	22	0.21	0.25	0.000*
			Test	27	0.37	0.42		24	1.40	1.02		24	1.36	1.01	
		2nd sextant	Control	26	0.22	0.42	0.194	23	0.23	0.47	0.000*	21	0.20	0.34	0.000*
			Test	27	0.35	0.45		24	1.38	1.21		24	1.32	1.17	
		5th sextant	Control	27	0.16	0.34	0.055	24	0.23	0.33	0.000*	22	0.22	0.30	0.001*
			Test	27	0.40	0.51		24	1.42	1.20		24	1.40	1.19	
	Radicular	All	Control	23	0.43	0.46	0.115	20	0.58	0.56	0.000*	20	0.63	0.64	0.000*
			Test	23	0.73	0.61		20	2.05	0.93		20	2.05	0.95	
		2nd sextant	Control	19	0.35	0.45	0.575	16	0.55	0.74	0.021*	16	0.52	0.76	0.032*
			Test	14	0.48	0.58		11	1.59	1.20		13	1.42	1.24	
		5th sextant	Control	18	0.57	0.57	0.201	17	0.72	0.57	0.000*	17	0.83	0.73	0.000*
			Test	22	0.83	0.65		20	2.19	0.97		20	2.22	0.97	
Extension * Intensity	Coronal	All	Control	27	0.61	0.76	0.053	23	0.37	0.64	0.000*	22	0.31	0.44	0.000*
			Test	27	0.61	0.76		24	2.67	2.11		24	2.55	2.15	
		2nd sextant	Control	26	0.24	0.46	0.137	22	0.35	0.74	0.000*	21	0.25	0.42	0.000*
			Test	27	0.52	0.73		24	2.56	2.62		24	2.50	2.65	
		5th sextant	Control	27	0.26	0.67	0.053	23	0.40	0.66	0.001*	22	0.37	0.63	0.002*
			Test	27	0.71	0.99		24	2.85	2.68		24	2.69	2.69	
	Radicular	All	Control	23	0.60	0.64	0.041	20	0.88	0.77	0.000*	20	1.00	1.01	0.000*
			Test	23	1.28	1.15		20	5.02	2.70		20	4.95	2.75	
		2nd sextant	Control	19	0.38	0.48	0.316	16	0.65	0.83	0.009*	16	0.57	0.81	0.017*
			Test	14	0.70	1.00		11	3.71	3.33		13	3.18	3.36	
		5th sextant	Control	18	0.87	0.95	0.139	17	1.18	0.88	0.000*	17	1.41	1.25	0.000*
			Test	22	1.54	1.39		20	5.44	2.97		20	5.53	2.90	

SD standard deviation

*Statistically significant differences

baseline to 6 months, irrespective of the sites evaluated were in agreement with the results reported in two recent systematic reviews [27, 43], which have confirmed the antiplaque and antigingivitis effects of CHX mouth rinses in the treatment of gingivitis. After 12 months, reductions were only statistically significant at lingual sites, which could be explained by the fact that these sites are more difficult to clean only by mechanical measures. Another reason for the dilution in the benefits of the tested mouth rinse may be explained by the additional improvements observed in the control group from 6 to 12 months, which may reflect the importance of continuous motivation and reinforcement in oral hygiene instructions.

Experimental studies on peri-implant mucositis and gingivitis in animals [18] have demonstrated that the area occupied by the inflammatory infiltrate is greater in the peri-implant lesions than in the gingivitis one. Similar studies in humans [17] have shown that even though the clinical parameters of both diseases reverted when oral hygiene measures were reinstalled, the biochemical markers associated with inflammation did not disappear after the hygienic phase in peri-implant sites. In a recent similar study, the reversibility in clinical

inflammation could not be demonstrated after experimental PiM, when the implant shoulder was located in vicinity with the bone crest [44]. The results observed in these experimental studies may reinforce the assumption that PiM is more difficult to revert than gingivitis. The anatomical and histological differences between the teeth and implants [45] and the current methods to assess peri-implant health [39, 40] might have an influence in this distinct behavior. Nevertheless, these results should not underscore the importance of early diagnosis and treatment of PiM as the main measure to prevent the onset of peri-implantitis [4].

