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Original Article

Comparative Evaluation of the Effects of Two Different Local Drug Delivery Systems Incorporating Green Tea and Turmeric Extracts in the Treatment of Chronic Periodontitis: A 2-month Clinical Trial

Vishwas Madaan[1], Ashwini M Padhye[2], Himani Gupta[3]

[1]Director, Ivory Dental and Physiotherapy Centre, Seawoods, Navi Mumbai, Maharashtra, India, [2]Professor and Head, Department of Periodontics, MGM Dental College and Hospital, Kamothe, Mumbai, Maharashtra, India, [3]Senior Lecturer, Department of Periodontics, MGM Dental College and Hospital, Kamothe, Mumbai, Maharashtra, India

Abstract

Aim: This randomized, triple-blinded parallel study was aimed to evaluate the effects of two different local drug delivery (LDD) systems incorporating green tea and turmeric extracts as an adjunct to scaling and root planing (SRP) in the treatment of chronic periodontitis (CP).

Materials and Methods: Thirty-four subjects randomized to receive either Gel A or Gel B containing green tea or turmeric extract were included in the study. Following SRP, probing pocket depth (PPD), relative attachment level, gingival margin position (GMP), bleeding on probing, gingival index, and periodontal inflammatory surface area were recorded at baseline and 8 weeks after treatment with Gel A or Gel B.

Results: Mean PPD reduction from baseline to 8 weeks was −24.57% for Gel A while for Gel B, it was −22.99%. On comparison of GMP values for Gel A and Gel B at baseline (3.03±1.10 and 2.80±1.06) and at the end of 8 weeks (3.27±1.41 and 3.27±1.14), a statistically significant difference was noted. However, the percentage change was positive (7.69% and 16.67%) in both groups.

Conclusion: Both LDD gel systems were equally beneficial and showed a noteworthy reduction in the clinical parameters recorded when used as an adjunct to SRP in the treatment of CP.

Key words: Chronic periodontitis, Drug delivery systems, Green tea extract, Turmeric extract

INTRODUCTION

The cornerstone of periodontal treatment is non-surgical mechanical therapy. The beneficial effects of scaling and root planing (SRP) are based on achieving a reduced mass of bacteria in the periodontal pockets[1] and an ecologic shift toward a less pathogenic microflora.[2] Nonetheless, mechanical debridement alone may fail to eradicate pathogenic organism from niches such as subepithelial gingival tissues, radicular dentinal tubuli, altered cementum, or furcation and other inaccessible areas difficult for adequate instrumentation.[3] Effects of combining SRP with local or systemic antimicrobial agents have been evaluated for additional improvements in clinical results.[4] Systemic antibiotics enter the periodontal tissues and counter the microorganisms beyond the reach of conventional mechanical debridement.[5] However, they are administered at a higher dose to achieve necessary concentration at the target site and may lead to the development of hypersensitivity reactions, drug toxicity, resistant bacteria, etc. This has led to the invention of the local drug delivery (LDD) system.[6]

Goodson in 1979 developed the concept of controlled release-LDD. This limits the drug to its target site,

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Corresponding Author: Dr. Vishwas Madaan, Ivory Dental and Physiotherapy Centre, Seawoods, Navi Mumbai, Maharashtra, India.

therefore, yielding higher concentrations. Various LDD systems incorporating an antimicrobial agent for use in the periodontal pocket include fibers, films, injectable systems, gels, strips and compacts, vesicular, and microparticle and nanoparticle systems. Of these, the injectable systems are particularly attractive due to the ease of application, the reduced cost of the therapy, and the ability of the gel to completely fill the periodontal pocket.[7]

An LDD gel comprises an active agent dispersed in a vehicle. Osmotically reactive thermosetting gels are widely used as porous solids that adhere on application of pressure. They configure as swollen networks possessing both the cohesive properties of solids and the diffusive transport characteristics of liquids. Poloxamer 407 is one such gel that remains stable in its native state and also harbors a hydrogel character that allows it to provide a time-dependent drug release making it suitable for subgingival use as a vehicle for sustained drug delivery.[8]

