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Treatment of peri-implantitis using multiple applications of chlorhexidine chips: a double-blind, randomized multi-centre clinical trial

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Abstract

Background: Universal strategies for managing peri-implantitis are yet to be adopted. The aim of this study is to examine a protocol of intensive application of chlorhexidine containing chips in sites with peri-implantitis.

Materials and Methods: This multi-centre, randomized, double-blind, parallel, two-arm clinical trial included 60 patients (77 implants) with probing depth (PD) 6–10 mm and bone loss $\geq$2 mm around 1–2 implants. One to two weeks following SRP, baseline measurements were made followed by implants' debridement. Patients were randomized to receive matrix chips (MatrixC) or chlorhexidine Chips (PerioC). Measurements and chips placement were repeated at weeks 2, 4, 6, 8, 12 and 18. At 6 months, patients returned for final examination.

Results: Probing depth reduction was greater in the PerioC (2.19 ± 0.24 mm) compared with MatrixC (1.59 ± 0.23 mm), $p = 0.07$. Seventy percentage of the implants in the PerioC and 54% in the MatrixC had PD reduction $\geq$ 2 mm. Likewise, 40% of the sites (PerioC) and 24% (MatrixC) had PD reduction $\geq$ 3 mm. Clinical attachment level gains for both groups were significant; however, the changes in the PerioC group were significantly greater than in MatrixC [2.21 ± 0.23 mm. and 1.56 ± 0.25 mm respectively, $p = 0.05$]. Bleeding on probing was reduced by half in both groups.

Conclusion: Frequent placement of PerioC and MatrixC together with implants debridement resulted in a substantial improvement in sites with peri-implantitis. Further studies will be required to fully appreciate the mechanism of this treatment.

Key words: anti-Inflammatory agents; antimicrobial agents; clinical trial; delayed-action preparations; dental implants; peri-implantitis; therapy

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Conflict of interest and source of funding statement

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Peri-implantitis is rapidly becoming a major oral disease entity that is frequently encountered in the dental office. With approximately ten million new implants placed annually worldwide (Markets for Dental

Implants and Final Abutments 2009), and tens of millions of implants that are currently functioning, the magnitude of this problem is ever growing.

In their systematic review, Zitzmann & Berglundh (2008) have reported that 50% of the implants and 80% of the patients had mucositis, while peri-implantitis was reported in 12–43% of the implants and 28–56% of the patients. Conversely, Jung et al. (2008) in a systematic review and meta-analysis on the 5 years survival and complications of dental implants supporting single crowns reported lower frequencies of peri-implantitis (~ 10%). These differences in the reported prevalence might be associated with the threshold used to define disease. Koldsland et al. (2010) studied 164 subjects treated with dental implants and followed for over 8 years; he was able to show that depending on the different clinical and radiographic threshold that was used, disease prevalence varied considerably between 11.3% and 47.1%. Another possible variable that might affect the prevalence of peri-implantitis is patient's periodontal status. Roccuzzo et al. (2012) reported their results of a 10-year prospective cohort study on implants in periodontally healthy and compromised patients treated with scaling and root planing (SRP): 10.7% of the implants in the periodontally healthy cases required some kind of adjunctive (surgical or non-surgical) treatment through these years compared with 15.9% and 27.2% for patients with initial diagnosis of moderate and severe chronic periodontitis. Similar findings were recently reported by Cho-Yan Lee et al. (2012).

Optimal treatment strategies for the treatment of peri-implantitis are yet to be commonly agreed upon. Renvert et al. (2008a) in a literature review have reported that non-surgical therapy was not found to be effective in these lesions. These authors, in a subsequent double-blind study (2009) of debridement of dental implants affected by peri-implantitis, using hand and ultrasonic instruments, have reported only minimal (0.2 mm.) and statistically insignificant change in probing depth (PD) 6-month post-operative for both treatment groups. Likewise, Lindhe & Meyle (2008) on behalf of the European workshop on Periodontology have concluded that non-surgical mechanical therapy causes the reduction of inflammation as evident in the decrease in bleeding on probing (BOP); however, the overall improvement in clinical parameters is at best unpredictable. Furthermore, Tonetti & Palmer (2012) on behalf of the 8th European workshop on Periodontology referred to the relatively small number of well-designed randomized clinical trials in implant dentistry as an impairment for our progress in this field.

