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Original Article

Subgingival Delivery of *Bifidobacterium* Gel versus Tetracycline Gel as an Adjunct to Scaling and Root Planing-A Randomized Controlled Trial

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ABSTRACT

Background: Periodontitis is a common chronic inflammatory condition in adult population affecting both the hard and soft tissues surrounding the teeth. Bacteriotherapy is an alternative way to suppress infections by using probiotic bacteria which have antimicrobial and anti-inflammatory effect to destroy pathogenic microorganisms. Till date many studies have been done to check the efficacy of probiotics delivered systemically and a very few as local drug delivery. Therefore, the present study was designed to clinically and microbiologically evaluate the efficacy of local drug delivery of *Bifidobacterium animalis subsp lactis* $2*10^9$ CFU/g gel as an adjunct to conventional mechanical periodontal therapy in comparison with tetracycline gel in stage II, III periodontitis patients. **Materials and Methods:** 45 systemically healthy Stage II, III periodontitis patients were selected and randomly allocated into 3 groups. All the groups received scaling and root planing, Group 2 and Group 3 received local drug delivery of probiotic and tetracycline gel respectively. Clinical and microbiological evaluations were done at baseline, 1 month and 3 months following the treatment in all the groups. Microbiological analysis was carried out by RT PCR. **Results:** At 3 months evaluation, all the clinical and microbiological parameters showed significant improvement in all the groups. On inter group analysis statistically significant improvement was seen in Group 2 and Group 3 when compared to Group 1. Group 2 and Group 3 showed no statistically significant difference. **Conclusion:** Local drug delivery of *Bifidobacterium* gel can be a useful adjuvant to scaling and root planing in periodontitis patients. Further long-term studies are required to evaluate the action of probiotics in periodontitis.

Keywords: *Bifidobacterium*, Probiotics, Periodontitis, Scaling and Root planing, Local drug delivery.

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INTRODUCTION

Periodontitis is a polymicrobial disease caused by a specific or a group of specific microorganisms. Therefore, the elimination of these pathogens by mechanical therapy remains the cornerstone of periodontal therapy.[1] But biochemical considerations and physical constraints pose a great challenge to mechanical therapy.[2] Over the years, these challenges have been overcome by the introduction of various adjunctive treatments to Scaling and Root Planing (SRP). Local Drug Delivery (LDD) is one of such adjunctive therapies that have shown promising results. Until now antimicrobials, especially the tetracycline group, have emerged as the gold standard.[3] But the emergence of several resistant strains is turning out to be a global challenge for clinicians. As a result of this development, scientists are looking for new ways to tackle infectious diseases. Probiotics have been shown to be a beneficial biomimetic agent against periodontal pathogens.[4] Their property of helping the recolonization of the pocket by beneficial bacteria and modulating the host's response remains the main mode of action.[5] They have been used in periodontal therapy in the form of mouth washes, lozenges, tablets, gums, etc.[3] The use of probiotics as LDD is limited due to their poor retention in the pocket, which is the crucial factor determining the success and efficacy of any LDD agent. This drawback of probiotics could be overcome by formulating the probiotic into a thermo-reversible gel using poloxamar 188. This thermo reversible probiotic gel can ensure the retention and release of the probiotic at the target site. Therefore, the aim of the present study was to evaluate the retention capacity of the probiotic gel and to compare the effectiveness of LDD of *Bifidobacterium animalis subsp lactis* $2*10^9$ CFU/g gel with tetracycline gel as an adjunct to conventional mechanical periodontal therapy in patients with stage II, III periodontitis.

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MATERIALS AND METHODS

A total of 45, systemically healthy participants were recruited in the age range of 25-50 years with at least 20 teeth present and 5-7 mm pocket depth and diagnosed as stage II-III periodontitis according to the 2017 World Workshop on Periodontal and peri-implant diseases and conditions.[6] The study protocol was approved by the Institutional Ethics Committee and was registered in the Indian Registry of Clinical Trials. Before the participants were matriculated for the study, the purpose and study methodology were explained and written informed consent was obtained from them in accordance with the Declaration of Helsinki of 1975, as revised in 2000.