Side effects of various antimicrobials, tested subgingivally, have led the researchers in the field of phytosciences, to harness antimicrobial activity of herbs and to utilize their medicinal aspects. Globally, plant extracts such as allicin, proanthocyanides, terpenes, alkaloids, catechol, and flavonoids[9] have been employed for their anti-inflammatory, antibacterial, antifungal, and antiviral activities.[10] *Camellia sinensis*, commonly known as tea, contains a number of bioactive chemicals and is particularly rich in flavonoids including catechins[11] that are strong antioxidants and possesses bactericidal effects that alleviate symptoms of periodontal disease. Turmeric, a rhizome of *Curcuma longa* which is a common antiseptic containing curcuminoids, acts as potent scavengers of oxidant radicals.[12]

Green tea extracts (GTEs)[13] and turmeric extracts[14] in LDD systems have been used in the treatment of periodontitis. However, there is no reported literature comparing the clinical effects of these two extracts in a novel Pluronic polymer-based LDD system. Hence, this study was designed as a randomized, triple-blinded, parallel trial that aimed to evaluate and compare the effects of two different LDD systems incorporating GTE and turmeric extracts as an adjunct to SRP in the treatment of chronic periodontitis (CP).

MATERIALS AND METHODS

Injectable biodegradable LDD gel systems with two different herbal extracts were prepared according to the cold method.[15] Poloxamer 407 (20% concentration) gave the best handling characteristics with regard to film thickness and viscosity and was used as a vehicle in our study.[16] About 20 g of Poloxamer 407 added to 100 ml of distilled water cooled at 2–8°C, agitated with a magnetic stirrer, and yielded a gel with 20% critical micellar concentration (CMC); and for this CMC, the sol–gel transition temperature was found to be 35–38°C. Each herbal extract along with 1.5% weight/volume of carbopol 934 was added separately to 20% Poloxamer 407 so as to yield two different gels with a drug concentration of 1 mg/ml as determined by ultraviolet spectrophotometer at 765 nm (UV-1800, Shimadzu, Japan). These gels were sterilized using gamma irradiation at 2.5 Mrad and supplied in 2 ml syringes covered and labeled as Gel "A" or Gel "B" by the pharmacist from C.U. Shah College of Pharmacy, Mumbai, India, fitted with a blunt cannula bent at 45° having a diameter of 0.9 mm. The LDD syringes were stored in a refrigerator at 2–8°C until further use.

Experimental Design and Treatment Protocols

The study protocol was previously approved by the institutional ethics committee and the study was conducted in accordance with the Declaration of Helsinki, 7th revision in 2013. The study population included 34 subjects (21 males and 13 females), 30–55 years of age, referred to the outpatient section, Department of Periodontics, MGM Dental College and Hospital, Navi Mumbai, India (First patient enrollment – September 5, 2014; last patient follow-up – October 6, 2015). The study aims together with any potential benefits or detrimental effects, and alternatives were discussed with the subjects, and a written, signed, and informed consent to participate in the study was obtained. To calculate the sample size[17] at 80% power, the level of significance was set at 0.05, to detect a standard deviation (SD) in relative attachment level (RAL) at 0.21.[18] This data when analyzed by MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2015) yielded a sample size of 34 per group. Hence, it was decided to select 34 subjects with CP amounting to a total of 68 sites to be evaluated.

All systematically healthy subjects diagnosed with CP willing to participate and maintain regular appointments were considered for the study. The sites were selected based on the following criteria: local factors, two non-adjacent sites with probing pocket depth of 5–7 mm and interproximal attachment loss of ≥3mm measured using North Caroline-15 probe with radiographic evidence of alveolar bone loss. Exclusion criteria included subjects with/who have a known history of allergic reactions to turmeric and/or green tea, presence of three or more adjacent periodontal pockets on the same potential test teeth, received any form of periodontal therapy, surgical or non-surgical within the past 6 months, received antibiotic/anti-inflammatory therapy within the past 6 months,

presence of pulpal or periapical involvement on qualifying teeth, pregnant and lactating women, and smokers.