To further improve treatment outcome, several adjunctive treatment modalities were employed. Renvert et al. (2011) reported similar and only modest improvement in PD, when using air abrasive or *Er:YAG* laser therapy in patients with peri-implantitis. Sahm et al. (2011) reported that 6 months after treatment of peri-implantitis with either air abrasive of mechanical cleaning and subgingival application of chlorhexidine solution and gel, mean pocket reduction and clinical attachment level (CAL) gain were both approximately 0.5 mm, which was similar in both groups. The use of local delivery of minocycline to enhance treatment response in these cases was reported by Salvi et al. (2007). Despite some pocket reduction, six patients (25% of the entire study population) were removed from the study as the implants were either explanted or required additional therapy due to $\geq$2 mm. increase in PD during the observation period. Similarly, Büchter et al. (2004) have utilized doxycyline gel for the treatment of peri-implantitis. PD reduction and CAL gain were greater (0.6 mm) in sites with the adjunctive treatment compared with subgingival debridement only.

Recently (Machtei et al. 2011), we have been able to demonstrate that frequent application of biodegradable matrix containing chlorhexidine (PerioChip®; Dexcel Pharma, Or-Akiva, Israel) in patients with chronic periodontitis with PD $\geq$ 5 mm resulted in a sizeable improvement in mean PD (2.1 mm) and gain in CAL (1.7 mm).

Several in vitro investigations have demonstrated that chlorhexidine (CHX) is adsorbed to the oxide layer of titanium surfaces. Recent data indicate that the type of oxide may influence the amount of CHX absorbed (Morra et al. 2004, Barbour et al. 2009). It has also been shown that the absorption kinetics is directly related to implants' surface roughness and was also positively correlated with the concentration of the CHX solution. A desorption occurs within 24 hours and inhibits bacterial growth (Kozlovsky et al. 2006).

Therefore, the aim of this study is to examine a novel protocol of intensive application of chlorhexidine chips on peri-implant health in sites with peri-implantitis.

Materials and Methods

This study was designed as a multicentre, randomized, double-blind, parallel, two-arm clinical trial. The study was initially approved by the institutional ethic committees (IECs) of both medical centres and posted on the NIH website.

Patients seeking treatment for peri-implant disease at either Rambam health care campus in Haifa or at the Sourasky Medical Center in Tel-Aviv were initially screened for this study (with first patient in 17.3.2010 and last patient out 27.10.2011).

Inclusion criteria

Patients 21 years or older with peri-implantitis characterized by the presence of at least one implant with PD of 6–10 mm in depth (potential target implant), with BOP and radiographic evidence of bone loss. Patients were required to read and if satisfied with it, sign a written consent form that was previously approved by the IECs. Also, patients needed to affirm their availability for the 6-month duration of the study. At screening, all patients had a periodontal examination and when necessary periodontal treatment for the existing teeth was rendered first and the study commencement was postponed.

Exclusion criteria

(i) History of allergy to CHX or regular use of it (ii) horizontal

inter-implant distance <2 mm (if an adjacent implant existed); (iii) Titanium Plasma-sprayed or hydroxylapatite coated implants; (iv) systemic conditions that might affect inflammation and bleeding; (v) Any local irritation that could not be negotiated (i.e. orthodontic appliances; ill-fitted restorations; apical pathology); (vi) systemic antibiotic therapy or periodontal/mechanical/local delivery therapy within 6 weeks prior to study entry and throughout the study duration; (vii) continuous use of non-steroidal anti-inflammatory drugs or drugs known to cause gingival overgrowth; (viii) pregnancy or intention to become pregnant in the next 6 months.

At Screening visit (Week 1), patients came to establish eligibility. At this time, the following information was recorded: Demographic data and smoking habits, relevant past medical history and concomitant diseases and medications (measurements were performed by a periodontist or oral surgeon).

Oral examination was performed and the following parameters were recorded: plaque index, gingival index and BOP. In addition, the following site measurements were performed for the target implants using a manual 15 mm. University of North Carolina probe (Hu-Friedy, Chicago, IL, USA): BOP using a dichotomized 0/1 scale; PD, gingival recession (GR) measured from the crown/restoration margins. CAL was calculated as the sum of PD+GR. Periapical radiographs were further used to confirm bone loss ($\geq$2 mm) and screen for any exclusion conditions.