Medical and dental histories were documented and subjects were excluded if they had any systemic disorder, were current or former smokers, were currently pregnant or lactating, had undergone periodontal surgery in the past year or consumed antibiotics in the last month before recruiting into the study and patients who were allergic to tetracycline.

Patients who met the inclusion criteria were randomized into 3 groups (Group 1-SRP alone, Group 2-SRP+Probiotic, Group 3-Tetracycline gel+SRP) by lottery method. All clinical parameters and subgingival plaque samples were collected at baseline, 1 month and 3 months after local drug delivery. All groups received scaling root planing, followed by LDD of probiotic gel and tetracycline gel in Group 2 and Group 3 respectively.

The clinical periodontal examination consisted of computing the Gingival Index (GI), Plaque Index (PI), Probing Depth (PD), Clinical Attachment Level (CAL) and Relative Attachment Level (RAL) scores (Figure 1). Measurements were recorded at six sites around each tooth using a manual periodontal probe by an experienced clinician. The relative level of attachment was measured from a pre-fabricated acrylic stent. Subgingival plaque sample was collected in all 3 groups at baseline, that is, before LDD, at 1 month and 3 months after LDD. In each patient, sub-gingival plaque samples were collected at the site with deepest probing pocket depth using a sterile gracey curette (Figure 3). The collected subgingival plaque sample was transferred to 1 mL of sterile RNA later solution containing vials and stored at a temperature of -20°C and sent to the laboratory where it was subjected to RTPCR for *Porphyromonas gingivalis* microbial analysis.

Bifidobacterium animalis subsp lactis $2^{*}10^{9}$ CFU/g[†], Tetracycline[‡] and Poloxamer 188[‡] were obtained and the probiotic and tetracycline gel were formulated (Figure 2). Oral hygiene instructions were given and scaling and root planing were performed to control supragingival and subgingival plaque. The SRP was performed with ultrasonic devices, manual scalers and curettes. No medications were prescribed during treatment. Appropriate oral hygiene instructions were provided to the patients. These edicts were consistently reinforced throughout

Table 1: Intragroup comparison of clinical parameters.

Clinical parameters	Group 1-SRP			Group 2-SRP+Probiotic			Group 3-SRP+Tetracycline			*p* value
	Baseline	1 month	3 months	Baseline	1 month	3 months	Baseline	1 month	3 months	
PI	2.136±0.624	1.019±0.370	0.492±0.146	2.024±0.509	1.599±0.401	0.381±0.148	2.017±0.370	0.654±0.207	0.275±0.137	<0.001*
GI	2.155±0.635	1.694±0.545	0.785±0.175	2.317±0.421	1.237±0.314	0.562±0.246	2.016±0.480	0.506±0.180	0.424±0.123	<0.001*
PPD	6.73±1.10	5.33±0.72	4.87±0.74	7.40±0.74	4.80±0.77	4.00±0.65	6.87±0.83	4.47±0.92	3.53±0.52	<0.001*
CAL	7.40±1.06	5.93±0.96	5.47±0.83	8.13±0.99	5.60±0.99	3.87±0.52	8.13±0.99	5.60±0.99	3.87±0.52	<0.001*
RAL	8.73±1.10	7.33±0.72	6.87±0.74	9.40±0.74	6.73±0.70	5.93±0.70	9.40±0.74	6.73±0.70	5.93±0.70	<0.001*

the course of treatment. Clinical parameters, subgingival plaque samples were collected at baseline before treatment and at 1 month, 3 months after local drug delivery.

The injectable gel of probiotic and tetracycline was placed subgingivally at the selected site using 24 gauge 2.5 mL syringe (Figure 4). In group 2 and group 3 patients, probiotic and tetracycline gels were placed, respectively. Firm pressure was applied with the fingers at the entrance of the pocket, until the material stabilized in the pocket. The patients were instructed not to disturb the area with tongue, finger, or toothpick, chew hard or sticky foods for at least one week and postpone brushing and flossing at the treated site for one week.