Initially, a full-mouth periodontal examination was performed and subjects fulfilling inclusion criteria underwent SRP. On recall after 1 week, which was considered as the baseline visit, two test sites with maximum PPD were selected to receive the gels. PPD, RAL, gingival margin position (GMP), bleeding on probing (BOP),[19] gingival index (GI),[20] and periodontal inflammatory surface area (PISA) score[21] were recorded at baseline and at the end of 8 weeks. The probing site measurements were standardized using a custom-made acrylic stent, considering the apical margin of stent as a fixed reference point for RAL and GMP measurements. BOP, GI, and PISA were also recorded at this visit. All measurements were performed by a single investigator. After isolation with cotton rolls, the two selected sites were randomized by coin toss method to receive either Gel A or Gel B, starting from apical end of the pocket and moving coronally till the pocket just overfilled. Both test sites were covered with a eugenol-free periodontal dressing (Coe-Pak™ GC America Inc., Alsip IL, USA). Subjects were advised to discontinue tooth brushing at the test sites for 7 days and refrain from any other unassigned means of oral hygiene practices during the tenure of this study. Subjects were recalled, after 7 days of gel application, for the removal of the periodontal dressing and home care instructions were reinforced to include brushing at the test sites as well. All subjects were instructed to report any untoward event. The contents of Gel A or Gel B were kept masked from the investigator; the patient and the statistician (triple-blind randomized parallel trial design) were revealed only after the completion of the study. Reduction in PPD, 0–8 weeks, was defined as the primary outcome variable while change in RAL, GMP, BOP, GI, and PISA was set as secondary outcome variables.

Statistical Analyses

Data collected at baseline and at the end of 8 weeks were analyzed using Windows PC-based software – MedCalc Statistical Software, version 15.8 at alpha 0.05 with 95% confidence limits. PISA was calculated based on 6-point PPD and BOP values from an Excel sheet freely available at www.parsprototo.in for the test teeth. Values were averaged (mean ± SD) for each parameter. The distributions of all variables were checked for normality using the D'Agostino-Pearson test which gave a statistically significant ($P < 0.05$). As all the distributions violated assumption of normality, a decision was taken to use non-parametric tests. Pair-wise comparison of means of all parameters between the two groups was done using Mann–Whitney U-test, to ascertain pairs that deviated considerably at $P < 0.05$. Wilcoxon signed-rank test was used to compare within group the means of all parameters at baseline and at the end of 8 weeks. Spearman's rank correlation coefficient analysis was done to identify any association between the parameters.

RESULTS

The present study was a triple0blinded, prospective cohort, and randomized trial with a sample size of 34 subjects diagnosed with CP. Four subjects were excluded from the study: Two reported using mouthwashes and two reported back with dislodged periodontal dressings; making the effective sample size as 60 sites in 30 subjects. During the course of the study, no untoward consequences were reported.

Table 1 represents mean ± SD for all parameters recorded at baseline and at the end of 8 weeks. Mean baseline PPD for Gel A and Gel B was 5.83 ± 0.79 and 5.80 ± 0.55 while at the end of 8 weeks; it was 4.40 ± 0.67 and 4.47 ± 0.57, respectively. PPD reduction [Graph 1] from baseline to 8 weeks for Gel A was −24.57% while for Gel B reduction was −22.99% which was statistically significant for both groups ($P < 0.0001$). Mean RAL reduction for Gel A from baseline (8.90 ± 1.42) to 8 weeks (7.50 ± 1.33) and similarly for Gel B (baseline 8.60 ± 1.07 to 8 weeks 7.57 ± 1.10) was statistically significant for both groups ($P < 0.0001$) [Table 2].