The long-term use of CHX has been associated with side effects such as tooth staining [46], being this staining proportional to the concentration of CHX in the formulation. In this study, even though a low CHX concentration (0.03%) was used in the tested formulation, the subjects in this test group presented significantly higher staining scores, as compared with the control group, both in terms of extension and intensity and at both root and crown areas. This finding may be explained by the fact that staining could be more related to the bioavailability of the active agents in whole formulation rather that the concentration of one the active agents [31, 32]. However, when these expected side effects were assessed by the subjects participating in the trial through the evaluated PROMs for taste disturbance, burning feeling, or mucosal irritation, their results were similar in both groups, and only tooth staining perception was reported with higher scores by patients in the test group. These PROMs, however, did not influence the compliance of the subjects, which at 12 months was even higher in the test group.

It is important to acknowledge some limitations of the present trial, including the differences detected at baseline, since the test group had a significant greater BOP at buccal sites around implants. Moreover, this study was designed to detect differences between the products around implants, and not around the teeth. In addition, the large variability observed for implant reconstructions (implant location, implant abutment, type of restorations) may have also influenced the reported results.

Conclusion

In conclusion, and within the limitations of the present study, this 12-month RCT demonstrated that additional benefits can be expected when using the tested mouth rinse, combined with PPR, in patients with gingivitis and PiM; statistically significant differences were only achieved in teeth with gingivitis.

Funding information The present study was funded through a contract (58/2015) between University Complutense and Dentaid S.A. (Barcelona, Spain), within the activities of the Dentaid-UCM Extraordinary Chair in Periodontal Research.

Compliance with ethical standards

Conflict of interest Author Juan Bollain declares that he has no conflict of interest with this research.

Author Alberto Pulcini declares that he has no conflict of interest with this research.

Author Ignacio Sanz-Sánchez declares that he has no conflict of interest with this research. He might present indirect conflict of interest due to the persona fees for lecturing from Colgate, Dentium, Mozograu, Camlog and EMS.

Author Elena Figuero declares that he has no conflict of interest with this research. She might present indirect conflict of interest due to the persona fees for lecturing from Colgate, Dentaid, Oral-B and Straumann.

Author Bettina Alonso declares that he has no conflict of interest with this research Dentium, Mozograu, Camlog and EMS.

Author Mariano Sanz declares that he has no conflict of interest with this research. He might present indirect conflict of interest due to the persona fees for lecturing from Dentaid, Oral-B, and Straumann; and due to grants (research contracts in university) from Dentsply and IMS outside the submitted work.

Author David Herrera declares that he has no conflict of interest with this research. He might present indirect conflict of interest due to the personal fees for lecturing from Oral-B, Straumman, Klockner, Dexcel, Dentaid and Colgate; and due to grants from Kulzer outside the submitted work.

Ethical approval All procedures performed in the study participants were in accordance with the ethical standards of an institutional ethical committee (C.I. 15/064, Comité de Ensayos Clínicos del Hospital Clínico de San Carlos, Madrid) and with the 1964 Helsinki declaration.

Informed consent All the included patients signed an informed consent which was previously approved by an institutional ethic committee.

References

1. Arweiler NB, Auschill TM, Sculean A (2018) Patient self-care of periodontal pocket infections. Periodontol 2000 76(1):164–179. https://doi.org/10.1111/prd.12152
2. Lindhe J, Westfelt E, Nyman S, Socransky SS, Haffajee AD (1984) Long-term effect of surgical/non-surgical treatment of periodontal disease. J Clin Periodontol 11(7):448–458. https://doi.org/10.1111/j.1600-051x.1984.tb01344.x
3. Matuliene G, Studer R, Lang NP, Schmidlin K, Pjetursson BE, Salvi GE, Bragger U, Zwahlen M (2010) Significance of periodontal risk assessment in the recurrence of periodontitis and tooth loss. J Clin Periodontol 37(2):191–199. https://doi.org/10.1111/j.1600-051X.2009.01508.x
4. Costa FO, Takenaka-Martinez S, Cota LO, Ferreira SD, Silva GL, Costa JE (2012) Peri-implant disease in subjects with and without preventive maintenance: a 5-year follow-up. J Clin Periodontol 39(2):173–181. https://doi.org/10.1111/j.1600-051X.2011.01819.x
5. Monje A, Aranda L, Diaz KT, Alarcon MA, Bagramian RA, Wang HL, Catena A (2016) Impact of maintenance therapy for the prevention of peri-implant diseases: a systematic review and meta-analysis. J Dent Res 95(4):372–379. https://doi.org/10.1177/0022034515622432
6. Derks J, Tomasi C (2015) Peri-implant health and disease. A systematic review of current epidemiology. J Clin Periodontol 42(Suppl 16):S158–S171. https://doi.org/10.1111/jcpe.12334
7. Lee CT, Huang YW, Zhu L, Weltman R (2017) Prevalences of peri-implantitis and peri-implant mucositis: systematic review and meta-analysis. J Dent 62:1–12. https://doi.org/10.1016/j.jdent.2017.04.011