Each qualified patient then underwent supragingival scaling of all the teeth and implants (if not done in the 6 weeks prior the Screening visit) using ultrasonic instruments (OEM; Electeo Medical System, Nyon, Switzerland) with standard periodontal tips (performed by a well experienced dental hygienists). Following oral hygiene instruction, patients were given a sodium fluoride toothpaste (Colgate cavity protection; Colgate–Palmolive, NJ, USA) and soft toothbrush to be used throughout the study. One to two weeks later, patients were invited to return for the baseline visit (week 0), at which time final eligibility was determined. Periodontal assessments and measurements were repeated for all potential target implants. For each patient, at least one and no more than two implants (if available) with PD 6–10 mm were selected. In cases where more than two eligible implants were present, the following selection grid was employed: implants with the deepest pocket/s (primary); different arch (secondary); furthest away from each other (tertiary).

Next, surface debridement was performed for the chosen target implant/s and the two adjacent teeth using ultrasonic instruments.

Randomization, allocation concealment and blinding

Patients were then randomized to receive either a biodegradable cross-linked gelatin matrix chip (matrix chip group, MatrixC) or matrix containing 2.5-mg chlorhexidine-gluconate chips (PerioC; Dexcel Pharma). Eligible patients at baseline visit were assigned a randomization number starting from 601. Each randomization number was randomly assigned to one of the two letters A or B; each letter assigned randomly to one of the two treatments MatrixC or PerioC. Randomization was performed using a computer-generated sequence of Random binomial numbers by SAS 9.2 RANBIN CALL. The blinding of the study could only be broken upon completion of the clinical phase of the study including adverse effects (AE) and database queries all being resolved. One set of sealed envelopes was provided to the investigator containing individual randomization codes which was kept at the investigational site in case of a severe adverse effect (SAE); however, none have occu-rred.

To ensure examiner's blindness, two separate investigators attended to each patient: one that placed the chips and another one making the clinical measurements. Also, the chips were identical in size, shape and colour so that even the examiner that placed them was unaware of the identity of the chips that were placed.

Upto four chips were inserted for each implant's sites which PD was 6–10, and patients were discharged with instruction to refrain from using toothpicks and other proximal hygiene aids for 10 days. To ensure blindness, chips were inserted by a different investigator than that performing the clinical measurements. Patients were also asked to notify the investigator of any adverse reaction. At each visit, they were also actively approached to inquire of any adverse reaction that they might have failed to report.

Patients returned at weeks 2, 4, 6, 8, 12 and 18 and clinical measurements were repeated. For target sites with PD still $\geq$6 mm new chips were re-inserted. At 12 weeks, supragingival debridement was also performed. At each of these visits, patients were asked to report of any AE that they might have encountered and this was recorded. In cases where the target pockets depths increased during the study in more than 2 mm (confirmed on a subsequent visit), the patient was withdrawn from the study and referred for surgical therapy. At 6 months, patients returned for the final clinical examination and determination of any further treatment needs.

Statistical analysis

Power calculation was initially performed to determine sample size. Assuming normal distribution, nominal power of 80%, α 0.05, a standard deviation of the difference between treatments of 1.18 mm (based on previous study), we need 28 volunteers in each treatment group (using Two sample *t*-test for mean difference) to achieve a mean difference between treatments of $-$0.9 mm (SAS 9.2 POWER PROCEDURE, SAS Institute, Cary, NC, USA). Thus, we chose to allocate 30 volunteers to each study treatment.

The statistical procedure used was SAS procedure GENMODE. The modelization method: Generalized mixed linear model with generalized estimating equations method for repeated measures. This method was used for linear models (ΔPPD, CAL) and for binary models (ΔBOP, success to achieve 1,2,3,4 mm PPD reduction) with different links and distribution functions for each variable.