On comparing the GMP values at baseline (3.03 ± 1.10 and 2.80 ± 1.06) and at the end of 8 weeks (3.27 ± 1.41 and 3.27 ± 1.14) for Gel A and Gel B, a statistically significant difference was noted ($P = 0.0313$ and $P = 0.010$,

Table 1: Results of Mann–Whitney "U"-test carried out at 5% level of significance to test the difference between the mean of the two test gels with respect to PPD, RAL, GMP, BOP, GI, and PISA

Parameters	Timeline	Gel A mean±SD	Gel B mean±SD	*P*-value
PPD (mm)	Baseline	5.83±0.79	5.80±0.55	0.850
	8 weeks	4.40±0.67	4.47±0.57	0.681
RAL (mm)	Baseline	8.90±1.42	8.60±1.07	0.360
	8 weeks	7.50±1.33	7.57±1.10	0.834
GMP (mm)	Baseline	3.03±1.10	2.80±1.06	0.407
	8 weeks	3.27±1.41	3.27±1.14	1.000
BOP (%)	Baseline	74.17±16.72	72.50±16.54	0.699
	8 weeks	38.33±14.28	35.83±12.60	0.475
GI score	Baseline	1.63±0.22	1.58±0.23	0.313
	8 weeks	1.23±0.16	1.23±0.15	0.837
PISA (mm^2)	Baseline	52.62±19.16	47.91±19.64	0.351
	8 weeks	21.45±7.05	18.93±8.54	0.218

PPD: Probing pocket depth, RAL: Relative attachment level, GMP: Gingival margin position, BOP: Bleeding on probing, GI: Gingival index PISA: Periodontal inflammatory surface area, SD: Standard deviation

respectively). However, the percentage change was positive (7.69% and 16.67%) in both groups [Table 2 and Graph 1].

BOP was present at baseline in most sites (74.17% and 72.50% for Gel A and Gel B, respectively); however, the proportions dropped significantly at week 8 (38.33% and 35.83%; $P < 0.0001$). These proportions were not statistically significant between the two groups at any of these time points. On comparison of GI scores at baseline (1.63 ± 0.22 and 1.58 ± 0.23) and at week 8 (1.23 ± 0.16 and 1.23 ± 0.15) for both groups, a statistically significant result was obtained ($P < 0.0001$). Similarly, statistically significant PISA score reduction was seen between baseline (52.62 ± 19.16 and 47.91 ± 19.64) and at week 8 (21.45 ± 7.05 and 18.93 ± 8.54) ($P < 0.0001$). However, the differences between the groups for all parameters were not statistically significant ($P > 0.05$).

Spearman's rank correlation coefficient analysis [Table 3] demonstrated a positive correlation between PPD and RAL and PPD and BOP for Gel A at the end of 8 weeks. GMP and RAL exhibited a strong positive correlation. PISA and BOP also exhibited a strong positive correlation. The results for Gel B after 2 months showed a strong positive correlation between GMP and RAL.

Table 2: Result of Wilcoxon signed-rank test was done to compare the changes in the mean PPD, RAL, GMP, BOP, GI, and PISA at baseline and after 8 weeks within the two test gels

Groups	PPD	RAL	GMP	BOP	GI	PISA
Gel A	<0.0001*	<0.0001*	0.0313*	<0.0001*	<0.0001*	<0.0001*
Gel B	<0.0001*	<0.0001*	0.010*	<0.0001*	<0.0001*	<0.0001*

*P<0.05 – Statistically significant. PPD: Probing pocket depth, RAL: Relative attachment level, GMP: Gingival margin position, BOP: Bleeding on probing, GI: Gingival index PISA: Periodontal inflammatory surface area

