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ORIGINAL ARTICLE

Different methods for subgingival application of chlorhexidine in the treatment of patients with chronic periodontitis

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ABSTRACT

Objective: The aim of this study was to evaluate clinical efficacy of different chlorhexidine gluconate (CHX) preparations applied subgingivally as an adjunct to scaling and root planing (SRP).

Material and methods: A total of 120 periodontal pockets was included in this randomized, controlled, split mouth designed study. According to protocols used in treatment, periodontal pockets were assigned to experimental and control groups as follows: CHX solution as an addition to SRP versus control SRP group; CHX gel as an addition to SRP versus control SRP; CHX chip as an addition to SRP versus control SRP group. Following clinical parameters were recorded at baseline, one and three months after the baseline: plaque index (PI), probing pocket depth (PPD), bleeding index (BI) and clinical attachment level (CAL).

Results: The most significant improvements were found concerning PI in CHX solution with SRP and CHX gel with SRP groups over controls at one month recall, as well as concerning BI and PPD in CHX chip with SRP group over SRP alone at three-month recall.

Conclusion: Results of this study favour combination therapy using CHX chip as an adjunct to SRP due to greater improvements in BI and PPD compared to those obtained by SRP alone in the treatment of chronic periodontitis.

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Introduction

Treatment of chronic periodontitis, widely spread disease of periodontal tissue, is still a challenge. Even though it is a multifactorial disease, the primary etiologic factor is the presence of dental plaque microorganisms (bacteria,[1] yeast,[2] viruses [3]).

The conventional periodontal therapy aims to reduce or eradicate periodontal pathogens. Scaling and root planing (SRP) is a basic part of the first phase in periodontal therapy and leads to significant improvement in the clinical parameters. However, SRP may fail to eliminate the subgingival microbiota located in areas such as deep pockets inaccessible to periodontal instruments, multirooted teeth, furcasions, gingival tissue, concavities and interproximal areas. Assuming that antimicrobials would facilitate overcoming the technical limitations of mechanical treatment, prevent early recolonization of microorganisms and provide the best conditions for clinical improvement, local or systemic antimicrobials have been introduced in the treatment of periodontal disease, as an adjunctive measure. Due to rising concern and high importance related to bacterial resistance development, nowadays administration of antibiotics is limited to strict indications.[4]

Chlorhexidine (CHX), one of the most investigated antiseptics, is effective against Gram-positive and Gram-negative bacteria, viruses and yeast, and is not known to any microorganisms resistance. In order to accomplish its activity in challenging environment, such as periodontal pocket area, the medication, like CHX, must reach the site of action and remain at an adequate concentration long enough for its pharmacological effect to occur. Many forms of local delivery are not able to effectively deliver medicaments to periodontal pocket. Irrigation solutions can be administered subgingivally via cannula or other devices. However, when placed subgingivally, its local concentration is rapidly reduced due to the high rate of gingival fluid clearance that presents one of major obstacles in subgingival application of medications.[5] In order to promote its pharmacotherapeutic effect, CHX has been incorporated in other vehicles. Assuming that viscosity of a gel would contribute to lower clearance of an active agent from the periodontal pocket, CHX became available in gels with concentrations higher than those in solutions. Furthermore, CHX has also been incorporated in controlled delivery devices. One of such products is PerioChip® (Perio Products, Jerusalem, Israel), biodegradable, local delivery system that contains 2.5 mg of CHX. Chip slowly degrades and

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releases CHX within the pocket over 7 to 10 days, maintaining an average concentration of CHX in gingival cervical fluid greater than 125 μg/ml, minimum inhibitory concentration for more than 99% periodontal pocket flora, for 7 days.[6]

Review of literature reveals inconclusive data regarding different modalities of subgingival application of CHX and until now there is no clearly defined protocol for subgingival use of CHX.[7–9]

The aim of this study was to evaluate clinical efficacy of different chlorhexidine gluconate preparations applied subgingivally as an adjunct to SRP as combined therapy in patients with chronic periodontitis.

Materials and methods

Study population

The subjects for this randomized controlled, split mouth–designed study were selected among patients who reported to Dental Clinic, Faculty of Medicine Foca, University East Sarajevo between September 2011 and July 2014. The study was approved by the institutional committee of ethics (No. 01-8/58 issued on 25 December 2009) and was conducted in accordance with the Helsinki Declaration of 1975, as revised 1983. After the study was explained to the patients, written informed consent was obtained from all.

