Original Article

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Dentistry Section

Adjunctive Effects of A Piscean Collagen-Based Controlled-Release Chlorhexidine Chip in the Treatment of Chronic Periodontitis: A Clinical and Microbiological Study

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ABSTRACT

Introduction: PerioChip a bovine origin gelatine based CHX chip has shown beneficial effects in the management of Chronic Periodontitis. A new fish collagen based CHX chip similar to PerioChip is currently available; however this product has not been thoroughly researched.

Aim: The aim of the present study was to evaluate the effectiveness of a new Piscean collagen-based controlled-release chlorhexidine chip (CHX chip) as an adjunctive therapy to scaling and root planing (SRP).

Settings and Design: The study was conducted as a randomised, split-mouth, controlled clinical trial at Krishnadevaraya College of Dental Sciences, Bangalore, India.

Materials and Methods: In a split–mouth study involving 20 sites in 10 patients with chronic periodontitis, control sites received scaling and root planing and test sites received scaling and root planing (SRP) and the intrapocket CHX chip placement as an adjunct. Subgingival plaque samples were collected from both control and test sites at baseline, 11 days and 11 weeks and the anaerobic colony count were assessed. Clinical parameters that were recorded at baseline and 11 weeks were gingival index, Plaque index, Probing pocket depth (PPD), and Clinical attachment level (CAL). Plaque index was recorded additionally at 11 days.

Results: In the test group there was a statistically significant reduction in the total anaerobic colony count, gingival index and plaque scores from baseline as compared to control sites at all time intervals. An additional 0.8mm reduction in mean probing pocket depth was noted in the test group. Gain in Clinical attachment level was comparable in both groups.

Conclusion: The adjunctive use of the new collagen-based CHX chip yielded significant antimicrobial benefit accompanied by a reduction in probing depth and a clinical attachment level gain as compared to SRP alone. This suggests that it may be a useful treatment option of nonsurgical periodontal treatment of chronic periodontitis.

Keywords: Chronic periodontitis, Dental plaque, Chlorhexidine, Drug delivery systems, Microbiological analysis

INTRODUCTION

Mechanical therapy may fail to eliminate the pathogenic bacteria located within the gingival tissues or in other areas inaccessible to periodontal instruments [1]. Adjunctive use of antimicrobials would compensate for technical limitations and prevent early microbial recolonization from other intraoral niches to ultimately ensure the best chance for clinical improvements [2]. Systemic delivery of antimicrobials achieves relatively low levels of drug at the site of infection, may lead to the development of bacterial resistance [1,3] is dependent on patient compliance and may result in side effects [4].

Chemical antimicrobial agents locally applied into periodontal pockets may further suppress periodontal pathogens and thereby augment the effects of conventional mechanical periodontal therapy [2]. This additional therapy provides an antimicrobial concentration adequate to penetrate the plaque biofilm in the periodontal pocket for prolonged time periods [5]. The constant outflow of gingival crevicular fluid with pocket fluid replacement of 40 times per hour requires prolonged maintenance of the drug at sufficient concentrations for the intended pharmaceutical effect to occur [6].

Chlorhexidine (CHX) a gold standard in plaque control since 30 y that does not cause any significant resistance to oral microorganisms [7], is a cationic bisbiguanide with activity against a broad spectrum of oral bacteria. It has low mammalian toxicity and high substantivity [8]. Subgingival irrigation of chlorhexidine failed to achieve useful results due to its inability to retain biologically significant concentrations of the drug for sufficient lengths of time within the confines of the periodontal pocket [9].

PerioChip which has been frequently reported in the literature is of bovine origin gelatine based CHX chip. Conflicting studies reported little benefit of reduction in microorganisms over SRP [5,10,11], whereas other studies reported significant benefit of SRP plus CHX chip treatment over SRP alone on the subgingival micro biota, an effect which diminished over time [12-14]. Local drug delivery has provided a plethora of treatment options, one among this is the recent introduction of Periocol CG – A new biodegradable collagen-based CHX chip (Periocol-CGTM, Eucare pharmaceuticals, Chennai, India) derived from fresh-water fish Collagen, which is a natural protein, non-allergenic, and known to be chemo tactic to fibroblasts [15,16] in a fish collagen matrix. The novelty and utility of this agent warrants further research. These clinical trials have attested the safety and non-toxicity of the product reporting no serious adverse effects [17-20]. The clinical efficacy of this chip in reducing probing depth, bleeding on probing and clinical attachment loss has been reported [18-21]. To the best of our knowledge, the microbiological

benefits of this chip have not been researched. Hence, the aim of this present study is to analyze the clinical and microbiological effects of fish collagen based CHX chip as an adjunct to SRP in the management of chronic periodontitis.