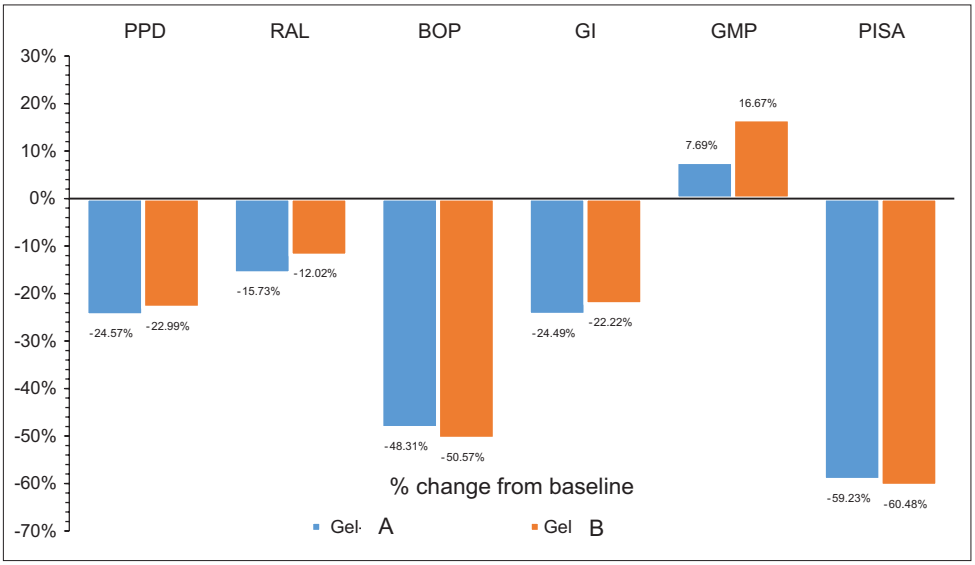
DISCUSSION

LDD systems have been developed with the aim of overcoming the limitations of conventional therapy and

Table 3: Spearman's rank correlation coefficient analysis was done to observe for any correlation between the PPD, RAL, GMP, BOP, GI, and PISA values

	Gel A						Gel B						
	PPD	RAL	BOP	GI	GMP	PISA		PPD	RAL	BOP	GI	GMP	PISA
PPD	1.000	0.432*	0.432*	0.151	−0.099	0.147	PPD	1.000	0.042	0.221	0.049	−0.447*	−0.102
RAL	-	1.000	0.211	0.075	0.788**	−0.304	RAL	-	1.000	−0.127	−0.041	0.681**	0.222
BOP	-	-	1.000	0.355	−0.059	0.469**	BOP	-	-	1.000	0.359	−0.117	0.307
GI	-	-	-	1.000	0.082	0.248	GI	-	-	-	1.000	−0.006	0.059
GMP	-	-	-	-	1.000	−0.409*	GMP	-	-	-	-	1.000	0.164
PISA	-	-	-	-	-	1.000	PISA	-	-	-	-	-	1.000

If the r value is−1, there is a perfect negative correlation, If the r value falls between−1 and−0.5, there is a strong negative correlation, If the r value falls between −0.5 and 0, there is a weak negative correlation, If the r value is 0, there is no correlation, *If the r value falls between 0 and 0.5, there is a weak positive correlation, **If the r value falls between 0.5 and 1, there is a strong positive correlation, If the r value is 1, there is a perfect correlation. PPD: Probing pocket depth, RAL: Relative attachment level, GMP: Gingival margin position, BOP: Bleeding on probing, GI: Gingival index. PISA: Periodontal inflammatory surface area



Graph 1: Percentage change in probing pocket depth, relative attachment level, gingival margin position, bleeding on probing, gingival index, and periodontal inflammatory surface area from baseline to 8 weeks

providing highly concentrated drugs at the target site, improved patient compliance with reduced propensity for the development of bacterial resistance.[22] The currently available LDD systems are often expensive and difficult to procure in developing nations like India.[7]

Green tea catechins (GTCs) are bactericidal against a variety of periodontopathogens such as *Porphyromonas gingivalis* (Pg),[23] *Prevotella intermedia* (Pi),[24] and *Aggregatibacter actinomycetemcomitans*.[25] They are known inhibitors of cysteine proteinases of Pg and protein tyrosine phosphatase in Pi,[26] along with inhibition of collagenase activity. Hirsawa *et al*.(2002) found that GTC showed a bactericidal effect against Pg and Pi with an minimum inhibitory concentration of 1.0 mg/ml. Turmeric has been employed traditionally in Indian medicine for several decades due to its proven properties as a potent anti-inflammatory, antioxidant, antimicrobial, and antimutagenic agent.[27] It exerts its anti-inflammatory action by inhibition of nuclear factor-kappa beta ligand activation[28] and downregulation of pro-inflammatory enzyme cyclooxygenase-2[29] by reducing the inflammatory mediators generated through arachidonic acid pathway.[30]