This study included 15 chronic periodontitis patients (7 females and 8 males; 21–52 years of age; mean age 35.87 ± 8.44). There were no patient withdrawals over the study period. Chronic periodontitis was diagnosed according to criteria proposed by Lindhe et al. [10] Patient selection criteria included patients affected by slight-to-moderate chronic periodontitis, with the presence of at least two bilateral periodontal sites probing ≥5 mm indicated for SRP as a definitive method of therapy. The selected patients could not have received antibiotic treatment within the past 6 months and/or received periodontal treatment within the past 3 months. Medically compromised patients, pregnant and lactating females were also excluded from this study.

Periodontal treatment

During the first visit, a medical history was taken, thorough clinical examination was carried out and analysis of radiographs, according to indications, in patients included in this study. Then, during the same visit, patients were motivated and educated about self-performed oral hygiene measures. At the same visit, all patients underwent full-mouth mechanical debridement using ultrasonic scaler (EMS, Nyon, Switzerland) and Gracey curettes (Medesy, Maniago, Italy). Periodondontal pockets were irrigated by sterile saline.

Periodontal pockets, total of 120, were randomly divided into experimental and control according to split-mouth design. According to the applied treatment protocol, patients were divided into three groups. Each group of patients was treated with 20 periodontal pockets in experimental and 20 in control regions as follows:

The first group of patients

The experimental group of periodontal pockets was thoroughly irrigated with 0.2% solution of chlorhexidine gluconate (CURASEPT ADS 220, Curaden Healthcare, Saronno, Italy), after SRP, using a syringe with blunted needle located in the area of the bottom of the pocket. Irrigation was performed once a day in five days. (SRP + CHX solution)

Control group of pockets underwent SRP. (SRP)

The second group of patients

Chlorhexidine gel (CURASEPT ADS 350, Curaden Healthcare, Saronno, Itally) was applied using a syringe with blunted needle placed near the bottom of the pocket until gel became visible at the entrance of the pocket, three times within 10 min [11] after SRP in the experimental group of pockets, once a day for five days. (SRP + CHX gel)

Control group of pockets underwent SRP. (SRP)

The third group of patients

Chlorhexidine chip (Perio Chip®, Perio Products, Jerusalem, Israel) was applied, according to the manufacturer's instructions, in experimental group of pockets after SRP. (SRP + CHX chip)

Control group of pockets underwent SRP. (SRP)

Periodontal therapy was performed by a single skilled therapist (author JL).

Randomization

Randomization was ensured by pulling one of three offered pieces of paper out from the opaque envelope. Each piece of paper was labelled with one of the listed protocols. In addition to that, according to split mouth design, regions were assigned to experimental and control by coin toss method.

Clinical measurements

In order to verify the oral hygiene level and assess the state of periodontal tissues the following parameters were recorded at the baseline, one and three months after the baseline, respectively, at the experimental and control sites:

- Plaque index (PI) using Silness and Löe plaque index;[12]
- Probing pocket depth (PPD);
- Bleeding on probing (BI) using Bleeding index of Muhlemann;[13]
- Clinical attachment level (CAL).

All of the clinical measurements were made by a single trained examiner (author OV) blinded to applied treatment protocol and to experimental and control sites.

Statistical analysis

Statistical data analysis was performed in SPSS 19.0 (IBM Corp., Armonk, NZ). Kolmogorov–Smirnov test showed

that clinical parameters did not follow a normal distribution ($p < 0.05$). Friedman two-way analysis of variance with the ranks, with *post hoc* analysis using the Wilcoxon test for paired samples was used to determine the influence of individual therapeutic protocols on clinical variables one and three months after the therapy. Mann–Whitney *U*-test used to determine the differences between the experimental and control groups at baseline and at different time intervals after the treatment. Value $p < 0.05$ was considered statistically significant.

Results

SRP + CHX solution and control SRP group of periodontal pockets showed significant reduction in clinical parameters values one and three months after the baseline compared to the baseline (Table 1). Statistically significant intergroup difference was observed only in respect to PI with the SRP + CHX solution group showing significantly higher as compared to SRP at baseline ($p < 0.05$) and SRP over SRP + CHX solution group one month after the baseline ($p < 0.01$) (Table 1).

