Comparative Clinical Evaluation of Two Local Drug Delivery Agents (*Neem* Chip and Turmeric Chip) in Chronic Periodontitis: An Experimental Study

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ABSTRACT

Aim and objective: This study aimed to evaluate the efficacy of herbal local drug delivery (LDD) agents as an adjunct to scaling and root planing (SRP) and SRP alone in the treatment of chronic periodontitis.

Material and methods: This split-mouth study was conducted at the Department of Periodontology, SGT Dental College, Haryana, in 30 patients between 30 years and 65 years of age where 90 sites (3 sites in one patient) were selected. Only those teeth with probing pocket depth (PPD) of ≥ 5 mm were included. Sites were randomized into three treatment groups. Group I with SRP + *neem* chip, group II with SRP + turmeric chip, and group III received SRP only. Clinical parameters plaque index (PI), gingival index (GI), PPD, and relative attachment level (RAL) were recorded at baseline, 1 month after the intervention, and at 3 months. Intergroup comparisons were done using Kruskal–Wallis test followed by *post hoc* comparison using Mann–Whitney *U* test.

Results: Mean PI and GI at 1 month for group I, II, and III were $(1.33 \pm 0.28, 1.37 \pm 0.28, \text{ and } 1.66 \pm 0.27)$ ($1.20 \pm 0.31, 1.24 \pm 0.26, \text{ and } 1.31 \pm 0.39$), respectively. Improvement in mean PI and mean GI of group I and group II at 1 month is significant when compared with group III ($p < 0.05$). Probing pocket depth at 1 month for group I, II, and III was $4.16 \pm 0.88, 4.21 \pm 0.61, \text{ and } 4.63 \pm 0.68$, respectively ($p < 0.05$ for all groups). Mean RAL at 1 month for group I, II, and III was $8.41 \pm 1.59, 8.43 \pm 1.66, \text{ and } 9.01 \pm 1.50$, respectively. The mean RAL of group I and group II is significant when compared with group III at 1 month ($p < 0.05$).

Conclusion: Better immediate results can be achieved in the management of chronic periodontitis by the use of locally delivered *neem* and turmeric extract in form of chips.

Clinical significance: These herbal chips are natural, cost-effective without any side effects, and can be used in treating chronic periodontitis.

Keywords: Chronic periodontitis, Curcumin, Local drug delivery, *Neem* chip, Turmeric chip.

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INTRODUCTION

Chronic periodontitis is an inflammatory condition of the supporting tissues of the teeth caused primarily by mixed microbial infection.¹ This complex inflammatory process results in loss of periodontal tissue attachment and alveolar bone resulting in periodontal pocket formation. The ultimate goal of all periodontal therapy is to restore the health of inflamed tissue, eliminate the diseased pockets, and reduce the number of pathogenic microorganisms.² Thus, surgical and nonsurgical treatment modalities for removing plaque biofilm are essential for the management of chronic periodontitis.³

Scaling and root planing (SRP) procedures have been used as the “gold standard” for nonsurgical mechanical therapy.⁴ This conventional therapeutic module effectively decreases the microbial load, but recolonization of the same cannot be prevented.⁵ Systemic antibiotics are often used as an adjuvant to this treatment. To avoid the undesired effect of systemic antibiotics, Goodson gives the concept of controlled drug delivery for treatment of chronic periodontitis and observed that 100-fold higher concentrations of the drug can be attained through the local route as compared to systemic drug regimen without side effects. This helps to avoid the development of drug resistance at nonoral body sites.^{6,7}

Various antimicrobial agents such as tetracycline, 10% doxycycline, 2% minocycline, metronidazole, and chlorhexidine (CHX) gluconate have been used and investigated as local drug delivery (LDD) in the treatment of periodontal diseases.⁸ In today's

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era, research is being focused mainly on the use of natural products as LDD agents. There have been various formulations under study which increased our curiosity about the medicinal value of natural products such as turmeric, aloe vera, *neem*, tulsi, cocoa husk, and pomegranate, and these all are tested widely these days.⁹

Neem and turmeric have a unique anti-inflammatory property. The advantage that these herbal plants can be fabricated into chips and delivered at the local site goes a long way in the management of the local inflammatory process. Easy application of these chips

and no side effects of herbal products leads to our thinking of utilizing them in chronic periodontitis treatment. Hence, in this study, we intend to evaluate the efficacy of these herbal chips as LDD agents adjuvant to SRP vs SRP alone in the treatment of chronic periodontitis.

