Evaluation of Curcumin Gel Compared to Green Tea Gel as an Adjunctive Therapy in Management of Chronic Periodontitis: A Clinical and Biochemical Study

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Abstract

Background: Periodontitis is defined as a chronic multi-factorial inflammatory disease associated with dysbiotic plaque biofilms caused by pathogenic microorganisms and disordered host immune inflammatory response and characterized by progressive destruction of the tooth-supporting apparatus. Scaling and root planing (SRP) can sometimes be ineffective in deep pockets as subgingival microflora can recolonize them so as an adjunctive approach to the mechanical debridement, systemic or local administration of antimicrobials may be used but none of them is without side effects so there was a need for natural phytochemicals isolated from plants for prevention and treatment of oral diseases.

Objective: The purpose of this study was to evaluate the clinical efficiency of curcumin gel compared to green tea extract gel as an adjunct to SRP in management of moderate periodontal pockets and to evaluate the concentration of TNF-∂ concentration in the GCF and the release profile of curcumin and green tea in the GCF.

Method: A total of 42 patients having Stage II or III Grade A periodontitis were selected from the outpatient clinic of Oral Medicine, Periodontology and Oral Diagnosis department, Faculty of Dentistry, Ain Shams University and were divided to 3 groups each group included 14 patients. SRP was performed to all candidates then curcumin gel was applied in group (A), green tea extract gel was applied in group (B) and group (C) (control group) were treated by SRP only. Clinical parameters (PI, GI, PD and CAL) were measured at baseline and after 3 months, TNF-∂ concentration in the GCF was measured at baseline, after 1 week and after 2 weeks and the release profile of both curcumin and green tea was measured after their application by 1, 3, 7 and 14 days.

Result: The results of this study showed a statistically significant difference in all clinical parameters between baseline and 3 months and a statistically significant difference in TNF-∂ concentration in the GCF. Group (A) showed the best improvement followed by group (B). Concerning the release profile, curcumin showed the highest mean concentration but there was no statistically significant difference between curcumin and green tea.

Conclusion: Our results revealed that local delivery of curcumin and green tea extract can overcome limitations of SRP and led to more reduction in probing depth, more clinical attachment level gain and more reduction in the levels of TNF-∂ compared to SRP alone and curcumin has more bioavailability than green tea in the GCF.

Keywords: Periodontitis, curcumin gel, green tea extract gel, local drug delivery.

Introduction

Periodontitis is defined as a chronic multi-factorial inflammatory disease associated with dysbiotic plaque biofilms caused by pathogenic microorganisms and disordered host immune inflammatory response leading to the release of many cytokines and chemokines and characterized by progressive destruction of the tooth-supporting apparatus. It is featuring the loss of periodontal tissue support that is manifested through clinical attachment level (CAL) loss, radiographically assessed alveolar bone loss, the presence of periodontal pocket and gingival bleeding leading to bone resorption, bony defects, and ultimately tooth loss *(Papapanou PN et al., 2018)*.

Scaling and root planing (SRP) is one effective mechanical treatment for most periodontal infections and remains an essential part for successful periodontal therapy. SRP can directly remove the biofilm present on the root surface and improves the periodontal status, but it is rarely possible to completely remove the periodontal pathogens with SRP. The efficacy of SRP can be limited in cases with less access to deep periodontal pockets and furcation involvements. So there was a need for adjunctive treatment modalities to promote its effect *(Sgolastra et al., 2014)*.

Due to factors affecting undesirable treatment outcomes following nonsurgical periodontal therapy include poor patient compliance with oral hygiene regiments and the presence of systemic diseases like diabetes mellitus that can affect long term therapeutic outcomes. Other risk factors that can affect the outcomes of conventional nonsurgical therapy include the presence of persistent deep pockets and molars with furcation involvement, so there was a need for the use of a local drug delivery system for chemotherapeutic agents *(Grossi & Genco, 1998)*.