Mean values of clinical parameters between SRP + CHX gel and control SRP group of periodontal pockets demonstrated statistically significant reduction in PI, BI and PPD values one and three months compared to the baseline values for both groups. SRP + CHX gel group failed to demonstrate significant reduction in CAL for the observed period of time. Control SRP groups have demonstrated significant reduction in CAL one ($p < 0.001$) and three ($p < 0.01$) months after the baseline compared to baseline (Table 2). Intergroup difference was observed in respect to PI with as SRP group have showed significantly higher values when compared to SRP + CHX gel one month after the baseline ($p < 0.05$) (Table 2).

As demonstrated in Table 3, comparison of mean values of clinical parameters between SRP + CHX chip and control SRP group of periodontal pockets show statistically significant reduction in clinical parameters values, at one and three months compared to the baseline values. Intergroup difference was observed in respect to BOP and PPD as SRP + CHX chip group showed significantly better results compared to SRP alone three months after the baseline, $p < 0.05$ and $p < 0.01$, respectfully (Table 3).

Discussion

This study, based on clinical trial, tested the efficacy of different therapeutic protocols for subgingival application of CHX, as an adjunct to conventional therapy of chronic periodontal disease for a period of three months.

After the initial measurements were performed at the baseline, recording of clinical parameters was repeated one month after baseline due to the fact that, as earlier mentioned in literature, bacterial flora return to pretreatment values 3–6 weeks after SRP. A period of three months follow-up interval was determined for this study as effects of locally delivered CHX were observed for 11 weeks after administration and also three months interval presents typical recall interval for patients after periodontal treatment.[14]

Table 1. Mean (SD) of clinical parameters at baseline, 1 and 3 months after the baseline for SRP + CHX solution group and control SRP group of periodontal pockets.

	Group	Baseline (mean ± SD)	One month after (mean ± SD)	Three months after (mean ± SD)	[a]p 0–1	[a]p 0–3
PI	SRP + CHX solution	1.36 ± 0.30	0.41 ± 0.01	0.44 ± 0.02	0.001	0.001
	SRP	1.22 ± 0.21†	0.51 ± 0.07	0.45 ± 0.06	0.001	0.001
[b]p		<0.05	<0.01	NS		
BI	SRP + CHX solution	1.60 ± 0.50	0.60 ± 0.50	0.40 ± 0.50	0.001	0.001
	SRP	1.50 ± 0.51	0.45 ± 0.51	0.60 ± 0.59	0.001	0.001
[b]p		NS	NS	NS		
PPD (mm)	SRP + CHX solution	5.25 ± 0.55	3.00 ± 0.45	2.65 ± 0.67	0.001	0.001
	SRP	5.15 ± 0.36	2.90 ± 0.78	2.85 ± 0.74	0.001	0.001
[b]p		NS	NS	NS		
CAL (mm)	SRP + CHX solution	3.20 ± 1.50	2.30 ± 1.03	2.35 ± 1.13	0.01	0.01
	SRP	3.10 ± 1.33	2.25 ± 0.91	2.10 ± 1.11	0.01	0.01
[b]p		NS	NS	NS		

PI: plaque index; BI: bleeding index; PPD: probing pocket depth; CAL: clinical attachment level; SRP : scaling and root planing; CHX : chlorhexidine.
[a]Intragroup comparison (Friedman test (*post hoc* Wilcoxon test for paired samples)).
[b]Intergroup comparison (Mann–Whitney *U*-test).

Table 2. Mean (SD) of clinical parameters at baseline, 1 and 3 months after the baseline for SRP + CHX gel group and control SRP group of periodontal pockets.