MATERIALS AND METHODS

Study Sample and Selection Criteria

This study was conducted in the Department of Periodontology, SGT Dental College, Gurugram, Haryana, from April 2018 to January 2019. A total number of 90 sites were selected in 30 patients with chronic periodontitis with no other comorbidity the selected patients were between 30 and 65 years of age and with ≥ 20 teeth in the mouth. Three test sites from any three quadrants of mouth were selected randomly in each patient. Only those teeth with probing pocket depth (PPD) of ≥ 5 mm were included. Smokers, tobacco chewers, and those with a history of allergy or previous dental surgery or previous treatment with antibiotics in the last 3 months were excluded. The study was approved by Institutional ethical committee No. SGTU/FDS/MDS/24/1/672 dt 21/12/2017. All the patients were well informed and written informed consent was taken.

Study Design

This study is a split-mouth experimental study of 3-month duration. The study design is explained in detail in Flowchart 1. All the procedures were done by a single investigator (KS). plaque index (PI) and gingival index (GI) were measured and recorded as baseline data.^{10,11} Probing pocket depth measured using a graduated periodontal probe (PCP UNC-15, Hu-Friedy® Manufacturing Co., Chicago, IL, USA) by inserting the probe into the gingival sulcus,

and readings were taken from the gingival margin till the base of the pocket. Alginate impressions were made to prepare customized acrylic stents that would act as a reference guide for recording PPD and relative attachment levels (RALs) at the experimental sites. All measurements at baseline, 1 month, and 3 months were done by an investigator (PC).

The study samples were stratified randomly into three groups with a stratified random sampling method:

Group I: Sites to be treated with *neem* chip in addition to SRP.

Group II: Sites to be treated with turmeric chip in addition to SRP.

Group III: Sites treated with the only SRP in addition to a placebo chip.

Group I and II were experimental groups and group III was a control group. Blinding was done by ensuring that the investigator involved in measurement was unaware of site allocations.

Preparation and Composition of Chips

Neem and turmeric chips used in the study were indigenously prepared in the laboratory in Guru Nanak Institute of Pharmacy, Ibrahimpatnam, Hyderabad. The chip was customized so that it measures 4×2 mm with a thickness of 0.3 mm and its weight was restricted to 10 mg in a biodegradable hydroxypropyl cellulose (HPC) matrix. Each chip was customized so that it will contain *neem*/turmeric 5%, HPC-1000 mg, poly vinylpyrrolidone-100 mg, poly ethylene glycol-100 mg, and ethanol/water-10 mL by weight. *Neem* chips were green in color and turmeric chips were yellow, respectively (Figs 1A and B). The placebo chip also measures 4×2 mm with a thickness of 0.3 mm and its weight was restricted to 10 mg in a biodegradable HPC matrix. Placebo chips did not contain any active ingredient. They were transparent as shown in Figure 1C. All chips were sterilized by gamma radiations and packed individually.

Flowchart 1: Study design

Figs 1A to C: (A) Neem chip; (B) Turmeric chip; (C) Placebo chip

Table 1: Intergroup comparison of plaque index score. Plaque index scores for three groups are given at baseline, 1 month, and 3 months

Plaque index scores		Mean	Std. deviation	Std. error	p value	Post hoc pairwise comparison
At baseline	Group I	1.9597	0.37135	0.06670	0.776	–
	Group II	1.9516	0.34411	0.06180		
	Group III	2.0403	0.32975	0.05923		
At 1 month	Group I	1.3306	0.28422	0.05105	0.04*, 0.03*	A-C*, B-C*
	Group II	1.3710	0.28041	0.05036		
	Group III	1.6677	0.27189	0.04883		
At 3 months	Group I	1.2984	0.29874	0.05366	0.045	
	Group II	1.3710	0.29489	0.05296		
	Group III	1.4435	0.30076	0.05402		