MATERIALS AND METHODS

Study design and Patient Selection

This 11-week randomized split-mouth design and single-blind controlled study was conducted in accordance with the ethical standards of the institutional ethical committee board affiliated with the Rajiv Gandhi University of Health Sciences, Bangalore and with the Helsinki Declaration of 1975 that was revised in 2000. Selected patients received a detailed explanation of the nature of the study and the alternatives, after which they signed an informed consent.

Study Patients

Twenty patients, 11 males and 9 females, aged 35–56 years (mean age 41.8 ± 5.6 years) were enrolled for the study was selected from the Outpatient Department of Periodontics of the institute. Patients with two or more sextants (from premolar to molar) containing one tooth that had one periodontal pockets measuring 6 to 7mm with bleeding on probing were enrolled. Patients with history of active treatment for chronic periodontitis within the past 5years, pregnancy, lactation, consumption of drugs that can affect the periodontium (Phenytoin, Calcium channel blockers, Cyclosporine, Coumadin, NSAIDS, Tetracyclines) patients with diabetes mellitus, presence of overhanging restorations, smoking , any history of systemic disease that could influence the course of periodontal disease or would require prophylactic antibiotics prior to dental treatment, allergy to chlorhexidine and patients on CHX or any other mouth rinses or antibiotics within the past 3 months were excluded.

Preparatory Phase

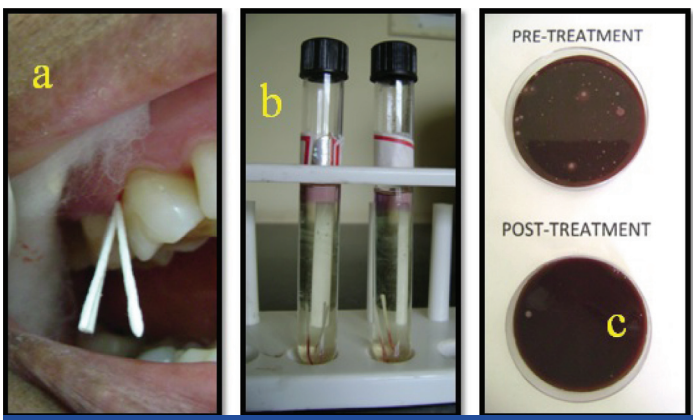
After enrolment a detailed case history was recorded, supragingival scaling and repeated oral hygiene instructions were administered. The patients were further qualified for the study if they established a plaque control of less than 10% [22].

CLINICAL ASSESSMENT METHOD

A blinder examiner recorded the clinical parameters [23] periodontal pocket depth (PPD), Gingival recession, Clinical attachment level (CAL) was measured at six sites per target tooth using periodontal probe (UNC-15 periodontal probe, Hu-Friedy, Chicago, IL) and an acrylic stent. Bleeding on probing (BoP), suppuration (Pus), Plaque Index [24] and Gingival Index [25] were recorded at baseline, 1 and 3 months after therapy.

Microbiological Analysis [Table/Fig-1a-c]

After removing supragingival plaque, subgingival plaque samples were collected from the target sites with three sterile fine (No 40) endodontic paper points (Diadent Group International, Korea) [26] and transferred to 10 ml of sodium thioglycollate media, and subsequently incubated for two hours. The samples were prepared for anaerobic analysis and [27] after 5 days, all the samples were inspected for total anaerobic colony count, using the digital colony counter (Delta Enterprises, Peenya, Bangalore). Microbial analysis was done at baseline, 11 days and 11 weeks.