	Groups	Baseline (mean ± SD)	One month after (mean ± SD)	Three months after (mean ± SD)	[a]p 0–1	[a]p 0–3
PI	SRP + CHX gel	1.30 ± 0.27	0.41 ± 0.07	0.41 ± 0.05	0.001	0.001
	SRP	1.38 ± 0.23	0.45 ± 0.04	0.41 ± 0.11	0.001	0.001
[b]p		NS	<0.05	NS		
BI	SRP + CHX gel	1.70 ± 0.47	0.40 ± 0.50	0.40 ± 0.50	0.001	0.001
	SRP	1.80 ± 0.41	0.70 ± 0.47	0.70 ± 0.47	0.001	0.001
[b]p		NS	NS	NS		
PPD (mm)	SRP + CHX gel	5.05 ± 1.00	2.55 ± 0.60	2.95 ± 0.75	0.001	0.001
	SRP	5.25 ± 0.55	2.90 ± 0.85	3.25 ± 0.55	0.001	0.001
[b]p		NS	NS	NS		
CAL (mm)	SRP + CHX gel	3.75 ± 1.20	3.45 ± 0.88	3.40 ± 0.82	NS	NS
	SRP	4.05 ± 1.35	2.95 ± 0.82	3.20 ± 0.76	0.001	0.01
[b]p		NS	NS	NS		

PI: plaque index; BI = bleeding index; PPD: probing pocket depth; CAL: clinical attachment level; SRP = scaling and root planing; CHX = chlorhexidine.
[a]Intragroup comparison (Friedman test (*post hoc* Wilcoxon test for paired samples)).
[b]Intergroup comparison (Mann–Whitney *U*-test).

Table 3. Mean (SD) of clinical parameters at baseline, 1 and 3 months after the baseline for SRP + CHX chip group and control SRP group of periodontal pockets.

	groups	Baseline (mean ± SD)	One month after (mean ± SD)	Three months after (mean ± SD)	[a]p 0–1	[a]p 0–3
PI	SRP + CHX chip	1.26 ± 0.36	0.40 ± 0.10	0.45 ± 0.04	0.001	0.001
	SRP	1.19 ± 0.33	0.40 ± 0.10	0.44 ± 0.04	0.001	0.001
[b]p		NS	NS	NS		
BI	SRP + CHX chip	1.65 ± 0.48	0.25 ± 0.55	0.26 ± 0.56	0.001	0.001
	SRP	1.40 ± 0.50	0.50 ± 0.51	0.60 ± 0.50	0.001	0.01
[b]p		NS	NS	<0.05		
PPD (mm)	SRP + CHX chip	5.70 ± 0.97	2.80 ± 1.28	2.75 ± 0.96	0.01	0.01
	SRP	5.25 ± 1.01	3.10 ± 0.71	3.40 ± 0.75	0.01	0.01
[b]p		NS	NS	<0.01		
CAL (mm)	SRP + CHX chip	3.70 ± 1.41	2.65 ± 1.69	2.70 ± 1.75	0.001	0.001
	SRP	3.90 ± 1.02	2.85 ± 1.13	2.95 ± 1.05	0.001	0.001
[b]p		NS	NS	NS		

PI: plaque index; BI: bleeding index; PPD: probing pocket depth; CAL: clinical attachment level; SRP: scaling and root planing; CHX : chlorhexidine.
[a]Intragroup comparison (Friedman test (*post hoc* Wilcoxon test for paired samples)).
[b]Intergroup comparison (Mann–Whitney *U*-test).

Recent study performed by Gottumukkala et al. [15] also questioned the effectiveness of multiple subgingival irrigation of periodontal pockets by 0.2% CHX gluconate and saline. One and three months after the therapy, BI values were significantly decreased after both irrigation with chlorhexidine and saline. CHX group showed statistically significant decrease in BI values ($p < 0.01$) one month after the start of treatment compared to the group with saline. Unlike those, our results did not find statistically significant difference between groups of periodontal pockets irrigated by CHX solution as an adjunct to SRP and SRP alone. This was in accordance with previous findings.[16,17]

Gottumukkala et al. [15] showed significantly higher reduction in PPD after irrigation of periodontal pockets with CHX gluconate solution over SRP one, three and six months after initial measurement. Another study, which performed an irrigation of periodontal pockets with the aid of pulsating irrigator twice a day, for the period of 56 days after SRP, showed a significantly better reduction of PPD in the group that used 0.2% CHX solution as an irrigant over placebo solution.[18] In contrast to those, results obtained in the study conducted by MacAlpine et al. [17] did not confirm the benefit of periodontal pockets irrigation with CHX solution over saline, after SRP. Analysing the results, authors did not find statistically significant difference in PPD values between observed groups what is consistent with our results.

Krishna et al. [19] found similar improvements in CAL value after irrigation of periodontal pockets with both chlorhexidine and saline, which is in accordance with the results of MacAlpine et al. [17] and the results of our study.