*Comparatively significant

Procedure

After SRP at the selected target sites with periodontal PPD ≥ 5 mm, subsequently deepest pocket in the quadrant was selected. Both hand and ultrasonic scaling methods were used for SRP. Before inserting the chip, the area was dried with the cotton rolls. A sterile pack of the individual chip was opened. The flat end of the chip was grasped with a tweezer and the rounded end of the chip was pressed apically into the test site so that the chip rests subgingivally at the base of the pocket and making sure that it is not exposed. After that periodontal dressing (Coe-pak) was placed to prevent the dislodgment of the chip.

The patients were then instructed to continue with regular oral hygiene measures, after treatment except for the use of any chemotherapeutic mouth rinses and oral irrigation devices. Patients were also advised not to do flossing for at least 10 days to avoid any possibility of dislodging the chips. All patients were recalled after 7 days for pack removal and evaluated for any adverse clinical signs. Patients were then recalled at 01 month after insertion of chip and all clinical parameters (PI, GI, PPD, and RAL) were recorded. Oral hygiene instructions were further reinforced. Patients were then again recalled after 2 months to record all clinical parameters (PI, GI, PPD, and RAL) for 03 months. No adverse effect was seen in any patient.

Statistical Analysis

All data were entered into a Microsoft Excel spreadsheet by an investigator (AB) and was checked for any discrepancies. Summarized data were presented using tables and graphs. The data were analyzed by SPSS (21.0 version). Shapiro–Wilk test

was used to check which all variables were following a normal distribution. Data were not normally distributed (p value was <0.05). Therefore, bivariate analyzes were performed using the nonparametric tests, i.e., Mann–Whitney U (for comparing two independent groups), Wilcoxon sum rank test for comparing two dependent means, and Kruskal–Wallis test (for comparing more than two groups).

RESULTS

Mean PI at 1 month for group I, II, and III was 1.33 ± 0.28 , 1.37 ± 0.28 , and 1.66 ± 0.27 , respectively. Improvement in mean PI of group I and group II is significant when compared with group III ($p < 0.05$). At 3 months, the mean PI was 1.29 ± 0.29 , 1.37 ± 0.29 , and 1.44 ± 0.30 for group I, II, and III, respectively. Improvement in mean PI from 1 to 3 months is not significant in any group ($p > 0.05$). This PI score for three test groups at baseline, 1 month, and 3 months is shown in Table 1.

Intergroup comparison showed no significant difference in GI at baseline. Mean GI at 1 month for group I, II, and III was 1.20 ± 0.31 , 1.24 ± 0.26 , and 1.31 ± 0.39 , respectively. Improvement in GI is significant in all groups at one month ($p < 0.05$). At 3 months, mean GI was 1.29 ± 0.28 , 1.37 ± 0.29 , and 1.39 ± 0.35 for group I, II, and III, respectively. Improvement in mean GI of both group I and group II at 1 month is significant when compared with group III ($p < 0.05$). This GI score for three test groups at baseline, 1 month, and 3 months is shown in Table 2

Probing pocket depth at 1 month for group I, II, and III was 4.16 ± 0.88 , 4.21 ± 0.61 , and 4.63 ± 0.68 , respectively ($p < 0.05$ for

Table 2: Intergroup comparison of gingival index score for three groups are given at baseline, 1 month, and 3 months

Gingival index score		Mean	Std. deviation	Std. error	p value	Post hoc pairwise comparison
At baseline	Group I	1.9355	0.37621	0.06757	<0.070	–
	Group II	1.9355	0.30254	0.05434		
	Group III	2.0726	0.33661	0.06046		
At 1 month	Group I	1.2016	0.31238	0.05610	0.034*, 0.024*	A-C*, B-C*
	Group II	1.2419	0.26991	0.04848		
	Group III	1.3145	0.39774	0.07144		
At 3 months	Group I	1.2961	0.27337	0.04910	>0.05	
	Group II	1.3790	0.28774	0.05168		
	Group III	1.3952	0.35809	0.06431		