The use of traditional plant-based medications and natural products in the prevention and treatment of oral diseases was based on a review by *Palombo* in 2011 stated that there is a need for natural phytochemicals isolated from plants for prevention and treatment of oral diseases. These alternatives are safe, efficient and economical as there are increased bacterial resistance to antibiotics and side effects of some currently used antimicrobials in dentistry *(Palombo, 2011)*.

Curcumin has a combined anti-inflammatory, antioxidant and antibacterial effect. This effect is mediated through its ability to inhibit cyclooxygenase II (COX-

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2), lipoxygenase (LOX) and inducible nitric oxide synthase (iNOS). Down-regulation of these pathways leads to suppression of proinflammatory cytokines such as IL-1ß, IL-6, IL-8, IL-12, TNF-∂, Matrix metalloproteinase-2 (MMP-2) and Matrix metalloproteinase-9 (MMP-9). Curcumin has antibacterial effect against periodontopathogenic bacteria. Curcumin inhibited the growth of P. gingivalis, Prevotella intermedia, Fusobacterium nucleatum and Treponema denticola in a dose dependent matter that demonstrated a decrease in alveolar bone resorption following curcumin administration in rats *(Zhou et al., 2013)*.

Tea polyphenols have a strong antioxidant effect. Particularly, the reducibility of ester catechin EGCG is 100 times more effective than that of L-ascorbic acid. Among the four main catechin compounds, the antioxidant capacity was EGCG > EGC > ECG > EC. TPs also have antibacterial capabilities and have preventive effects mainly through mechanisms inhibiting the growth and adhesion of microorganisms on the enamel surface, as well as the expression of their virulence factors and can inhibit the virulence of plaque in different ways. Epigallocatechin-3-gallate (EGCG) is main polyphenol component in green tea. Compared with other polyphenolic compounds, EGCG shows the highest inhibitory effect on P. gingivalis growth and adherence to human epithelial cells *(Ramage et al., 2012)*.

Aim

The objectives of the present study are comparing the clinical efficiency of natural curcumin gel and green tea extract gel as local drug delivery agents in the management of periodontal pockets and evaluating their release profile and effect on TNF-∂ concentration in the gingival crevicular fluid (GCF).

Subjects 2and Methods

- This randomized clinical study was carried out on a total of 42 patients having Stage II or III Grade A periodontitis. The subjects were recruited from the outpatient clinic of Oral medicine, Periodontology, Oral diagnosis and Radiology department, Faculty of Dentistry, Ain Shams University. The purpose of the study was explained to all patients and an informed consent was signed before the conduction of the study.

- Inclusion criteria included:

  1. Age between 30 and 60 years.

  2. Belonging to both sexes.

  3. Patients with Stage II or III Grade A periodontitis (Caton et al., 2018).

  4. No systemic diseases which could influence the outcome of the therapy according to Cornell medical index.

  5. Good compliance with the plaque control instructions following initial therapy.

- Exclusion criteria included:

  1. Subjects with any systemic disease or conditions.

  2. Patients using antibiotic, anti-inflammatory, immunosuppressive therapy during the preceding 3 months before the start of the trial and during the study.

  3. Patients who have undergone any periodontal therapy in the last 6 months.

  4. Pregnancy and lactation.

  5. Reported allergy to curcumin or green tea.

  6. Subjects who are tobacco or alcohol users.

  7. Vulnerable group of patients (prisoners or handicapped patients).

- The candidates for this randomized clinical trial were 42 patients and they were randomly divided into 3 groups, each group included 14 patients. Each patient has periodontal pockets ranging from 4 to 6 mm. The patients were randomly assigned for each group. The procedures of this study were explained to them and a signed consent was obtained from each

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patient.

Group A: Will be 14 periodontal pockets that will be treated by SRP followed by curcumin gel placement.

Group B: Will be 14 periodontal pockets that will be treated by SRP followed Green tea extract gel placement.

Group C (Control group): Will be 14 periodontal pockets that will be treated by SRP only.

- Preparation of curcumin gel and green tea gel:

Curcumin gel: Curcumin gel was prepared from pure curcumin powder (98% Curcumin) to a concentration of 2% *(Hugar et al., 2016)*.