8. Rodrigo D, Sanz-Sanchez I, Figuero E, Llodra JC, Bravo M, Caffesse RG, Vallcorba N, Guerrero A, Herrera D (2018) Prevalence and risk indicators of peri-implant diseases in Spain. J Clin Periodontol 45(12): 1510–1520. https://doi.org/10.1111/jcpe.13017
9. Cosgarea R, Sculean A, Shibli JA, Salvi GE (2019) Prevalence of peri-implant diseases - a critical review on the current evidence. Braz Oral Res 33(suppl 1):e063. https://doi.org/10.1590/1807-3107bor-2019.vol33.0063
10. Rakic M, Galindo-Moreno P, Monje A, Radovanovic S, Wang HL, Cochran D, Sculean A, Canullo L (2018) How frequent does peri-implantitis occur? A systematic review and meta-analysis. Clin Oral Investig 22(4):1805–1816. https://doi.org/10.1007/s00784-017-2276-y
11. Dreyer H, Grischke J, Tiede C, Eberhard J, Schweitzer A, Toikkanen SE, Glockner S, Krause G, Stiesch M (2018) Epidemiology and risk factors of peri-implantitis: a systematic review. J Periodontal Res 53(5): 657–681. https://doi.org/10.1111/jre.12562
12. Albandar JM, Rams TE (2002) Global epidemiology of periodontal diseases: an overview. Periodontol 2000 29:7–10. https://doi.org/10.1034/j.1600-0757.2002.290101.x
13. Frencken JE, Sharma P, Stenhouse L, Green D, Laverty D, Dietrich T (2017) Global epidemiology of dental caries and severe periodontitis - a comprehensive review. J Clin Periodontol 44(Suppl 18): S94–S105. https://doi.org/10.1111/jcpe.12677
14. Pontoriero R, Tonelli MP, Carnevale G, Mombelli A, Nyman SR, Lang NP (1994) Experimentally induced peri-implant mucositis. A clinical study in humans. Clin Oral Implants Res 5(4):254–259. https://doi.org/10.1034/j.1600-0501.1994.050409.x
15. Loe H, Theilade E, Jensen SB (1965) Experimental gingivitis in man. J Periodontol 36:177–187. https://doi.org/10.1902/jop.1965.36.3.177
16. Zitzmann NU, Berglundh T, Marinello CP, Lindhe J (2001) Experimental peri-implant mucositis in man. J Clin Periodontol 28(6):517–523. https://doi.org/10.1034/j.1600-051x.2001.028006517.x
17. Salvi GE, Aglietta M, Eick S, Sculean A, Lang NP, Ramseier CA (2012) Reversibility of experimental peri-implant mucositis compared with experimental gingivitis in humans. Clin Oral Implants Res 23(2):182–190. https://doi.org/10.1111/j.1600-0501.2011.02220.x
18. Ericsson I, Berglundh T, Marinello C, Liljenberg B, Lindhe J (1992) Long-standing plaque and gingivitis at implants and teeth in the dog. Clin Oral Implants Res 3(3):99–103. https://doi.org/10.1034/j.1600-0501.1992.030301.x
19. Trombelli L, Farina R, Silva CO, Tatakis DN (2018) Plaque-induced gingivitis: case definition and diagnostic considerations. J Periodontol 89(Suppl 1):S46–S73. https://doi.org/10.1002/JPER.17-0576
20. Heitz-Mayfield LJA, Salvi GE (2018) Peri-implant mucositis. J Clin Periodontol 45(Suppl 20):S237–S245. https://doi.org/10.1111/jcpe.12953
21. Lang NP, Adler R, Joss A, Nyman S (1990) Absence of bleeding on probing. An indicator of periodontal stability. J Clin Periodontol 17(10):714–721. https://doi.org/10.1111/j.1600-051x.1990.tb01059.x
22. Carcuac O, Derks J, Abrahamsson I, Wennstrom JL, Petzold M, Berglundh T (2017) Surgical treatment of peri-implantitis: 3-year results from a randomized controlled clinical trial. J Clin Periodontol 44(12):1294–1303. https://doi.org/10.1111/jcpe.12813
23. Jepsen S, Berglundh T, Genco R, Aass AM, Demirel K, Derks J, Figuero E, Giovannoli JL, Goldstein M, Lambert F, Ortiz-Vigon A, Polyzois I, Salvi GE, Schwarz F, Serino G, Tomasi C, Zitzmann NU (2015) Primary prevention of peri-implantitis: managing peri-implant mucositis. J Clin Periodontol 42(Suppl 16):S152–S157. https://doi.org/10.1111/jcpe.12369
24. Brecx M, Brownstone E, MacDonald L, Gelskey S, Cheang M (1992) Efficacy of Listerine, Meridol and chlorhexidine mouth rinses as supplements to regular tooth cleaning measures. J Clin Periodontol 19(3):202–207. https://doi.org/10.1111/j.1600-051x.1992.tb00640.x