*Comparatively significant

Table 3: Intergroup comparison of probing pocket depth for three groups is given at baseline, 1 month, and 3 months

Probing pocket depth		Mean	Std. deviation	Std. error	p value	Post hoc pairwise comparison
At baseline	Group I	5.435	0.761	0.137	0.320	–
	Group II	5.431	0.597	0.107		
	Group III	5.419	0.660	0.118		
At 1 month	Group I	4.161	0.8887	0.1596	0.020*, 0.026*	A-C*, B-C*
	Group II	4.210	0.6161	0.1107		
	Group III	4.632	0.6823	0.1226		
At 3 months	Group I	3.919	0.8573	0.1540	0.064	
	Group II	4.181	0.6843	0.1229		
	Group III	4.323	0.6525	0.1172		

*Comparatively significant

Table 4: Intergroup comparison of relative attachment level for three groups is given at baseline, 1 month, and 3 months

Relative attachment level		Mean	Std. deviation	Std. error	p value	Post hoc pairwise comparison
At baseline	Group I	9.742	1.5910	0.2857	0.070	–
	Group II	9.629	1.6123	0.2896		
	Group III	9.935	1.4591	0.2621		
At 1 month	Group I	8.419	1.5389	0.2764	0.024	A-C*, B-C*
	Group II	8.435	1.6620	0.2985		
	Group III	9.016	1.5027	0.2699		
At 3 months	Group I	8.261	1.5351	0.2757	0.423	–
	Group II	8.371	1.6831	0.3023		
	Group III	8.842	1.6677	0.2995		

*Comparatively significant

all groups). At 3 months for group I, II, and III was 3.91 ± 0.85 , 4.18 ± 0.69 , and 4.32 ± 0.62 , respectively. Improvement in mean PPD of group I and group II is significant when compared with group III ($p < 0.05$). However, improvement in mean PPD of group I and II in comparison to group III is not statistically significant at 3-month follow-up ($p > 0.05$) as shown in Table 3.

Relative attachment level at 1 month for group I, II, and III was 8.41 ± 1.59 , 8.43 ± 1.66 , and 9.01 ± 1.50 , respectively. At 3 months for group I, II, and III was 8.26 ± 0.27 , 8.37 ± 0.3 , and 8.74 ± 0.29 , respectively. Improvement in mean RAL of group I and group II is significant when compared with group III ($p < 0.05$) at 1 month. However, improvement in mean RAL of both test groups in comparison to group III is statistically insignificant at 3-month follow-up ($p > 0.05$) as shown in Table 4.

DISCUSSION

Since the prime etiological factor is plaque formation, so till date the goal of periodontal therapy is aimed at removing supra- and subgingival plaque biofilm by mechanical debridement, keeping this context in mind study is planned to compare control group SRP along with placebo chip (Hawthorne effect) to herbal LDD agents adjunct to SRP.

Local drug delivery agents directly act on periopathogens residing in periodontal pockets and aids in controlling the disease. They are available as a gel, strips, nanosphere, microspheres, chips, etc. The various locally delivered antimicrobials agents available are listed below:

- Tetracycline fibers.
- Metronidazole gel.

- Minocycline ointment.
- Chlorhexidine chips.
- Doxycycline hyclate in a resorbable polymer.
- Resorbable tetracycline in fibrillar collagen.
- Minocycline microspheres.
- Azithromycin gel, etc.¹²

Oral rinses and irrigating devices are easy to use and commonly employed but irrigation system is not much successful in managing periodontitis as the desired concentration of a drug is not achieved in the pocket, as well as there is inadequate penetration of drug in the deep pocket.¹³

In the present study, we have used antimicrobial agents in form of biodegradable chips as this route provides more sustainability for the drug. One of the commercially available FDA-approved LDD agents containing 0.02% chlorhexidine (Periochip) is considered as the gold standard by some authors in the treatment of periodontitis.^{14,15} The disadvantage is that they are expensive, so we used indigenously produced biodegradable chips that were cost-effective.