Poloxamer 407 has unique thermoreversible characteristics as it behaves like a mobile viscous liquids at 2–8°C, which is transformed into a semisolid gel at body temperature (37°C).[31] As an LDD vehicle, it possesses a surfactant ability that accounts for its higher biocompatibility and bioadhesivity, allowing adhesion to the periodontal pocket and, finally, it can be rapidly eliminated through normal catabolic pathways, with a half-life of 25 h,[32] decreasing the risk of irritative or allergic host reactions.[33]

GTE and turmeric extracts were relatively easy and inexpensive to prepare when compared to other herbal formulations such as garlic, pomegranate, and cranberry, which require extensive extraction process and specialized reagents to stabilize the extracts. To date, no study has compared the effects of GTEs with that of turmeric extracts in an LDD system in the treatment of CP. Hence, the main purpose of this study was to assess and compare the clinical efficacy of two different herbal agents, i.e., GTE and turmeric extract in a novel gel-based LDD system, consisting of Poloxamer 407 as vehicle, as an adjunct to SRP in the treatment of CP.

Clinical parameters such as PPD, RAL, BOP, and GI were recorded at baseline and after 8 weeks. PISA quantifies the inflammatory burden posed by periodontitis as it reflects the surface area of bleeding pocket epithelium in square millimeters. It was calculated using conventional parameters of periodontal assessment, such as PPD and BOP measurements. GMP was measured along with PPD and RAL to account for probing depth reduction due to gingival recession.

In the present study, PPD significantly decreased from the baseline to 8 weeks for both the test gels (PPD reduction for Gel A 1.43 and for Gel B 1.33) with a significant gain in RAL (baseline – 8.90 ± 1.42 and 8.60 ± 1.07; 8 weeks – 7.50 ± 1.33 and 7.57 ± 1.10), but there was no statistically significant difference between the two groups (PPD baseline $P = 0.850$ and 8 weeks $P = 0.681$ and RAL baseline $P = 0.360$ and 8 weeks $P = 0.834$), indicating that green tea and turmeric were both equally beneficial for reducing the PPD and obtaining gain in RAL. PPD and RAL results for Gel A consisting of GTE are in accordance with a study by Chava and Vedula[18] and with findings of a meta-analysis done by Kalsi *et al*.[4] PPD and RAL results of Gel B containing turmeric extract are similar to those presented by Bhatia *et al*.[34] (PPD reduction of 1.60) and Behal *et al*.[35] (PPD reduction of 1.40). The significant gain in RAL of Gel B has been attributed to curcumin that enhances wound healing by causing an increase in fibronectin and promotes migration of epithelial cells to wounded sites by promoting localization of TGF-β1, thus helping reepithelization.[36]

A statistically significant reduction in the percentage of sites with BOP ($P < 0.0001$) and GI ($P < 0.0001$) was seen in both the test groups. Similar results were obtained by Awadal[37] and Sarin *et al*.[38] with GTE and Jaswal *et al*.[39] and Mali *et al*.[40] with turmeric extract.

The values of GMP for Gel A ($P = 0.0313$) and Gel B ($P = 0.010$), though minor, showed a statistically significant increase after 8 weeks when compared to baseline. This observation indicates that PPD reduction could also be attributed to gingival recession. Consequently, the Spearman's correlation coefficient test at 8 weeks shows a weak correlation between GMP and PPD ($r = 0.447$) in Gel B; however, no such correlation was found between GMP and PPD in Gel A. This confirms the observation that Gel B containing turmeric extract caused more recession.

The LDD agents used in this study prove to be equally effective when used as an adjunct to SRP in the treatment of CP. However, it should be noted that both the test gels were used as an adjunct to SRP and no attempt was made to evaluate the gels as a monotherapy agent. Additional long-term studies are recommended to evaluate the microbiologic and biochemical effects of GTE and turmeric extract LDD systems. Furthermore, the effective therapeutic concentrations achieved in gingival crevicular fluid need to be elucidated.

CONCLUSION

This study is first of its kind that has compared the efficacy of GTE and turmeric extract in a poloxamer gel when used as an LDD agent, as an adjunct to SRP in the treatment of CP. Both the LDD agents were equally beneficial and showed a reduction in the clinical parameters which were statistically significant. Hence, they prove as a safe and cost-effective treatment modality.

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