- Green tea extract gel: The green tea gel was prepared from 100% pure green tea extract to concentration of 12% w/w *(Rattanasuwan et al., 2016)*.

Curcumin gel and green tea gel were prepared for local drug application after SRP. The prepared gel consisted of hydrophilic and hydrophobic polymer mixture of polyvinylpyrrolidone (PVP) combinations.

- Procedure of the periodontal therapy:

1 After each patient enrollment, a detailed medical and dental history was recorded. The procedures of the study were explained to each patient and signed consent was taken from each one.

2 Baseline samples from the GCF were collected from all selected sites using absorbent paper strip (Oraflow periopaper®) inserted into the deepest part of each periodontal pocket and left in situ for 30 seconds for assessment of TNF-∂ concentrations.

3 All patients underwent phase I periodontal therapy was done by single visit full mouth supragingival scaling using ultrasonic scaler followed by subgingival scaling and root planning using universal curettes (2R-2L and 4R-4L).

4 In both test groups, the area of selected pocket in each patient was completely dried using oil free air syringe, and then the site was isolated with cotton rolls to prevent salivary contamination. The local drug delivery gel was placed in the periodontal pockets using a dedicated insulin syringe until the gel flowed out from the gingival margin.

5 The patients were given instructions for self-performed plaque control measures with soft dental brush and interdental cleaning using dental floss or interdental brush.

- Clinical assessment: The following parameters were recorded for the 3 groups on the following occasions:

a) Baseline: Immediately following phase I periodontal therapy.

b) 3 months: 3 months after phase I periodontal therapy.

Clinical parameters include:

1. Plaque index (PI).

2. Gingival index (GI).

3. Probing depth (PD).

4. Clinical attachment level (CAL).

- Biochemical assessment: Gingival crevicular fluid (GCF) was collected from all the 3 groups at baseline, 1 week and 2 weeks occasions following phase 1 periodontal therapy for evaluation of TNF-∂ concentration. And from group A and group B at day 1, day 3, day 7 and day 14 occasions following phase 1 periodontal therapy for evaluation of high-performance liquid chromatography (HPLC) to test both curcumin gel and green tea gel availability in the GCF.

Statistical analysis

Numerical data were presented as mean, standard deviation (SD) and confidence interval values. Data were explored for normality by checking the data distribution, calculating the mean and median values and using Kolmogorov-Smirnov and Shapiro-Wilk tests. Parametric data were analyzed using one-way ANOVA followed by Tukey's post hoc test for intergroup comparisons and one-way repeated measures ANOVA followed

by bonferroni post hoc test for intra group comparisons. Non-parametric data were analyzed using Kruskal Wallis test followed by multiple pairwise comparisons utilizing Mann-Whitney U test with bonferroni correction for intergroup comparisons and Friedman's test of repeated measures followed by multiple pairwise comparisons utilizing Wilcoxon signed-rank test with bonferroni correction for intragroup comparisons. The significance level was set at P ≤0.05 within all tests. Statistical analysis was performed with IBM® SPSS® Statistics Version 25 for Windows.

Results:

Clinical assessment:

1. Plaque index: At baseline, there was no significant difference between values recorded in different groups (p=0.846). The highest (PI) was found in group (B) (1.21±0.43), followed by groups (A) and (C) (1.14±0.36). After 3 months, all participants of the 3 groups had a (PI) of zero.

2. Gingival index: At baseline, all participants of the 3 groups had a (GI) of 2. After 3 months, there was no significant difference between values recorded in different groups (p=0.752). The highest (GI) was found in group (C) (0.50±0.52), followed by group (B) (0.43±0.51), while the lowest value was found in group (A) (0.36±0.50).