In addition to the large flow of gingival fluid that prevents the retention of chlorhexidine solution in the area of periodontal pocket and presents one of the limiting factors for the efficiency of the solution in the subgingival environment, affinity of CHX for serum proteins [20,21] and its weak binding to the surface of the root [22] are also mentioned in literature as possible causes for its poor effect after subgingival application.

It was found that 20 ml/h flow of gingival fluid leads to 1-min half-life of the gel in periodontal pocket.[11] Accordingly, Oosterwaal et al. [23] suggested that the most effective way for subgingival application of the gel is its application three times in 10 minutes and reported 99% reduction in periodontal pocket microflora half an hour after application of CHX gel under this regime.

In order to extend presence of gel in the periodontal pocket, we performed aforementioned regime once a day for five days in this study. Consequently, PI values have shown a significant reduction for the group treated with CHX gel as an adjunct to SRP and SRP group one and three months after baseline compared to the baseline which is in accordance to the results of Vinholis et al.[24]

Despite the fact that bleeding from the gingiva is not an indicator of periodontal destruction, the absence of bleeding is reliable indicator of periodontal health.[25] Even though BI values after administration of CHX gel as adjunct to SRP and SRP in this study showed a statistically significant decrease in BI value both one and three months after the baseline compared to the baseline values, difference between the groups did not reach levels that could be considered statistically significant for the observed period of time, what is consistent with the results of Unsal et al.[26] In contrast to this, results obtained by Chitsazi et al. [27] show statistically significant difference of BOP value in favour of CHX group one and three months after the beginning of therapy.

After application of CHX gel as an adjunct to SRP in this study, the improvement in the value of CAL was noted, but not at in the level of statistical significance, as opposed to a control SRP where a significant improvement of the value of CAL one and three months after baseline compared to the baseline scores was found. This result may be explained by the physical presence of gel in the area of periodontal pockets after the mechanical treatment, which may affect the early stages of the healing process.[26]

The use of CHX chip as an addition to SRP and contralateral SRP in this study proved to be effective in treating patients with periodontal disease. Both therapeutic protocols have led to a significant improvement of clinical parameters, one and three months after completion of therapy compared to the baseline, which is in correspondence with the results from Soskolne et al. [28] and Srivastava et al.[29]

Soskolne et al.,[28] Heasman et al.,[30] Rodriguez et al.,[31] Grover et al.,[32] Paolantonio et al. [33] in their studies have shown that the use of CHX chip as the adjunct to SRP and SRP have led to a significant reduction in the value of BI one and three months after the baseline compared to the baseline, which is in accordance with the results of this study. Haesman et al. [30] noted a significant improvement in BI values after application of CHX chip in relation to the SRP, 6 months after the baseline. Soskolne et al. [28] have reported statistically significant reduction of BI in the group in which the CHX chip had been applied compared to SRP alone 3 months after the baseline, which is consistent with our results. In contrast to this, Paolantonio et al. [33] did not notice any difference in BI value between the therapeutic procedures during 6 months of the study, as well as Rodrigues et al.[31]

The PPD is one of the most frequently used diagnostic tools for the assessment of the destruction of tooth supporting structures. PPD and CAL are crucial indicators both in the diagnosis of periodontal disease and in the assessment of the therapy success. Results of this study show that the use of CHX chip as an adjunct to SRP have led to significant improvements in PPD in comparison to SRP alone. This additional effect of CHX was observed 3 months after the baseline, which is in agreement with the results of Soskolne et al.[28] However, Rodriguez et al. [31] came to different results. The authors did not find a significant difference in PPD values after application of chlorhexidine chip when compared to SRP alone. In a study carried out by Rodriguez et al., biofilm was not removed prior to the placing of CHX chip. The complex structure of the biofilm prevents the diffusion of antimicrobial agents and protects its residents from internal and external influences.[34] Removal or disruption of biofilm prior to the application of local antimicrobial agent leads to its greater efficiency against subgingival microorganisms, which may explain the results different from ours.