Subgigival plaque samples were collected at baseline, 1 month and 3 months and subjected to a Real-Time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) to assess *P. gingivalis* levels. DNA was isolated from all samples and was subjected to NANODROP[§] spectrophotometer at 260/280 nm. The PCR detection of the putative periodontal pathogen *Porphyromonas gingivalis* in subgingival samples was carried out detecting the 16S ribosomal RNA gene. Two *Porphyromonas gingivalis*-specific primers described by *Slots et al.*[7] were used to amplify a 404-bp fragment of the 16S rRNA gene: *P. gingivalis* 16S rRNA gene Forward (Primer 1) :(5′-AGG CAG CTT GCCATA CTG CG-3′) *P. gingivalis* 16S rRNA gene Reverse (Primer 2) :(5′-ACT GTT AGC AACTAC CGA TGT-3′). *P. gingivalis* primers and positive *P. gingivalis* DNA positive control [k, ¶].

Statistical Package for Social Sciences [SPSS] for Windows Version 22.0 Released 2013. Armonk, NY: IBM Corp. was used to perform statistical analyzes. Descriptive analysis of all the explanatory and outcome parameters was done using frequency and proportions for categorical variables, where in Mean and SD for continuous variables. The Kruskal Wallis test followed by Mann Whitney's post hoc test was used to compare the mean age, mean values of clinical and RT-PCR values [Log10] of *P. gingivalis* between 3 groups at different time intervals. Friedman's test followed by the Wilcoxon Signed Rank Post hoc test was used to compare the mean values of clinical and RT-PCR values [Log10] of *P. gingivalis* between different time intervals in each group. The Chi-square test was used to compare the gender distribution between 3 groups. The level of significance was established at $p<0.05$.

RESULTS

Demographic variables of the study groups are described in Graphs 1A and 1B. There were no significant differences in the age and sex distribution between the study groups ($p>0.05$).

The intragroup comparison enumerated in Table 1, all 3 groups showed a significant improvement ($p=<0.001$) from baseline to 1 month and 3 months in all clinical parameters.

The intergroup comparison of clinical parameters described in Table 2, at baseline in all clinical parameters, the groups did not show significant differences when compared between them. At one month, plaque index and gingival index when compared between the groups showed statistically significant differences.

Table 2: Intergroup comparison of clinical parameters.

Plaque index			Gingival index		PPD		CAL		RAL	
Time	Sig. Diff	*p*-value	Sig. Diff	*p*-value	Sig. Diff	*p*-value	Sig. Diff	*p*-value	Sig. Diff	*p*-value
Baseline	G1 vs G2	..	G1 vs G2	..	G1 vs G2	..	G1 vs G2	..	G1 vs G2	..
	G1 vs G3	..	G1 vs G3	..	G1 vs G3	..	G1 vs G3	..	G1 vs G3	..
	G2 vs G3	..	G2 vs G3	..	G2 vs G3	..	G2 vs G3	..	G2 vs G3	..
1 Month	G1 vs G2	<0.001*	G1 vs G2	0.005*	G1 vs G2	0.18	G1 vs G2	..	G1 vs G2	0.14
	G1 vs G3	0.01*	G1 vs G3	<0.001*	G1 vs G3	0.02*	G1 vs G3	..	G1 vs G3	0.04*
	G2 vs G3	<0.001*	G2 vs G3	<0.001*	G2 vs G3	0.50	G2 vs G3	..	G2 vs G3	0.90
3 Months	G1 vs G2	0.04*	G1 vs G2	0.006*	G1 vs G2	0.002*	G1 vs G2	<0.001*	G1 vs G2	0.003*
	G1 vs G3	<0.001*	G1 vs G3	<0.001*	G1 vs G3	<0.001*	G1 vs G3	<0.001*	G1 vs G3	<0.001*
	G2 vs G3	0.12	G2 vs G3	0.15	G2 vs G3	0.13	G2 vs G3	0.38	G2 vs G3	0.73

At 3 months when Group 1 was compared with Group 2 and Group 3 there was a significant difference, while when Group 2 was compared with Group 3 there was no significant difference.