Continuous variables were analysed and compared using *t*-test when appropriate. Discrete variables were compared using two-sided fisher's

exact test. PD reduction, baseline to 6 months served as the primary outcome variable. Secondary outcome variables included changes in CAL, GR, BOP and PD at weeks 2, 4, 6, 8, 12 and 18. Change in PD and CAL was modelled using a linear-mixed model (SAS 9.2 Mixed Procedure) with treatment, and centre as fixed factors. Patient and pocket were entered as random effects. Analysis was done for subjects that completed the study and again for all patients that were enrolled [intention to treat (ITT)] subjects, with data missing being complemented using last observation carried forward (LOCF) method.

Contrasts with 95% confidence intervals for the difference or ratio between the changes were computed.

Analysis for the number of pockets with at least 1/2/3/4 mm reduction in PD, and analysis for BOP for the target implant/s measured at each visit were analysed by a Cochran–Mantel–Haenszel (CMH) test.

All treatment comparisons were two-sided at the 0.05 level of significance. Similar mixed model with a binary distribution and Logit link was used for BOP changes during the trial.

Similar mixed models for PD and CAL with time as a fixed repeated covariate were used to reveal the changes over time of these parameters.

Results

Sixty patients, 35 females and 25 males, age 27–77 years (mean ± SD 59.18 ± 9.2) with a total of 77 dental implants were initially accepted into the study. Thirty-six patients (44 implants) were in Centre A and 24 patients (33 implants) in Centre B (Table 1). Thirty patients with 40 implants were randomly assigned into the chlorhexidine group (PerioC), whereas an equal numbers of patients with 37 implants were included in the matrix chip group (MatrixC). Of the original 60 patients that were enrolled, 56 patients (93.3%) were available and eligible for the final examination 6 months later (the corresponding implant level retention rate was 94.8%, 73/77). Four patients, all from the MatrixC were exited from the study. One required extended antibiotic use (non-related to the study), one had total hip replacement and could not come for the follow-up and the other two were withdrawn, due to emergency dental treatment which interfered with the study endpoints.

Table 1. Patients and groups' baseline demographic data

		Variable				
Centre	Group	Patients (implants)	Mean age (±SD)	Gender (F:M) distribution	Smoking habits Current/ former/ Never	BMI Mean (±SD)
Both centres	PerioC	30 (40)	57.42 ± 10.5	20:10	5/7/18	27.2 ± 4.5
Both centres	MatrixC	30 (37)	60.95 ± 7.9	15:15	5/6/19	26 ± 3.5
Centre A	PerioC	17 (20)	54.88 ± 12.1	12:5	2/3/12	26.9 ± 4.3
Centre A	MatrixC	19 (24)	61.83 ± 7.6	9:10	2/4/13	26.0 ± 2.3
Centre B	PerioC	13 (20)	60.75 ± 7.0	8:5	3/4/6	27.4 ± 4.8
Centre B	MatrixC	11 (13)	59.43 ± 8.4	6:5	3/2/6	25.9 ± 5.1

MatrixC, Matrix Chip Group; PerioC, Periochip Group.

Five patients in each group were current smokers, whereas the rest were former smokers or never smoked. Both groups and both centres were similar in their baseline demographic and smoking habits.

Baseline PDs (7.60 and 7.21 mm for the PerioC and MatrixC groups respectively) have shown continuous improvement throughout the study (Fig. 1). Greater reduction was noticeable in the first 8 weeks with continuous improvement, although at slower rate thereafter. Mean pocket depth at 6 months were 5.47 and 5.48 mm PerioC and MatrixC respectively, which were significantly different from baseline ($p = 0.0001$). PD improvement in the PerioC (2.13 mm.) was greater than that for the MatrixC (1.73 mm.), $p = 0.17$ (Table 2a). When data were analysed with LOCF, these changes (2.19 and 1.59 mm respectively, Table 2b) were borderline significant ($p = 0.07$, mixed model). Probing depth reduction was further dichotomized into sites with PD reduction that was equal to/or greater than a threshold (Table 3). At 6 months, 93% of the implants in the PerioC and 88% in the MatrixC achieved at least 1-mm pocket reduction. For pocket reduction ≥ 2 mm, 70% of the sites in the PerioC and 54% in the MatrixC reached this threshold ($p = 0.077$). Likewise, 40% of the sites in the PerioC and 24% of the sites in the MatrixC have had pocket reduction that was equal to or greater than 3 mm ($p = 0.073$). Chips were inserted until PD was reduced to $\leq$ 5mm. To this end, 11 of the 40 implants in the PerioC (28%) and 5 of the 33 implants (15%) in the MatrixC group reached this goal at 6 months. At baseline, 60 implants (78%) required one or two chips, whereas three implants required four chips each. At the last treatment visit, 43 implants (56%) did not require any chip placement, 30 required 1–2 chips (Table 4).