3. Probing depth: At baseline, there was a significant difference between values recorded in different groups (p=0.017). The highest (PD) was found in group (B) (5.64±0.50), followed by group (A) (5.36±0.50), while the lowest value was found in group (C) (5.00±0.68). Pairwise comparisons showed a significant difference between groups (B) and (C) (p<0.001). After 3 months, there was a significant difference between values recorded in different groups (p=0.021). The highest (PD) was found in group (C) (3.79±0.43), followed by group (B) (3.64±0.50), while the lowest value was found in group (A) (3.29±0.47). Pairwise comparisons showed a significant difference between groups (A) and (C) (p<0.001).

4. Clinical attachment level: At baseline, there was a significant difference between values recorded in different groups (p=0.017). The highest (CAL) was found in group (B) (3.64±0.50), followed by group (A) (3.36±0.50), while the lowest value was found in group (C) (3.00±0.68). Pairwise comparisons showed a significant difference between groups (B) and (C) (p<0.001). After 3 months, there was a significant difference between values recorded in different groups (p=0.015). The highest (CAL) gain was found in group (B) (1.64±0.50), followed by group (A) (1.29±0.47), while the lowest value was found in group (C) (1.00±0.68). Pairwise comparisons showed a significant difference between groups (B) and (C) (p<0.001).

Biochemical assessment:

1. Tumor necrosis factor-alpha (TNF-∂): At baseline, there was a significant difference between values recorded in different groups (p=0.020). The highest (TNF-∂) value was found in group (C) (241.36±16.40), followed by group (B) (225.07±19.07) while the lowest value was found in group (A) (222.00±20.47). Pairwise comparisons showed that there was a significant difference between groups (A) and (C) (p<0.001). After 1 week, there was a significant difference between values recorded in different groups (p<0.001). The highest (TNF-) value was found in group (C) (136.57±11.26), followed by group (B) (114.14±6.60) while the lowest value was found in group (A) (113.00±6.10). Pairwise comparisons showed group (C) value to be significantly higher than groups (A) and (B) (p<0.001). After 2 weeks, was a significant difference between values recorded in different groups (p<0.001). The highest (TNF-

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∂) value was found in group (C) (103.71±4.16), followed by group (B) (81.07±9.71) while the lowest value was found in group (A) (74.57±7.67). Pairwise comparisons showed group (C) value to be significantly higher than groups (A) and (B) (p<0.001). Overall, there was a significant difference between values recorded in different groups (p<0.001). The highest percentage reduction of (TNF-∂) value was found in group (A) (66.10±4.99), followed by group (B) (63.67±5.76) while the lowest value was found in group (C) (56.85±3.40). Pairwise comparisons showed group (C) to have a significantly lower value than group (A) and group (B) (p<0.001).

2. High-performance liquid chromatography (HPLC): At day 1, group (A) (1.67±0.34) had a significantly higher value of drug release than group (B) (1.09±0.11) (p<0.001). At day 3, group (A) (1.09±0.41) had a significantly higher value of drug release than group (B) (0.75±0.08) (p=0.006). At day 7, group (A) (0.70±0.35) had a significantly higher value of drug release than group (B) (0.45±0.10) (p=0.019). At day 14, group (A) (0.34±0.27) had a significantly higher value of drug release than group (B) (0.16±0.06) (p=0.021). Overall, group (B) (84.95±5.37) had a higher reduction percentage than group (A) (80.66±11.59), yet there was no significant difference between both groups (p=0.220).

Discussion

The objectives of the study are comparing the clinical efficiency of natural curcumin gel and green tea extract gel as local drug delivery agents in the management of periodontal pockets and evaluating their release profile and effect on TNF-∂ concentration in the gingival crevicular fluid (GCF).

These results may be due to the use of curcumin in group A and green tea extract in group B which could be explained by their abilities to enhance wound healing.

Curcumin affects all phases of wound healing, it reduces inflammation at wounded sites, it increases the ability of fibroblasts, collagen deposition and angiogenesis and helps in re-epithelialization *(Mohanty et al., 2012)*. Green tea may even reduce the progression of an existing periodontitis. Overall, green tea has an antioxidant and antibacterial effect on pathogens such as *Porphyromonas gingivalis* and *Prevotella intermedia*. The mechanism of action is through the inhibiting effect of EGCG on cysteine proteases of *Porphyromonas gingivalis* *(Kushiyama M et al., 2009)*.