[Table/Fig-1]: a) Subgingival plaque collection using paper points b) Processing of Paper points c) Counting of colony forming units

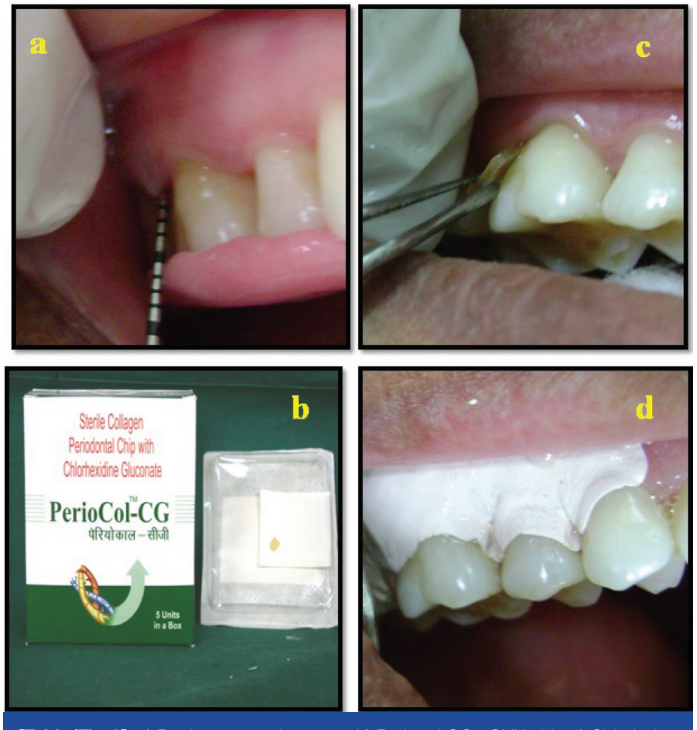
Periodontal Treatment [28]

After the baseline examinations during the initial visit, SRP was performed with sharp Gracey curettes (Hu-Friedy, Chicago, IL) and an ultrasonic scaler (PS, miniPiezon, EMS Piezon Systems, Nyon, Switzerland) in combination till all the root surfaces were smooth and clean to an explorer tip (EXD 11/12, Hu-Friedy, Leimen, Germany). During the SRP phase patients were prescribed Ibuprofen 400 mg (Brufen 400, Abbott India Limited, Mumbai) as an analgesic when required. Patients were recalled 1 week after SRP was completed. During this visit the teeth were supragingivally scaled and polished by a masked independent clinician and reinforcement of oral hygiene instruction was given. Microbiological sampling of test and control sites was done by using sterile endodontic paper points. Following debridement, target sites were irrigated gently with cold saline and then left for 10 min to achieve haemostasis prior to placement of the CHX chips. The patients were subsequently randomly allocated to SRP plus chlorhexidine chip group or SRP group

Randomization [28]

Block randomization table (four-unit block size) was generated. Numbered opaque envelopes were assigned before commencement of the study. The patients were randomly assigned to one of the two treatments SRP alone or SRP plus Chip. The envelope containing the treatment allocation was opened by the coordinator after transfer of the patient with the corresponding number by the blinded study examiner at the conclusion of the 1 week post-treatment control visit. The investigator was blinded to the treatment options (double randomized trial design). The test site was isolated and dried with compressed air and the CHX chip was inserted into the pocket with a forceps and pushed to the base of the pocket [Table/Fig-2a-d].

The drug delivery agent used here is a small orange-brown rectangular chip which contains approximately 2.5mg of chlorhexidine



[Table/Fig-2]: a) Pocket measuring 7mm b) Periocol CG –CHX chip c) Chip being placed in the pocket d) Periodontal dressing placed after chip placement

in a biodegradable matrix of fish collagen type I derived from the air bladder of fresh water fishes [16,17]. If needed the chip was trimmed with a scalpel. Patients were instructed to avoid flossing on the treated site for 1 week, using mouthwashes or antibiotics, not to disturb the area with tongue, finger or tooth pick, and to report immediately if the material is dislodged before the scheduled recall visit or if pain, swelling or any other problem occurred. Patients were also instructed to report of any adverse event (AE). Appointments were scheduled only in case of a need for an intervention. Patients were recalled 11 days later for evaluation. In the control site no chip was placed. All treatment procedures and measurements were performed by the same calibrated, trained and blinded study Investigator. During the recall visits at 11days and 11 weeks after SRP and medication, patients received routine SPT consisting of clinical measurements, supragingival scaling, polishing of all teeth and oral hygiene instructions.