Intragroup comparison (Table 3) of mean RTPCR of *P. gingivalis* values between different time intervals in each group showed a significant reduction from baseline to 3 months in the 3 groups. At baseline and at 1 month the intergroup comparison (Table 4) of the mean RT PCR values of *P. gingivalis* showed no statistically significant differences between Group 1 and Group 2, Group 1 and Group 3 and Group 2 and Group 3. At 3 months, there was a statistically significant difference when Group 1 was compared with Group 2 and Group 1 was compared with Group 3, but there was no significant difference when Group 2 was compared with Group 3.

DISCUSSION

The gold standard treatment for periodontal disease is scaling and root planing.[8] Therefore, the current mainstay therapeutic approach for periodontal disease is to change a dysbiotic biofilm from the previous periodontopathogens to a more health-associated eubiotic entity through a combination of improved oral hygiene measures and subgingival debridement.[9,10] Various therapeutic approaches such as antimicrobial agents, lasers and photodynamic therapy have been proposed as adjunctive treatment to reduce bacterial recolonization. These approaches demonstrate promising clinical results, but microbiological improvements were found to be inconsistent.[11]

The different probiotics used recently in the field of periodontics are *Lactobacillus* species, *Saccharomyces* species and species of *Bifidobacterium*.[12] In the present study the probiotic of choice was *Bifidobacterium*. The *Bifidobacterium* exhibits its effect against various periodontal pathogens by its antimicrobial and host modulating effect and also activation of innate immunity. Recent molecular findings in animal studies have also shown their influence on the RANKL/OPG ratio, suggesting their important role in the inhibition of the Nuclear Factor kappa Beta (NFκβ) pathway leading to bone formation.[13]

To our knowledge, most of the studies have systemically used the *Bifidobacterium* probiotic as an adjunct to SRP. In this study, we have used the probiotic as a local drug delivery agent, as studies have proven that the local route of drug delivery can achieve a 100-fold higher concentration of a drug in the sub gingival sites compared to its systemic use.[14]

In the current study, the probiotic was compared with tetracycline, which is considered the gold standard among the various local drug delivery agents available.[15] Both drugs were fabricated into a thermo reversible gel using poloxomer 188. This ensured that the mode of application and form of both test drugs were the same except for the active agent, thus avoiding any kind of bias. The thermo reversible property of the gel formulation has the advantage of delivering it in liquid form, hence easing the application and once the drug reaches the body temperature in the oral environment, i.e., the periodontal pocket it solidifies hence increasing its retention in the oral cavity. This is the first

Figure 1: Armamentarium.

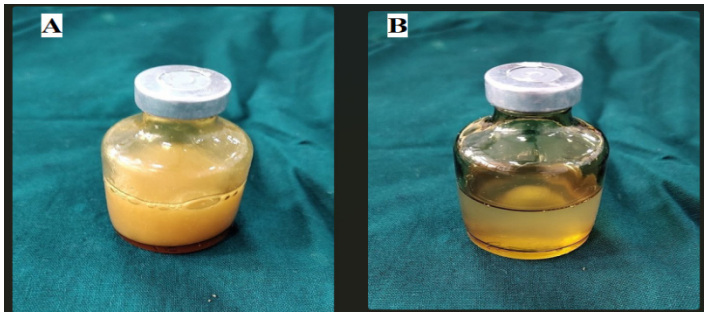
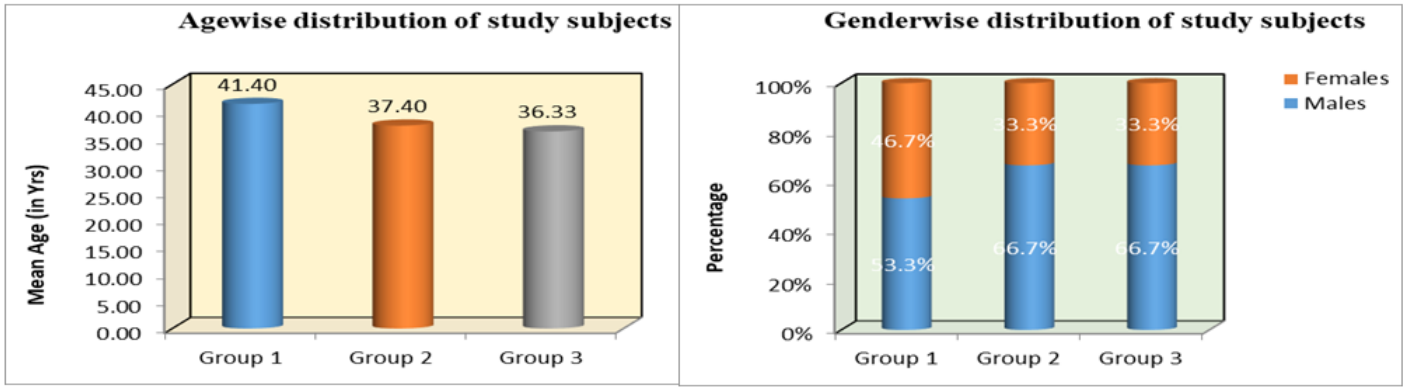