25. James P, Worthington HV, Parnell C, Harding M, Lamont T, Cheung A, Whelton H, Riley P (2017) Chlorhexidine mouthrinse as an adjunctive treatment for gingival health. Cochrane Database Syst Rev 3:CD008676. https://doi.org/10.1002/14651858.CD008676.pub2
26. Escribano M, Figuero E, Martin C, Tobias A, Serrano J, Roldan S, Herrera D (2016) Efficacy of adjunctive anti-plaque chemical agents: a systematic review and network meta-analyses of the Turesky modification of the Quigley and Hein plaque index. J Clin Periodontol 43(12): 1059–1073. https://doi.org/10.1111/jcpe.12616
27. Figuero E, Herrera D, Tobias A, Serrano J, Roldan S, Escribano M, Martin C (2019) Efficacy of adjunctive anti-plaque chemical agents in managing gingivitis: a systematic review and network meta-analyses. J Clin Periodontol 46(7):723–739. https://doi.org/10.1111/jcpe.13127
28. Schwarz F, Becker K, Sager M (2015) Efficacy of professionally administered plaque removal with or without adjunctive measures for the treatment of peri-implant mucositis. A systematic review and meta-analysis. J Clin Periodontol 42(Suppl 16):S202–S213. https://doi.org/10.1111/jcpe.12349
29. Pulcini A, Bollain J, Sanz-Sanchez I, Figuero E, Alonso B, Sanz M, Herrera D (2019) 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. J Clin Periodontol 46(3):342–353. https://doi.org/10.1111/jcpe.13088
30. Brecx M, Netuschil L, Reichert B, Schreil G (1990) Efficacy of Listerine, Meridol and chlorhexidine mouthrinses on plaque, gingivitis and plaque bacteria vitality. J Clin Periodontol 17(5):292–297. https://doi.org/10.1111/j.1600-051x.1990.tb01092.x
31. Herrera D, Roldan S, Santacruz I, Santos S, Masdevall M, Sanz M (2003) Differences in antimicrobial activity of four commercial 0.12% chlorhexidine mouth rinse formulations: an in vitro contact test and salivary bacterial counts study. J Clin Periodontol 30(4): 307–314. https://doi.org/10.1034/j.1600-051x.2003.00341.x
32. Garcia-Gargallo M, Zurlohe M, Montero E, Alonso B, Serrano J, Sanz M, Herrera D (2017) Evaluation of new chlorhexidine- and cetylpyridinium chloride-based mouthrinse formulations adjunctive to scaling and root planing: pilot study. Int J Dent Hyg 15(4):269–279. https://doi.org/10.1111/idh.12254
33. Lang NP, Berglundh T, Working Group 4 of Seventh European Workshop on P (2011) Periimplant diseases: where are we now?–Consensus of the seventh European workshop on periodontology. J Clin Periodontol 38(Suppl 11):178–181. https://doi.org/10.1111/j.1600-051X.2010.01674.x
34. Chapple ILC, Mealey BL, Van Dyke TE, Bartold PM, Dommisch H, Eickholz P, Geisinger ML, Genco RJ, Glogauer M, Goldstein M, Griffin TJ, Holmstrup P, Johnson GK, Kapila Y, Lang NP, Meyle J, Murakami S, Plemons J, Romito GA, Shapira L, Tatakis DN, Teughels W, Trombelli L, Walter C, Wimmer G, Xenoudi P, Yoshie H (2018) Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: consensus report of workgroup 1 of the 2017 world workshop on the classification of periodontal and peri-implant diseases and conditions. J Clin Periodontol 45(Suppl 20):S68–S77. https://doi.org/10.1111/jcpe.12940
35. Lobene RR (1968) Effect of dentifrices on tooth stains with controlled brushing. J Am Dent Assoc 77(4):849–855. https://doi.org/10.14219/jada.archive.1968.0298
36. Ramberg P, Lindhe J, Botticelli D, Botticelli A (2009) The effect of a triclosan dentifrice on mucositis in subjects with dental implants: a six-month clinical study. J Clin Dent 20(3):103–107
37. Zeza B, Farina R, Pilloni A, Mongardini C (2018) Clinical outcomes of experimental gingivitis and peri-implant mucositis treatment with professionally administered plaque removal and

