

Clinical Effects of Probiotic or Azithromycin as an Adjunct to Scaling and Root Planing in the Treatment of Periodontitis Stage III: A Pilot Randomized Controlled Clinical Trial

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Abstract

Background

The aim of this triple-blind placebo-controlled parallel-arm randomized clinical trial was to evaluate the clinical effects of *Lactobacillus rhamnosus* SP1 or azithromycin as an adjunct to scaling and root planing (SRP) in patients with periodontitis stage III.

Methods

Forty-seven systemically healthy participants with periodontitis stage III were recruited. Following SRP, the participants were randomly assigned to one of three treatment modalities; 1) placebo (n = 15), 2) probiotics (n = 16) and 3) antibiotics-azithromycin (n = 16). The participants were monitored at baseline, 3, 6, 9 and 12 months after therapy. Probing pocket depth (PPD), bleeding on probing (BOP), clinical attachment loss (CAL) and plaque accumulation (PI) were evaluated.

Results

All 47 participants completed the study. At 12 months, all groups showed significant improvements of PPD and PI ($p < 0.012$) irrespective of the treatment modality and without significant differences between the groups. Probiotics and azithromycin showed no added benefit in terms of CAL. While the placebo ($p = 0.002$) and the antibiotic-azithromycin ($p = 0.002$) group showed a significant reduction of BOP, only the placebo group revealed a significant reduction of CAL at 12 months follow-up ($p = 0.003$). The number of sites and teeth with PPD ≥ 5 , ≥ 6 and ≥ 7 mm were significantly reduced in all groups at 12 months follow-up ($p < 0.025$) irrespective of the treatment regime and without significant differences between the groups.

Conclusion

The use of probiotics or azithromycin as an adjunct to SRP failed to provide additional benefits in the treatment of periodontitis stage III. The benefits of these two treatment regimes as an adjunct to SRP remain unclear.

Background

Periodontitis is characterized by a microbially-associated and host-mediated inflammation resulting in the loss of periodontal attachment [1]. This is caused by a dysbiotic microbiome in the subgingival biofilm in a susceptible host. The gold standard treatment to manage periodontitis is scaling and root planing (SRP) [2, 3]. This treatment allows the removal of supra- and subgingival deposits, cementum or surface dentin that is rough, impregnated with calculus or contaminated with toxins or microorganisms

[4]. However, SRP may also fail. This failure could be due to the presence of deep pockets and the ensuing difficulties during the instrumentation, apart from the inaccessibility of certain areas such as furcations [5]. Therefore, patients with deep pockets, progressive or 'active' disease, or specific microbiological profile, can benefit from an antibiotic adjunctive therapy [6].

Systemic antibiotics have the advantage of reaching all oral surfaces and fluids, in addition to having the potential to reach periodontal pathogens that eventually invade the host's tissue [7]. Azithromycin is a broad-spectrum bacteriostatic antibiotic [8] with immunomodulatory properties [9]. Due to its pharmacological properties azithromycin allows a once a day administration during 3 or 5 days, thus increasing patient compliance [8] and limiting the side effects. Azithromycin as an adjunct to SRP significantly improves the efficacy of non-surgical periodontal therapy in terms of probing pocket depth (PPD) and bleeding on probing (BOP) reduction along with clinical attachment level gain [5, 7]. SRP in conjunction with antibiotics is nevertheless not always associated with superior clinical results. The frequent recolonization of treated sites by periodontopathogens, as well as microbial resistance emergency calls for new therapeutic approaches for managing periodontitis. One such approach is the use of probiotics [10].

Probiotics are "living microorganisms, mainly bacteria, that are safe for the human consumption and when taken in proper quantities may provide beneficial effects for the human health" [11]. The modes of action of probiotics are related to their ability to enhance mucosal barrier, produce antimicrobial agents, compete and exclude pathogenic agents, and modulate immune response. *Lactobacillus* and *Bifidobacterium* are the most common genera of bacteria in probiotics [12]. *Lactobacillus rhamnosus* SP1 also known as *L. rhamnosus* GG, has been proposed as an adjunct to SRP, thanks to its ability to inhibit the growth of periodontopathogens through bacteriocins [13, 14], its resistance to environmental stress [15], its immunomodulatory effect [16–18] and its inability to influence the acidogenicity of the supragingival plaque[19]. However, the available evidence regarding the clinical effects of probiotics as an adjunct to scaling and root planing (SRP) is controversial. While some systematic reviews and narrative reviews [20] claim improved clinical outcomes, a recent systematic review concluded that probiotics did not provide clear clinical benefits [21]. Thus, it remains unclear whether probiotics have an added benefit to SRP thereby preventing their wide use in clinical practice.

The aim of the present study was, therefore, to evaluate the clinical effect of *L. rhamnosus* SP1 or azithromycin in the treatment of patients with periodontitis stage III generalized grade B.