Statistically significant improvement in CAL in our study was observed both after application of CHX chip as an adjunct to SRP and after SRP alone, one and three months after the baseline when compared with pretreatment values, which is consistent with the findings of other researchers.[31,33,35,36] However, intergroup statistical difference was not observed in this study, for the observed period, what is in accordance with the results of Rodriguez et al. [31] and Grisi et al.[35]

Available literature provides controversial data on effectiveness of different forms of CHX preparations for subgingival application. The large flows of gingival fluid, pocket anatomy, pharmacodynamic properties of antimicrobial agent, represent some of the challenges for subgingival application of CHX in the treatment of patients with periodontal disease. In addition, proper indication, cost-effectiveness, need for multiple dental visits and patient compliance are factors that clinicians should also have in mind in decision-making of proper treatment that involves local drug delivery. While CHX chip is more expensive than CHX gel or solution, single application of the chip provides less dental visits and requires less chair side time what may justify its cost effectiveness and may provide better patient compliance.

In conclusion, although all treatment protocols have led to the improvement of clinical parameters, results of this study favour combination therapy using CHX chip as an adjunct to SRP due to greater improvements in BI and PPD compared to those obtained by SRP alone in the treatment of chronic periodontitis. However, further well-controlled clinical studies that would evaluate and compare the effects of different forms of CHX preparation for subgingival application are needed, due to complexity and importance of this matter. This might provide sufficient data that would help in creating most efficient protocol for subgingival use of chlorhexidine in future.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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References

[1] Ximénez-Fyvie LA, Haffajee AD, Socransky SS. Comparison of the microbiota of supra- and subgingival plaque in health and periodontitis. J Clin Periodontol. 2000;27:648–657.
[2] Sardi JC, Duque C, Mariano FS, et al. Candida spp. in periodontal disease: a brief review. J Oral Sci. 2010;52:177–185.
[3] Slots J. Periodontal herpesviruses: prevalence, pathogenicity, systemic risk. Periodontol 2000. 2015;69:28–45.
[4] World Health Organization. WHO's first global report on antibiotic resistance reveals serious, worldwide threat to public health. Geneva: World Health Organization; 2014.
[5] Rams TE, Slots J. Local delivery of antimicrobial agents in the periodontal pocket. Periodontol 2000. 1996;10:139–159.
[6] Soskolne WA, Chajek T, Flasher M, et al. An in vivo study of the chlorhexidine release profile of the PerioChip in the gingival crevicular fluid, plasma and urine. J Clin Periodontol. 1998;25:1017–1021.
[7] Cosyn J, Sabzevar MM. A systematic review on the effects of subgingival chlorhexidine gel administration in the treatment of chronic periodontitis. J Periodontol. 2005;76:1805–1813.
[8] Cosyn J, Wyn I. A systematic review on the effects of the chlorhexidine chip when used as an adjunct to scaling and root planing in the treatment of chronic periodontitis. J Periodontol. 2006;77:257–264.
[9] Eberhard J, Jervøe-Storm P-M, Needleman I, et al. Full-mouth treatment concepts for chronic periodontitis: a systematic review. J Clin Periodontol. 2008;35:591–604.
[10] Lindhe J, Ranney R, Lamster I, et al. Consensus report: chronic periodontitis. Ann Periodontol. 1999;4:38.
[11] Oosterwaal PJ, Mikx FH, Van 't Hof MA, et al. Short-term bactericidal activity of chlorhexidine gel, stannous fluoride gel and amine