photodynamic therapy. Int J Dent Hyg 16(2):e58–e64. https://doi.org/10.1111/idh.12302
38. Coli P, Christiaens V, Sennerby L, Bruyn H (2017) Reliability of periodontal diagnostic tools for monitoring peri-implant health and disease. Periodontol 2000 73(1):203–217. https://doi.org/10.1111/prd.12162
39. Gerber JA, Tan WC, Balmer TE, Salvi GE, Lang NP (2009) Bleeding on probing and pocket probing depth in relation to probing pressure and mucosal health around oral implants. Clin Oral Implants Res 20(1):75–78. https://doi.org/10.1111/j.1600-0501.2008.01601.x
40. Serino G, Turri A, Lang NP (2013) Probing at implants with peri-implantitis and its relation to clinical peri-implant bone loss. Clin Oral Implants Res 24(1):91–95. https://doi.org/10.1111/j.1600-0501.2012.02470.x
41. Armitage GC, Svanberg GK, Loe H (1977) Microscopic evaluation of clinical measurements of connective tissue attachment levels. J Clin Periodontol 4(3):173–190. https://doi.org/10.1111/j.1600-051x.1977.tb02271.x
42. Sanz-Sanchez I, Sanz-Martin I, Carrillo de Albornoz A, Figuero E, Sanz M (2018) Biological effect of the abutment material on the stability of peri-implant marginal bone levels: a systematic review and meta-analysis. Clin Oral Implants Res 29(Suppl 18):124–144. https://doi.org/10.1111/clr.13293
43. Serrano J, Escribano M, Roldan S, Martin C, Herrera D (2015) Efficacy of adjunctive anti-plaque chemical agents in managing gingivitis: a systematic review and meta-analysis. J Clin Periodontol 42(Suppl 16):S106–S138. https://doi.org/10.1111/jcpe.12331
44. Chan D, Pelekos G, Ho D, Cortellini P, Tonetti MS (2019) The depth of the implant mucosal tunnel modifies the development and resolution of experimental peri-implant mucositis: a case-control study. J Clin Periodontol 46(2):248–255. https://doi.org/10.1111/jcpe.13066
45. Eggert FM, Levin L (2018) Biology of teeth and implants: host factors - pathology, regeneration, and the role of stem cells. Quintessence Int 49(6):497–509. https://doi.org/10.3290/j.qi.a40289
46. Smith RG, Moran J, Addy M, Doherty F, Newcombe RG (1995) Comparative staining in vitro and plaque inhibitory properties in vivo of 0.12% and 0.2% chlorhexidine mouthrinses. J Clin Periodontol 22(8):613–617. https://doi.org/10.1111/j.1600-051x.1995.tb00814.x