Methods

Ethical guidelines

This trial started in June 2014 and finished in August 2016. This triple-blind placebo-controlled parallel-arm randomized clinical trial was performed following guidelines recognized by the Declaration of Helsinki, as revised in 2013 for experimentation involving human participants. The study was approved

by the Local Ethical Committee of the Faculty of Dentistry at the University of Chile (Decision number: 2012/ 08). The present report adheres to Consolidated Standards of Reporting Trials (CONSORT) guidelines and was registered in clinicaltrial.gov (identifier no. NCT02839408). The protocol of the study was explained to all patients, and informed consent was obtained after explanation of the purpose, nature, risks and benefits of participating in this study. The study details have been reported elsewhere [22].

Patient selection criteria

Ninety-six volunteers were initially examined in Faculty of Dentistry, University of Chile, of which 47 were included in the present study. Eligibility criteria for participants were as follows: (a) Adult patients - aged 35 or older; (b) Self-reported 'good health', with an absence of a medical history of a chronic disease or taking medication known to affect periodontal disease; (c) Non-institutionalized male or female; (d) Presence of a minimum of 14 teeth (excluding third molars); (e) presence of at least 10 posterior teeth (f) Presence of at least 5 teeth with periodontal sites with PPD \geq 5 mm and clinical attachment loss (CAL) \geq 3 mm, BOP \geq 20% and extensive radiographically determined bone loss.

The exclusion criteria were as follows: (a) Pregnancy or lactation; (b) Having received any periodontal treatment in the 6-month period before study; (c) Having received non-steroidal anti-inflammatory medication, antibiotics or probiotics therapy in the past 6 months (prior to study).

Randomization of the study participants

Eligible individuals were randomly (simple randomization) allocated to groups according to gender, age, and smoking status after the basal examination using a computer-generated list. All participants were enrolled to one of the three groups: 1) placebo (SRP + azithromycin placebo + probiotic placebo), 2) probiotic (SRP + probiotic + azithromycin placebo) or antibiotic (SRP + azithromycin + probiotic placebo) group (Fig. 1). Concealed allocation was performed using opaque, sealed envelopes containing probiotics or antibiotics arranged by an appointed research assistant. For the purpose of maintaining full blinding throughout the study period, the randomization code and details of the study groups were held by research assistant only from the day of recruitment and were not revealed until all data had been collected and analyzed.

Clinical assessment

Periodontal clinical parameters including probing pocket depth (PPD), bleeding on probing (BOP), clinical attachment loss (CAL) and plaque index (PI) were evaluated at six sites in all teeth, excluding third molars using a manual probe (UNC probe; Hu-Friedy Mfg. Co. Inc., Chicago IL, U.S.A). All measurements were conducted by one calibrated examiner (AM). Clinical examinations were performed at baseline, 3, 6, 9 and 12 months after treatment.

Periodontal therapy

After baseline examinations, all patients received non-surgical periodontal therapy (NSPT). Scaling and root planing (SRP) per quadrant (4–6 sessions, by PC, RC and NS) were performed using an ultrasonic scaler (Cavitron, Dentsply, York, PA, U.S.A) and Gracey curettes (Hu Friedy Mfg. Co. Inc., Chicago, IL, U.S.A). Treatment included oral hygiene instructions, using manual toothbrush. The patients started taking the placebo, probiotic or antibiotics after the last session of SRP. Placebo group received probiotic placebo sachet and antibiotic placebo capsule. Probiotic group received a probiotic sachet and antibiotic placebo capsule. Antibiotic group received antibiotic capsule and probiotic placebo sachet. Identical sachets were presented to patients. Individuals were instructed to dissolve 1 sachet (*Lactobacillus rhamnosus* SP1 (2×10^7 colony forming units/day) (Macrofood S.A., Santiago, Chile) or probiotic placebo sachet in 150 ml of water and ingest it once a day after brushing their teeth, for 3 months. Azithromycin 500 mg (capsules) or antibiotic placebo capsules was ingested once a day, for 5 days. Placebo sachet (probiotic placebo) and placebo capsule (antibiotic placebo) were identical taste, texture, and appearance to the probiotic sachet and antibiotic capsule. Periodontal supportive therapy was performed every 3 months (by PC), monitoring the of individual's compliance, the medical history and the diet throughout the study period.

Compliance and adverse reactions

All patients returned capsules with antibiotics or placebo at 6-week visits and probiotics or placebo sachets at 1, 2 and 3-month visits. At every visit, patients received new sachets. In order to check the patient's compliance, they were called by phone every week. In each control visit or phone call, the clinical examiner (AM) inquired after general health changes, use of mouth rinses, use of probiotic products and any adverse events.

Outcome variables

The primary outcome was the change in CAL. Secondary outcome variables were changes in PPD, PI and BOP, percentages of patients, teeth and sites with PPD ≥ 5 mm, ≥ 6 mm, ≥ 7 mm. Sub-analyses were performed on CAL and PPD, taking into account the initial PPD. A pocket was considered moderate if its initial PPD was between 4–6 mm and deep if ≥ 7 mm. Changes or delta (Δ) in clinical parameters (at subject level) from baseline to 3, 6, 9 and 12 months were determined. "Pocket" closure was defined as mean and SD of percentage of sites going from PPD ≥ 4 mm to PPD ≤ 3 mm at 3- and 12-months follow up [7]. "Risk for disease progression" was defined at the patient level according to Land and Tonetti (2003). Low risk was defined as ≤ 4 sites with PPD ≥ 5 mm, moderate risk was defined as 5–8 sites with PD ≥ 5 mm, and high risk was defined as ≥ 9 sites with PD ≥ 5 mm [23]. The "need for additional periodontal treatment" was defined as persisting pockets ≥ 5 mm with BOP [24].