fluoride gel tested in periodontal pockets. J Clin Periodontol. 1991;18:97–100.
[12] Silness J, Loe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. Acta Odontol Scand. 1964;22:121–135.
[13] Mühlemann HR, Son S. Gingival sulcus bleeding-a leading symptom in initial gingivitis. Helv Odontol Acta. 1971;15:107–113.
[14] Puri K, Dodwad V, Bhat K, et al. Effect of controlled-release Periochip™ on clinical and microbiological parameters in patients of chronic periodontitis. J Indian Soc Periodontol. 2013;17:605–611.
[15] Gottumukkala SNVS, Koneru S, Mannem S, et al. Effectiveness of sub gingival irrigation of an indigenous 1% curcumin solution on clinical and microbiological parameters in chronic periodontitis patients: a pilot randomized clinical trial. Contemp Clin Dent. 2013;4:186–191.
[16] Braatz L, Garrett S, Claffey N, et al. Antimicrobial irrigation of deep pockets to supplement non-surgical periodontal therapy. II. Daily irrigation. J Clin Periodontol. 1985;12:630–638.
[17] MacAlpine R, Magnusson I, Kiger R, et al. Antimicrobial irrigation of deep pockets to supplement oral hygiene instruction and root debridement. I. Bi-weekly irrigation. J Clin Periodontol. 1985;12:568–577.
[18] Walsh TF, Glenwrith HD, Hull PS. Clinical effects of pulsed oral irrigation with 0.2% chlorhexidine digluconate in patients with adult periodontitis. J Clin Periodontol. 1992;19:245–248.
[19] Krishna MK, Ravindran SK, Vivekanandan G, et al. Effects of a single episode of subgingival irrigation with tetracycline HCl or chlorhexidine: a clinical and microbiological study. J Indian Soc Periodontol. 2011;15:245–249.
[20] Rölla G, Löe H, Schiott CR. The affinity of chlorhexidine for hydroxyapatite and salivary mucins. J Periodont Res. 1970;5:90–95.
[21] Hjeljord LG, Rolla G, Bonesvoll P. Chlorhexidineprotein interactions. J Periodontal Res Suppl. 1973;12:11–16.
[22] Stabholz A, Kettering J, Aprecio R, et al. Retention of antimicrobial activity by human root surfaces after in situ subgingival irrigation with tetracycline HCl or chlorhexidine. J Periodontol. 1993;64:137–141.
[23] Oosterwaal PJM, Mikx FHM, Renggh HH. Clearance of a topically applied fluorescein gel from periodontal pockets. J Clin Periodontol. 1990;17:613–615.
[24] Vinholis AH, Figueiredo LC, Marcantonio Júnior E, et al. Subgingival utilization of a 1% chlorhexidine collagen gel for the treatment of periodontal pockets. A clinical and microbiological study. Braz Dent J. 2001;12:209–213.
[25] Lang NP, Adler R, Joss A, et al. Absence of bleeding on probing. An indicator of periodontal stability. J Clin Periodontol. 1990;17:714–721.
[26] Unsal E, Akaya M, Walsh TF. Influence of a single application of subgingival chlorhexidine gel or tetracycline paste on the clinical parameters of adult periodontitis patients. J Clin Periodontol. 1994;21:351–355.
[27] Chitsazi MT, Kashefimehr A, Pourabbas R, et al. Efficacy of subgingival application of xanthan-based chlorhexidine gel adjunctive to full-mouth root planing assessed by real-time PCR: a microbiologic and clinical study. J Dent Res Dent Clin Dent Prospects. 2013;7:95–101.
[28] Soskolne WA, Heasman PA, Stabholz A, et al. Sustained local delivery of chlorhexidine in the treatment of periodontitis: a multi-center study. J Periodontol. 1997;68:32–38.
[29] Srivastava R, Verma PK, Tandon P, et al. Chlorhexidine chip and tetracycline fibers as adjunct to scaling and root planning – a clinical study. Braz J Oral Sci. 2009;8:201–205.
[30] Heasman PA, Heasman L, Stacey F, et al. Local delivery of chlorhexidine gluconate (PerioChip) in periodontal maintenance patients. J Clin Periodontol. 2001;28:90–95.
[31] Rodrigues IF, Machion L, Casati MZ, et al. Clinical evaluation of the use of locally delivered chlorhexidine in periodontal maintenance therapy. J Periodontol. 2007;78:624–628.
[32] Grover V, Kapoor A, Malhotra R, et al. To assess the effectiveness of a chlorhexidine chip in the treatment of chronic periodontitis: a clinical and radiographic study. J Indian Soc Periodontol. 2011;15:139–146.
[33] Paolantonio M, D'Angelo M, Grassi RF, et al. Clinical and microbiologic effects of subgingival controlled-release delivery of chlorhexidine chip in the treatment of periodontitis: a multicenter study. J Periodontol. 2008;79:271–282.
[34] Walker CB, Karpinia K, Baehni P. Chemotherapeutics: antibiotics and other antimicrobials. Periodontol 2000. 2004;36:146–165.
[35] Grisi DC, Salvador SL, Figueiredo LC, et al. Effect of a controlled-release chlorhexidine chip on clinical and microbiological parametersof periodontal syndrome. J Clin Periodontol. 2002;29:875–881.
[36] Carvalho J, Novak MJ, Mota LF. Evaluation of the effect of subgingival placement of chlorhexidine chips as an adjunct to scaling and root planing. J Periodontol. 2007;78:997–1001.