Enhanced clinical outcomes (PD reduction, PI reduction, GI reduction and CAL gain) reported in the present study was in accordance to previous studies that involved SRP and curcumin gel application and SRP and green tea extract gel application. Regarding curcumin, our results were in accordance with Hugar et al who recorded PD reduction, PI reduction, GI reduction and CAL gain after application of 2% curcumin gel as an adjunct to SRP (Hugar et al., 2016). Regarding green tea extract, our results were in accordance with Rattanasuwan et al who recorded PD reduction, PI reduction, GI reduction and CAL gain after application of 12%w/w green tea extract gel (Rattanasuwan et al., 2016).

Conclusion

Within the limitations of this study we could conclude that local delivery of curcumin and green tea extract can overcome limitations of SRP and the use of curcumin and green tea after SRP of periodontal pockets lead to more reduction in probing depth and more clinical attachment level gain compared to SRP alone as they have anti-inflammatory effects so they led to more reduction in the levels of TNF-∂ in the GCF compared to SRP alone. Curcumin also had more bioavailability than green tea in the GCF.

Recommendations

Using different concentrations of curcumin and green tea extract needs to be evaluated in order to figure out the optimal concentration

that leads to maximum stimulation and radiographic evaluation before and after treatment should be done.

References

1. Amid R, Kadkhodazadeh M, Fekrazad R, Hajizadeh F, Ghafoori A. Comparison of the effect of hand instruments, an ultrasonic scaler, and an erbium-doped yttrium aluminium garnet laser on root surface roughness of teeth with periodontitis: a profilometer study. J Periodontal Implant Sci. 2013;43(2):101–105. doi: 10.5051/jpis.2013.43.2.101.

2. Grossi SG, Genco RJ. Periodontal disease and diabetes mellitus: a two-way relationship. Annals of periodontology. 1998;3(1):51-61.

3. Hugar SS, Patil S, Metgud R, Nanjwade B, Hugar SM. Influence of application of chlorhexidine gel and curcumin gel as an adjunct to scaling and root planing: A interventional study. J Nat Sc Biol Med. 2016;7:149-54.

4. Kushiyama M, Shimazaki Y, Murakami M, Yamashita Y. Relationship between intake of green tea and periodontal disease. Journal of periodontology. 2009 Mar;80(3):372-7.

5. Maldupa I, Brinkmane A, Rendeniece I, Mihailova A. Evidence based toothpaste classification, according to certain characteristics of their chemical composition. Stomatologija. 2012;14(1):12-22.

6. Mohanty C, Das M, Sahoo S. Sustained wound healing activity of curcumin loaded oleic acid based polymeric bandage in a rat model. Mol Pharm 2012;9:2801–11.

7. Palombo EA. Traditional medicinal plant extracts and natural products with activity against oral bacteria: potential application in the prevention and treatment of oral diseases. Evidence-Based Complementary and Alternative Medicine. 2011;2011.

8. Papapanou PN, Sanz M, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions.J Clin Periodontol. 2018;45(Suppl 20):S162–S170.

9. Ramage G, Milligan S, Lappin DF, Sherry L, Sweeney P, Williams C, Bagg J, Culshaw S. Antifungal, cytotoxic, and immunomodulatory properties of tea tree oil and its derivative components: potential role in management of oral candidosis in cancer patients. Frontiers in microbiology. 2012 Jun 18; 3:220.

10. Sgolastra F, Severino M, Petrucci A, et al. Effectiveness of metronidazole as an adjunct to scaling and root planing in the treatment of chronic periodontitis: A systematic review and meta-analysis. J Periodont Res. 2014;49:10–19.

11. Zhou T, Chen D, Li Q, Sun X, Song Y, Wang C. Curcumin inhibits inflammatory response and bone loss during experimental periodontitis in rats. Acta Odontologica Scandinavica 2013; 71:349-356.

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