Both treatment modalities have shown significant improvement in CAL (Fig. 2). Sites in the PerioC had a mean baseline CAL of 7.88 ± 0.2 mm (SE) with an ultimate 6 months CAL level of 5.70 ± 0.3 mm ($p = 0.001$, mixed model). Similarly, Sites in the MatrixC had a mean baseline CAL of 7.63 ± 0.3 mm (SE) with a final 6 months CAL level of 5.94 ± 0.3 mm ($p = 0.001$, mixed model). These differences in CAL gain amounted to 2.18 mm in the PerioC and 1.69 mm in the MatrixC ($p = 0.12$, mixed model), while when using all IIT patients, CAL gain (2.21 and 1.56 mm respectively) were significantly different ($p = 0.05$, mixed model).

At baseline, 100% of the sites in both groups had shown BOP in the peri-implantitis site (Fig. 3). As early as week 6, these percentiles were already declining (65.8% and 71.4% for the PerioC and MatrixC respectively); by 6 months, more than half of these sites had had no signs of BOP. Yet, sites with BOP were observed post-operatively more often in the MatrixC (59.0%) compared with 42.5% in the PerioC ($p = 0.17$, Mixed models)

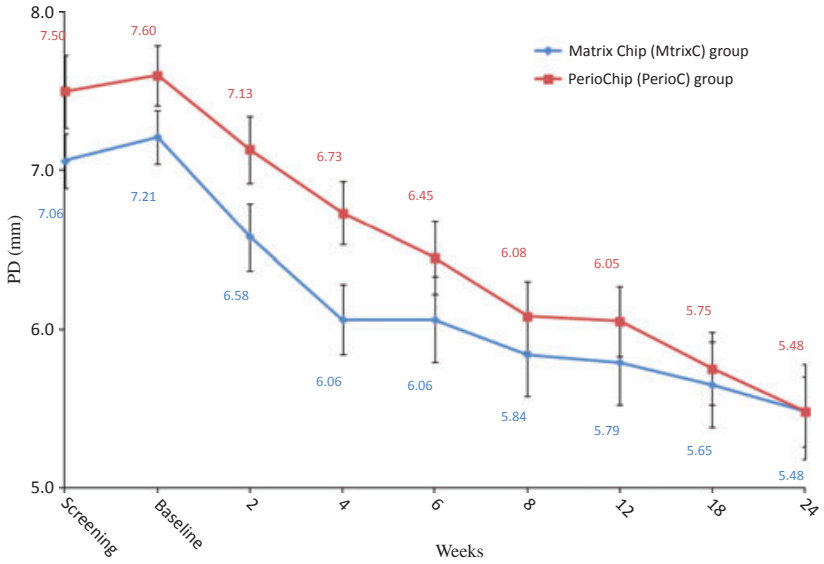

Fig. 1. Probing depth exhibited continues reduction throughout the study. In the first 8 weeks, the rate of this improvement seems greater.

Table 2a. Changes in clinical parameters baseline to six months: comparison between treatment

	Variable			
Group	Implants (patients)	ΔPD (±SE) (mm)	ΔCAL (±SE) (mm.)	ΔBOP (±SE) (%)
PerioC	40 (30)	2.13 ± 0.22	2.18 ± 0.22	57.5 ± 7.92
MatrixC	33 (26)	1.73 ± 0.19	1.69 ± 0.21	45.5 ± 8.8
Differences	–	0.40 ± 0.31	0.48 ± 0.32	12.1 ± 6.7
p-value	–	0.1780	0.1216	0.3125

PerioC, Chlorhexidine Group; MatrixC Matrix Chip Group.

Adverse effects were minimal and generally included toothache and gingival tenderness; all of these have spontaneously resolved after several days. Additional remedy or intervention was not required.