Figure 2: A) Probiotic gel B) Tetracycline gel.

Figure 3: Collection of sub-gingival plaque sample with Gracey curette.

Figure 4: Local drug delivery.



Graph 1: Agewise and Genederwise distribution of study subjects.

study to fabricate probiotic and tetracycline in gel form and compare them.

45 systemically healthy patients of both genders who satisfied all inclusion and exclusion criteria were randomly allocated into 3 groups. All clinical parameters at baseline when compared between the groups did not show statistically significant differences. Intra and intergroup comparisons made at 1 month and 3 months after treatment showed improvement in all clinical parameters in all three groups. This result can be attributed to the effect of scaling and root planing done in all 3 groups. Mechanical therapy has been accepted as the gold standard for the treatment of periodontitis, which reduces inflammation, causing an improvement in clinical parameters[16] that was in accordance with previous studies.[17-19]

The clinical parameters evaluated in the study where the PI, GI, PPD and CAL. There was no statistically significant difference between the three groups at baseline. However, at 3 months, both test groups showed a significant difference compared to the control group. This result is in agreement with the studies by Inverenci *et al.*,[5] Dina R *et al.*,[20] Silva levi[21] *et al.*, Kuru *et al.*,[22] and Toiviainen *et al.*[23]

Table 3: RTPCR of *P. gingivalis* [Log 10] Values.

	Baseline	1 month	3 months	P value
Group 1	80.57±18.28	64.47±20.92	57.37±19.98	<0.001*
Group 2	76.17±30.60	59.72±18.45	32.09±16.06	0.002*
Group 3	74.02±29.63	43.73±32.72	26.75±6.48	0.002*

Table 4: Comparison of mean RT-PCR of *P. gingivalis* (Log10) values between groups at different time intervals.

Time	Groups	N	Mean	SD	*p*-value [a]	Sig. Diff	*p*-value [b]
Baseline	Group 1	15	80.57	18.28	0.89	G1 vs G2	..
	Group 2	15	76.17	30.60		G1 vs G3	..
	Group 3	15	74.02	29.63		G2 vs G3	..
1 Month	Group 1	14	64.47	20.92	0.12	G1 vs G2	..
	Group 2	10	59.72	18.45		G1 vs G3	..
	Group 3	11	43.73	32.72		G2 vs G3	..
3 Months	Group 1	12	57.37	19.98	0.001*	G1 vs G2	0.01*
	Group 2	6	32.09	16.06		G1 vs G3	0.001*
	Group 3	6	26.75	6.48		G2 vs G3	0.51

The present study did not show statistically significant differences in clinical parameters between both test groups. However, group 3 (SRP+tetracycline) showed a better improvement in clinical parameters. This result could be attributed to the potential of tetracycline to enhance fibroblast attachment to the root surface.[24]