STATISTICAL ANALYSIS

Twenty patients were analysed as the unit of statistical assessment [29]. The primary outcome that is change in the mean PD from baseline to 11 days and 11 weeks and secondary outcomes – changes in CAL, PI and GI were measured. The Student t-test (two tailed, dependent) was used to assess the degree of statistical significance between each groups at different time points. The cut-off for statistical significance was set at $p < 0.05$. Wilcoxon Signed rank test has been used in non-parametric condition for assessing the difference in microbial analysis from baseline to 11 days and 11 weeks. Statistical software was used for the analysis of the data.

RESULTS

Demographics

Twenty patients were enrolled with a split mouth distribution of SRP alone and SRP plus CHX randomly. The patients were evenly distributed for sex and age. The mean age was 41.8 ± 5.6 years. Clinical parameters (PPD, CAL, BoP and PI) were not statistically significantly different between treatment groups at baseline. All the subjects completed the tenure of the study and none of the patients in either group had experienced any severe adverse effects.

The fish collagen based CHX chip as an adjunct to SRP in the management of chronic periodontitis showed beneficial clinical and microbiological effects such as better reduction in PPD, CAL gain, improvement in GI, PI and BOP. A significant improvement in the microbial counts was also noted with the CHX chip group.

Statistically significant reduction in PPD [Table/Fig-3] from baseline to week 11for SRP and SRP plus CHX group was noted.

Pocket depth (mm)	SRP	SRP plus Chip	p-value
Baseline	6.2±0.79	6.5±0.53	0.279
11 weeks	5.1±0.99	4.6±0.52	0.138
Change	1.10±0.32	1.9±0.32	-
95% CI	0.87 to 1.33	1.67 to 2.13	-
p-value	<0.001**	<0.001**	-

[Table/Fig-3]: Comparison of Probing Pocket depth
Assessed with Paired students test, ** Highly significant

When the extent of PPD reduction was dichotomized, almost all these sites (94% and 96% for the SRP and SRP plus CHX groups, respectively) had at least 1 mm reduction between baseline and 11 weeks [Table/Fig-3]. More important, almost 70% and 72% for the SRP and SRP plus CHX groups respectively had at least 2 mm reduction in PPD and 33% and 36% for the SRP and SRP plus CHX groups, respectively had 3 mm or more pocket reduction in these sites. 6–15% had a 4 mm PPD reduction

Likewise, mean CAL reduction [Table/Fig-4] from baseline to week 11 for SRP group and SRP plus CHX group was statistically significant ($p < 0.001$). The differences between the groups were not statistically significant ($p > 0.05$). However, there was greater gain in attachment in the test group as compared to the control group, though the difference did not assume statistical significance.

CAL	SRP	SRP+Chip	p-value
Baseline	6.50±1.08	6.90±0.74	0.104
11 weeks	5.50±1.43	5.00±0.94	0.138
Change	1.00±0.47	1.9±0.32	-
95% CI	0.66 to 1.34	1.67 to 2.13	-
p- value	<0.001**	<0.001**	-

[Table/Fig-4]: Comparison of CAL Reduction
Assessed with Paired students test, *p<0.05, ** Highly significant

The gingival Index decreased from baseline to 11 weeks, both in the SRP and SRP plus CHX groups. Significant difference between groups (p=0.003), with greater improvement in the test group was reported [Table/Fig-5]. Similar improvement was also seen with PI [Table/Fig-6].

GI	SRP	SRP plus Chip	p-value
Baseline	2.60±0.43	2.52±0.42	0.488
11 weeks	1.80±0.23	1.07±0.50	0.003**
Change	0.8±0.48	1.45±0.53	-
95% CI	0.45 to 1.15	1.07 to 1.83	-
p-value	0.001**	<0.001**	-

[Table/Fig-5]: Comparison of Gingival Index (GI)
Assessed with Paired students test, ** Highly significant