Discussion

Intensive placement of chips in the gingival pockets around implants with peri-implantitis resulted in a significant improvement of their periodontal parameters as evident in mean PD reduction of 1.59 mm. (MatrixC) to 2.19 mm. (PerioC), CAL gain of 1.56 mm. (MatrixC) to 2.21 mm (PerioC) and BOP reduction of 41.0% (MatrixC) to 57.5% (PerioC) at 6-month post-operative. These results are much superior compared with previously reported results for non-surgical treatment for peri-implantitis: Persson et al. (2011) have recently published the clinical and microbiological results of non-surgical treatment of peri-implantitis using air abrasive or laser; PD reductions in both groups were 0.8 and 0.9 mm respectively. Similarly, Sahm et al. (2011) using manual debridement or air-abrasive device reported approximately half a millimetre pocket reduction and CAL gain in both groups. Faggion et al. (2011) in a network meta-analysis comparing different treatment modalities for peri-implantitis have calculated an overall weighted mean PD reduction of 0.77 mm. and CAL gain of 0.79 mm 4 months after non-surgical treatment. Finally, Lindhe & Meyle (2008) in their consensus report have therefore concluded that non-surgical therapy in peri-implantitis is as of yet unpredictable.

The sizeable response that was achieved in this study was not previously reported even with the adjunctive local application of antimicrobial

Table 2b. Changes in clinical parameters baseline to 6 months (intention to treat subjects): comparison between treatment groups*

	Variable			
Group	Implants (patients)	ΔPD (±SE) (mm)	ΔCAL (±SE) (mm)	Δ%BOP ± SE
PerioChip	40 (30)	2.19 ± 0.24	2.21 ± 0.23	57.5 ± 7.92
Matrix Chip	37 (30)	1.59 ± 0.23	1.56 ± 0.25	41.0 ± 8.1
Differences	–	0.59 ± 0.331	0.65 ± 0.34	17.0 ± 10.9 (1.83 odd ratio)
p-value (95% CI)	–	0.07 (−0.05 to 1.24)	0.05 (−0.01 to 1.31)	0.17 (0.65–5.12)

*Model derived last square means (generalized mixed model – SAS GenMod procedure), model controlled for centre.

Table 3. Proportions of changes in probing depth greater than a threshold

Reduction number (%)	2 weeks 77 implants	4 weeks 76 implants	6 weeks 73 implants	8 weeks 73 implants	12 weeks 75 implants	18 weeks 71 implants	6 months 73 implants
				MatrixC			
	37 implants	36 implants	35 implants	34 implants	35 implants	31 implants	33 implants
1 mm	18(49%)	26 (72%)	24 (69%)	27 (79%)	29 (83%)	25 (81%)	29 (88%)
2 mm	3 (8%)	13(36%)	11 (31%)	14 (41%)	16 (46%)	17 (55%)	19 (54%)
3 mm	1 (3%)	2 (6%)	4 (11%)	4 (12%)	4 (11%)	7 (23%)	8 (24%)
4 mm	0	0	2 (6%)	0	0	0	2 (6%)
				PerioC¶,*			
	40 implants	40 implants	38 implants	39 implants	40 implants	40 implants	40 implants
1 mm	23 (58%)	26 (65%)	28 (74%)	31 (79%)	31 (78%)	36 (90%)	37 (93%)
2 mm	1 (3%)	10 (25%)	18 (47%)	22 (56%)	22 (55%)	27 (68%)	28 (70%)
3 mm	0	2 (5%)	5 (13%)	5 (13%)	8 (20%)	10 (25%)	16 (40%)
4 mm	0	1 (3%)	0	2 (5%)	3 (8%)	3 (8%)	6 (15%)

*$p = 0.077$.
¶$p = 0.073$.