Studies by Dina,[20] Iniesta,[25] Teughels[26] have used culturing, Polymerase Chain Reaction (PCR) and quantitative Polymerase Chain Reaction (q PCR) respectively to detect the levels of *P. gingivalis*, however in the present study RT-PCR was used for the microbiological analysis of *Porphyromonas gingivalis*. At baseline and 1 month, the inter-group comparison did not show statistically significant differences between the three groups. At 3 months there was a statistically significant difference when the control group was compared to the test groups, but there was no statistically significant difference between the test groups. The intra-group comparison at all time points showed a significant reduction in *P. gingivalis* counts in all groups with maximum reduction in the probiotic and tetracycline groups. Studies by Invernici[5] *et al.*, Dina R[20] *et al.* showed a similar result. This reduction could be credited to the antibacterial effect of tetracycline and guided pocket recolonization[27] and the antibacterial property of the probiotic.[28]

An *in vitro* study was conducted prior to this study in order to formulate and evaluate the properties of probiotic gel containing *Bifidobacterium animalis subsp lactis* (2*10 CFU/g). The observed strong inhibitory effect of the probiotic gel against *P. gingivalis* and *Fusobacterium nucleatum* at specific concentrations highlights its potential as an antimicrobial agent. Additionally, the fact that the gel showed sustained release of bacteria over the 90-day period without complete degradation is promising, as it suggests a prolonged therapeutic effect.[29] These findings indeed support the results of the subsequent clinical study regarding the effectiveness of the probiotic gel as an adjunct to scaling and root planing in periodontal therapy. However, as with any *in vitro* study, further validation through clinical trials is necessary to confirm the efficacy and safety of the probiotic gel in real-world settings. These positive outcomes in the in vitro study laid the groundwork for the subsequent *in vivo* study, which likely aimed to validate these findings in a more realistic clinical context.

Of both drugs, tetracycline showed a better clinical and microbiological result compared to probiotic, however, this difference was not statistically significant. Although tetracycline is considered the gold standard in periodontal therapy, studies have shown the drug to develop antibiotic resistance and also to be harmful to commensal organisms. Therefore, we encourage research to find a better or suitable alternative drug.

The results of the present study show that *Bifidobacterium* LDD gel is equally effective as tetracycline; hence, it could be considered as a viable and effective alternative local drug delivery agent to treat periodontitis.

One of the main shortcomings of the present study was the short duration and the failure to check the time taken to recolonize the area by periodontal pathogens.

CONCLUSION

Using a probiotic gel derived from *Bifidobacterium animalis subsp lactis* as a local drug delivery agent alongside scaling and root planing seems promising for periodontal therapy. While initial findings suggest effectiveness, the need for more long-term controlled clinical trials is crucial to establish stronger evidence for its adjunctive use. Periodontal therapy is a critical aspect of oral

health and if probiotic gel proves to be a safe and effective adjunct, it could offer a valuable alternative or complement to existing treatments. The emphasis on further research underscores the importance of thorough evaluation before widespread adoption in clinical practice.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

Footnotes

± Sponsored by Unique Biotech Private Limited, Hyderabad, India.

ǂ Sigma-Aldrich Chemicals Private Limited Bangalore, India.

§ Thermoscientifics, United States.

k Bioserve Biotechnologies Pvt. Ltd., Hyderabad.

¶ Luna® Universal qPCR Master Mix [cat. No. NEB #M3003S-New England Biolabs, Inc. Ipswich, MA 01938-2723, USA].

AUTHOR'S CONTRIBUTION

Dr. Kavya was involved in conceptualisation of the study, acquisition of data, defining the intellectual content, literature search, analysis of the data, statistical analysis, manuscript preparation and writing of original draft.

Dr. Shruthi was involved in conceptualisation and designing of the study, defining the intellectual content, analysis and interpretation of the results and critical review and editing of the manuscript.Dr. Nisha K J was involved in defining the intellectual content, analysis of data, statistical analysis, manuscript preparation and writing of original draft.

Dr. Vidyadhar was involved in literature search, analysis of data, statistical analysis interpretation of results, manuscript review and writing the original draft.

SUMMARY

The probiotic gel was equally effective as tetracycline gel which is considered as the gold standard among local drug delivery agents. Hence it can substitute the antibiotic in future.

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