PI	SRP	SRP plus Chip	p-value
Baseline	2.20±0.45	2.07±0.39	0.138
11 days	1.03±0.08	1.00±0.00	0.004**
11 weeks	1.44±0.36	1.22±0.30	0.095+
Change			
BL-11 days	1.17±0.43	1.07±0.39	-
BL-11 weeks	0.76±0.46	0.86±0.44	-
11 days-11 weeks	-0.42±0.35	-0.22±0.3	-
95% CI			
BL-11 days	0.87 to 1.47	0.79 to 1.35	-
BL-11 weeks	0.43 to 1.08	0.54 to 1.17	-
11 days-11 weeks	-0.66 to -0.17	-0.43 to 0.00	-
Significance			
BL-11 days	<0.001**	<0.001**	-
BL-11 weeks	0.001**	<0.001**	-
11 days-11 weeks	0.004**	0.052+	-

[Table/Fig-6]: Comparison of Plaque Index (PI)
Assessed with Paired students test, *p<0.05, * Statistically Significant ** Highly significant + not significant

In the SRP plus CHX group, total anaerobic colony count significantly reduced and the difference between the two groups was significant [Table/Fig-7].

DISCUSSION

The use of CHX in conjunction with SRP significantly reduced PPD more than SRP alone. Mean PPD reduction from baseline to week 11 visit for the SRP plus CHX group was 1.9 ± 0.32 mm similar to the results obtained by Kondreddy K et al., [30] where he noted a mean reduction in probing pocket depth between 0 and 90th day of 1.6±0.5 mm and 1.26+1.19 mm as seen by Grover V et al., [17]. Mean PPD reduction of 2.08 mm was noted in a similar study after 8 weeks and could be attributed to the repeated placement of CHX chips as opposed to the single time placement in the present

Mean Microbiological changes	SRP	SRP plus CHX	p-value
Baseline	42.25±34.66	31.72±32.24	0.007**
11 days	22.12±18.30	07.53±5.05	0.005**
11 weeks	30.76±21.02	14.67±12.57	0.013*
Change			
BL-11 days	20.13±17.5	24.19±33.46	-
BL-11 weeks	11.49±14.64	17.05±32.61	-
11 days-11 weeks	-8.64±6.60	-7.14±10.81	-
Significance			
BL-11 days	0.005**	0.005**	-
BL-11 weeks	0.005**	0.007**	-
11 days-11 weeks	0.005**	0.028*	-

[Table/Fig-7]: Comparison of Microbiological Assay
Comparison of Microbiological changes in million cfu from baseline to 11 days and 11 weeks, Non-parametric Wilcoxon signed rank test used for analysis
* Statistically Significant ** Highly significant

study [31]. An additional PPD reduction of 0.8 mm was obtained in the SRP plus CHX group as compared to the SRP group at 11 weeks. Similarly an additional 0.4mm and 0.3 mm PPD reduction were noted by Soskolne et al., [32] and Jeffcoat et al.,[33] in clinical trials with PerioChip. Complex root morphology and difficulty in access can limit the efficacy of SRP [34]. In such situations the CHX chip can play a beneficial role in eliminating the pathogenic burden. Significant Clinical attachment level gain of 0.6mm was observed in SRP plus CHX group. These results are comparable to that obtained with the usage of PerioChip by Azmak et al.,[14], Rodrigues IF et al., [35] and Paolantonio et al.,[12]. Plaque levels were similarly low after completion of the hygiene phase and were maintained throughout the study, thus indicating good compliance by all patients. Interestingly, significant reduction of plaque scores in the SRP plus CHX group was seen, which was comparable to the results obtained by Mizrak et al.,[13] and Rodrigues IF et al., [35] with PerioChip. As demonstrated by Patrick Adriaens et al., [36], professional plaque control reduced microbial counts of both supra and subgingival plaque. Subgingival Chlorhexidine has also shown to reduce crevicular PGE_2 [13] and crevicular MMP-8 [14], which may explain the resolution of Inflammation [33,37]. In the present study, the ability of subgingivally delivered chlorhexidine helped to significantly reduce gingival index scores in the test group [17-20].

Collagen- based chip CG™ has shown statistically significant reduction in probing depth and gain of CAL as seen by PerioChip [17-19].