Table 4. Changes in the number of chips placed baseline to 18 weeks

	Baseline				18 weeks			
No. used	Frequency	Per cent	Cumulative frequency	Cumulative per cent	Frequency	Per cent	Cumulative frequency	Cumulative per cent
0	0	0	0	0	43	55.84	43	55.84
1	35	45.45	35	45.45	15	19.48	58	75.32
2	25	32.47	60	77.92	15	19.48	73	94.81
3	14	18.18	74	96.10	4	5.19	77	100.00
4	3	3.90	77	100.00	0	0	77	100.00

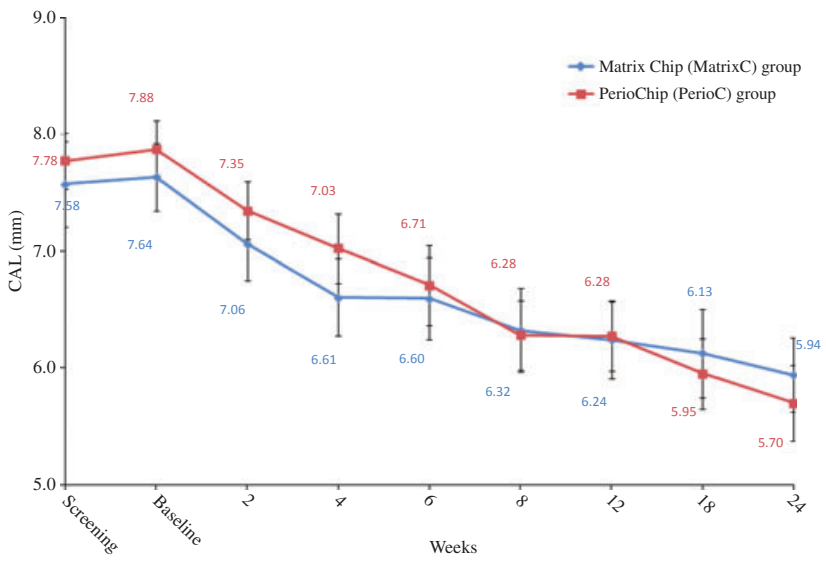

Fig. 2. Gain in CAL is also more rapid in the first 8 weeks; however, this improvement continues for the duration of the study.

agents. Sahm et al. (2011) reported PD reduction of 0.8 mm and CAL gain of 0.8 mm using mechanical debridement and adjunctive subgingival irrigation with CHX solution and gel application into the pockets. Salvi et al. (2007) using adjunctive minocycline microspheres (Arestin®, Orapharma, Horsham, PA, USA) reported similar clinical response (PD reduction of 1.0 mm. and CAL gain of 1.1 mm.) 1-year post-operative; Renvert et al. (2008b) in a similar study reported even less favourable results (mean PD reduction of 0.5 mm). Büchter et al. (2004) using adjunctive doxycycline gel reported slightly better results (PD reduction and CAL gain of 1.15 and 1.17 mm respectively) 4-month post-operative. Yet, the response in this study with the intensive use of CHX chips (2.13 mm.) was twice as big, thus highlighting the persistent nature of the peri-implant infection.

Patients in the PerioC have had greater PD reduction (2.19 mm.), CAL gain (2.21 mm) and reduction of BOP (57.5%) compared with the MatrixC (1.59, 1.56 mm and 41.0% respectively), these differences were only statistically significant for the CAL changes. The considerable response in the MatrixC would tend to suggest that matrix degradation by itself might have exerted some antibacterial effect. The hydrolysed gelatin matrix (cross-linked with Glutaraldehyde) is undergoing an initial rapid degradation with concomitant slower continuous resorption for 7–10 days via collagenolytic

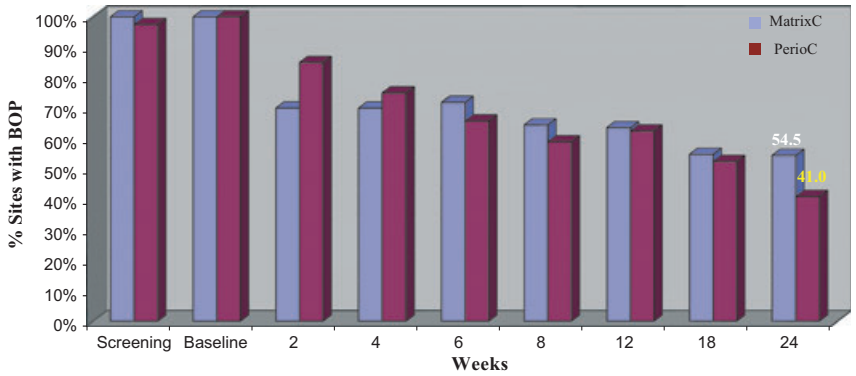

Fig. 3. At baseline, 100% of the sites with peri-implantitis exhibited BOP. As early as 4 weeks into the treatment, 25% of these sites ceased to bleed; at the conclusion of the study, less than 50% of these sites had BOP.