We have used *neem* (*Azadirachta indica*) and turmeric (*Curcumin longa*) in the treatment of periodontitis because of their anti-inflammatory, antimicrobial, antioxidant, immunostimulant, and anticancer properties. Turmeric is an easily available, renewable resource, and cost-effective, so used in various inflammatory diseases including chronic periodontitis as a LDD agent.¹⁶ Curcumin acts as an anti-inflammatory agent by down-regulating the activity of cyclooxygenase-2 (COX-2), lipoxygenase, and inducible nitric oxide synthase (iNOS) enzymes.¹⁷

Neem twigs are in use since ancient times for cleaning teeth and gum massage. The antibacterial activity of *neem* against periodontal pathogens has been proven in various studies. Rao et al. have proved the efficacy of *neem* in reducing plaque cultures and gram-negative bacteria as compared to the other denitrifiers which are available commercially.¹⁸ Studies done by Chatterjee et al. and Chaudhary et al. showed that mouth rinse prepared from leaf extract is highly efficacious in controlling gingivitis.^{19,20}

It is seen that the effect of the locally delivered controlled-release drug is evident up to 11 weeks after administration. Hence, planned our follow-up at 1-month and 3-month interval.²¹

In the present study, we have used *Neem* and Turmeric because these two products are well known among our study population and also easily acceptable. Moreover, both *Neem* and turmeric chips were available commercially, cost-effective, and can be stored at room temperature. On comparison of *neem* chip and turmeric chip as an adjunct to SRP vs SRP alone in microbial plaque accumulation (PI) from baseline to 1 month and 3 months by using Silness and Loe, PI we found that after 1-month follow-up group I and II with *neem* and turmeric were more efficient than group III in reducing plaque. Results can be attributed due to the additional antibacterial properties of these LDD agents. Contrary to the results of our study, Singh et al. stated that no significant difference in PI from baseline to 1 month was seen while comparing curcumin chip as an adjunct to scaling and root planing.²² Similar to our results, study done by Vennila et al. in 2016 showed that plaque accumulation decreases significantly on day 7 and 21.¹³ At 3 months, no difference in plaque accumulation among the test and control group.

In our study, changes in GI showed a significant reduction at 1 month. At 3 months, there is a slight increase in gingival scores that can be attributed due to noncompliance to oral hygiene instructions. Comparison of PI and GI of all three groups represented in Figure 2. Gottumukkala et al. showed that curcumin gel and chlorhexidine were better in reducing the gingival inflammation at 1 month but at 3 months chlorhexidine group was better as there was a recurrence of inflammation in the curcumin group. Contrary to our results, Singh et al. showed after a 1-month interval GI have no significant difference in all three groups Periochip + SRP, curcumin chip + SRP, and SRP.^{23,24}

Both the test groups showed a decrease in PPD and RAL from baseline to 1 month significantly as compared to the control group. Jain et al. in a similar study compared the *neem* chip + SRP with SRP alone and the results were in favor of our study at 6 weeks.²⁴ Contrary to our results, Mehta et al. in 2015 used *neem* extract as an LDD agent and found it to be marginally better than SRP but not significant.²⁵ Comparison of PPD and RAL at baseline 1 month and 3 months is shown in Figure 3.

Both agents *neem* and turmeric chip were found to be effective in reducing clinical parameters such as PI, GI, PPD, and RAL.

Fig. 2: Comparison of PI, GI at baseline, 1 month, and 3 months in group I, II, and III. *PI, plaque index; GI, gingival index

Fig. 3: Comparison of PPD, RAL at baseline, 1 month, and 3 months in group I, II, and III. *PPD, probing pocket depth; RAL, relative attachment level

CONCLUSION

Neem and turmeric as LDD agents adjunct to SRP are more effective in controlling chronic periodontitis as compared to SRP alone in a short duration of 1 month. However, the long-term effects of these agents are still debatable. Further studies with large sample size, long-term follow-ups, and microbiological culturing for evaluating the specific bacterial inhibitory effects of indigenously produced herbal chips are required.

CLINICAL SIGNIFICANCE

These herbal substitutes, i.e., *neem* chip and turmeric chip are natural products free from side effects and cost-effective LDD agent in managing chronic periodontitis.

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