The slow release of chlorhexidine from the chip probably reduced the micro flora and the inflammatory state of the tissues. This has also been seen by PerioChip as noted by Stabholz et al.,[9] and Soskolne et al., [32]. At baseline, sites receiving SRP plus CHX and sites receiving solely SRP exhibited similar levels of periodontal pathogens. Microbiological sampling was done at 11 days post-treatment, as most of the diffusible CHX would have been depleted leaving the remainder to subsequently biodegrade along with the collagen-base which is reported to partially degrade by 10 days [16,17]. There was a significant reduction in anaerobic colony count between test and control groups, with a significantly greater reduction in the test group. The total anaerobic colony count showed a significant increase from baseline to 11 days and 11 weeks in the control group but less significant in the test group. The antimicrobial benefit of this collagen-based chip is comparable with the microbiological studies of PerioChip. Mizrak et al., [13] showed that a significant reduction occurs in the percentage of subgingival spirochetes when chlorhexidine chips were placed. This is the first of its kind report of microbiological analysis of Periocol CG and hence the results cannot be compared with the same drug delivery agent.

Fish collagen has physical properties that closely resemble mammalian collagens, differing in composition with decreased amounts of proline and hydroxyproline, but increased serine and threonine [16]. It is suitably cross linked and incorporated with 2.5mg of CHX, after which it is sterilized by gamma radiation before packing. This chip bears an EN ISO 10993 certification. It is processed aseptically using cGMP facilities. It is self retentive. The size of the chip is 4x5mm and thickness is 0.25-0.32mm, weighing about 10mg. It has an in vitro release profile of 40-45% in the first 24 hours and then in a linear fashion for the next 7 days [17-19]. Its coronal edge is known to degrade in 10 days. Its safety and efficacy in reducing probing depth and bleeding on probing has been tested in clinical trials [19-22]. An in vitro release profile of chlorhexidine of 1105µg at 24 hours to 40µg by 7 days has been noted which is however not similar to the release profile of Periochip [19,38]. Periochip is a controlled local delivery system containing 2.5 mg of chlorhexidine gluconate incorporated into a biodegradable chip of hydrolyzed bovine gelatine has proven to inhibit more than 99% of subgingival microorganisms from periodontal pockets. The chip maintains concentrations of 125µg/ml which is above the Minimum Inhibitory Concentration (MIC) (90) for over one week with no detectable systemic absorption [8] Prolonged exposure to chlorhexidine was proposed to suppress pocket flora to negligible amounts for 11 weeks [9].

This concentration exceeds the minimum inhibitory concentration for more than 99% of subgingival microorganisms. In Periochip [38] an initial peak concentration of CHX in the GCF at 2 h post-Chip insertion (2007 µg/ml) was seen with slightly lower concentrations between 1300-1900 µg/ml being maintained over the next 96 h. The CHX concentration then progressively decreased until 9th day with significant CHX concentrations (mean=57 µg/ml) still being detectable at 9th day [38]. However, the results of this are in contradiction to those of Medaiah S et al., [39] study that showed no improvement with the adjunctive use of CHX chip.No adverse clinical events occurred in any of the study patients after placement of the collagen- based chlorhexidine chip. No serious side effects have been reported in other similar studies with CHX chip [16,18-20]. The beneficial clinical and microbiological results achieved with the CHX chip may reduce the need for further surgical periodontal treatment, which would limit morbidity for the subject, the time of treatment and the cost of the therapy as also noted by Kumar AJ et al., [40]. However, the limited sample size of this study requires that the results be validated by future studies with larger study populations. This product could probably reduce requirement for surgical treatment by raising the threshold of pocket depth indicated for surgical treatment. The clinical and microbiological data in the present study suggest that the use of a locally delivered fish collagen-based CHX chip provides positive therapeutic effects as an adjunct to SRP in the treatment of chronic periodontitis in terms of significant reduction in probing depth and in anaerobic colony count as compared to that achieved by use of scaling and root planing as sole treatment.

CONCLUSION

The results of this study show that chlorhexidine chip (PerioCol-CG) is an effective adjunctive therapy to scaling and root planing in the treatment of chronic periodontitis with a remarkable improvement in clinical parameters and microbiological profile. It can be concluded that the use of 2.5% chlorhexidine chip (Periocol CG™) as an adjunct to scaling and root planing was safe, and provided significant reduction in plaque index score and gingival bleeding sites. It was more favorable than scaling and root planing alone in reduction of probing pocket depth and gain in clinical attachment level. There was also significant benefit in reduction of subgingival microflora of chronic periodontitis

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