activity (Soskolne et al. 1998). This native collagenase once released might have an antimicrobial effect on the pathogenic flora around these implants, thus reducing inflammation and improving peri-implant gingival indices (Spitznagel & Shafer 1985, McGarry-Houghton et al. 2009). Also, such degradation is realizing Glutaraldehyde which is embedded in the matrix. This latter material is well known for its antibacterial properties, thus probably contributing to the overall improvement (Gorman et al. 1980, Russell 1994).

The sizeable response in the MatrixC group might also be attributed to the overwhelming effect of implant debridement that was performed in both groups. Similarly, Jeffcoat et al. (1998) in a periodontitis treatment study reported that the SRP+matrix chip were not significantly different from the SRO+CHX chips in the first 3 months. Even at 9 months, these differences, though statistically significant, were only 0.26 mm compared with 0.59 mm in this study. Consequently, this study might be under power due to the major effect of the SRP together with the MatrixC. Also, the repeated application protocol might be acting to disrupt the biofilm thus exerting a beneficial mechanical effect. Similarly, Varela et al. (2011) using repeated mechanical therapy have reported no difference between placebo and systemic antibiotics in sites with initial PPD and CAL $\geq$ 7 mm.

Bleeding on probing, initially 100% at baseline was completely eliminated in 57.5% (PerioC) and 41.0% (MatrixC) of these sites at 6 months. Heitz-Mayfield et al. (2011) in a randomized control multi-centre study reported a somewhat lower percentile (38%). Renvert et al. (2009) reported that only 15% of the sites treated with hand instrument or ultrasonic were free of BOP 6 months later. In contrary, Büchter et al. (2004) reported similar results in sites treated with doxycycline (from 54% to 27% at 4 months). The relatively considerable proportions of sites with persistent BOP even post-operatively, further emphasize the aggressive nature of the inflammatory process in peri-implantitis. Thus, sites with residual BOP would require constant monitoring and in time further therapy in the unlikely event of further attachment loss.

Of particular interest is the lack of GR in most of these sights (mean change of 0.04 and −0.05 mm for the MatrixC and PerioC respectively). This observation tends to suggest that pocket reduction resulted primarily from re-attachment/adherence or increased resistance to probe penetration of the peri-implant mucosa. Similar results were previously reported; however, these have received limited attention (Büchter et al. 2004, Faggion et al. 2011, Sahm et al. 2011). In comparison, the overall mean GR reported in a meta-analysis of non-surgical periodontal therapy for pockets that were initially moderate to deep was 0.5 mm. (Hung & Douglass 2002). More recently, we have reported (Machtei et al. 2011) on the clinical response to a similar intensive protocol of chlorhexidine chips placement around teeth: Mean PD reduction was incredibly similar (2.09 mm) compared with that around implants in this study (2.13 mm); In contrary, CAL gain in this study (2.18 mm) was much greater than what we have achieved around teeth (1.66 mm). This phenomenon would require further research as it may lend some clues to the less favourable response to therapy often reported with dental implants (Lang & Berglundh 2011).

In conclusion, A protocol that included an intensive programme for placement of PerioC and MatrixC resulted in a substantial reduction in PD, gain in CAL and reduction in BOP in sites with peri-implantitis. Further studies will be required to fully appreciate the mechanism by which these chips reduce the peri-implant inflammation.

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Clinical Relevance

Scientific rational for the study: Peri-implantitis is becoming an ever growing health issue for dental practitioners. Yet, current treatment protocols for the treatment of this condition are unpredictable. The purpose of this study was to explore the use of repeated application of CHX chips on peri-implantitis.

Principal findings: Both treatment groups had PD reduction > 2 mm. and BOP reduction of approximately 50%, which was maintained at 6 months. This response is greater that what was previously reported with non-surgical therapy of peri-implantitis.

Practical implications: If these findings will be further substantiated in future research, this protocol of frequent chips placement together with mechanical debridement might prove useful in negotiating peri-implantitis.