Statistical analysis

Sample size calculation was performed using CAL as primary outcome variable. A significance level of $\alpha = 5\%$ and a power level of 80% was defined. Considering a difference ≥ 1 mm between groups in CAL changes and a standard deviation of 0.8 mm [25], 14 participants per group were necessary to detect potential differences. For all statistical evaluations, the patient was the unit of measurement. The

Shapiro–Wilk test was used to test the normality of the data sets. Quantitative data were recorded as the mean value \pm standard deviation (SD) or percentage (%). The inter-group differences were determined using Fisher’s exact test, Kruskal Wallis test and ANOVA depending on the distribution of the data. Intra-group differences in clinical parameters over time were determined by the Related Samples Friedman's test ($p < 0.05$) and. The Bonferroni-corrected Wilcoxon signed-rank test and Bonferroni-corrected Mc Nemar test were used to evaluate the intragroup multiple comparisons ($p < 0.0125$ or $p < 0.025$). Effect Sizes ('mean change' divided by 'standard deviation of the baseline values') were calculated based on changes in clinical parameters from baseline to 3, 6, 9 and 12 months or from baseline to 3 and 12 months follow-up [26]. The statistical analysis was performed using a statistical package (StataCorp, College Station, TX, USA).

Results

Forty-seven patients, 16 in the probiotic group, 16 in the antibiotic group and 15 in the placebo group were analyzed. All participants completed the study period and complied with the study requirements (Fig. 1). Adverse events were observed in one participant from antibiotic group (nausea). The periodontal diagnosis of all participants was Periodontitis Stage III generalized Grade B. Demographic, medical and clinical characteristics are described in Table 1. No significant differences were found between groups at baseline ($p > 0.05$).

The mean CAL, PPD, BOP and PI values at baseline and at 3, 6, 9, and 12 months follow-up of all groups are presented in Table 1 and Table 2. All treatment groups showed a significant reduction of PPD and PI at all timepoints, inter- group comparison however revealed that there were no significant differences between the treatment modalities ($p > 0.05$) (Table 1). In terms of CAL, the probiotic group showed a significant reduction at 3- and 9- months follow-up whereas the antibiotic group showed a significant reduction at 3- and 6- months follow-up. The placebo group on the other hand, showed a significant reduction of CAL at all time points ($p < 0.0125$). With respect to BOP, the antibiotic and placebo groups showed a significant reduction at 3- 6- and 12- months follow up ($p < 0.0125$) whereas the probiotic group did not exhibit any improvement at any time point ($p > 0.05$).

The magnitude of statistical changes (Effect size) in all clinical parameters from baseline to 3-, 6-, 9- and 12- month follow-up was similar in all treatment modalities (Table 2). Furthermore, inter-group comparison revealed no significant differences in the changes (Δ) of any clinical parameter between the treatment groups ($p > 0.05$)

Moderate pockets (PPD = 4–6 mm) in the antibiotic group revealed an increase in CAL at 3 months and a significant reduction of PPD at 12 months. Moderate pockets also showed a significant reduction in PPD in the placebo group at 3- and 12- month follow up in placebo group (Table 3. All, $p < 0.025$).

At 12 months follow-up, 80.3%, 77.8% and 77.2% of the baseline moderate pockets (PPD = 4–6 mm) presented a PPD \leq 3 mm in the probiotic, antibiotic and placebo group respectively, without significant differences between the groups ($p > 0.05$) (Table 4). With respect to the baseline deep pockets (PPD >

7 mm), 42.4%, 41.7% and 38.8% of these pockets presented a PPD \leq 3 mm, and 47%, 50% and 45.9% presented PPD = 4–6 mm, without significant between the treatment groups ($p > 0.05$) (Table 4). Pocket closure was 78.1%, 76.7% and 74.4% in the in the probiotic, antibiotic and placebo group, without significant differences between the treatment modalities ($p > 0.05$) (Table 4).

The number of teeth and sites with PPD \geq 5, \geq 6 and \geq 7 mm were significantly reduced in all groups and without significant difference between the treatment modalities at 12 months follow-up ($p > 0.05$) (Table 5). While probiotics reduced the percentage of patients with PPD \geq 5 mm and PPD \geq 6 mm at 12 months, antibiotics reduced the percentage of patients with PPD \geq 6 mm and PPD \geq 7 mm ($p < 0.025$) (Table 6).

The use of antibiotics significantly increased the number of patients with low risk for disease progression at 12 months, and also significantly reduced the number of patients at higher risk for disease progression (Table 6). In addition, the antibiotic and placebo group showed at 12 months a reduced necessity for additional therapy in \geq 3 sites but without significant differences between the both groups (Table 6).

Discussion

This triple-blind placebo-controlled parallel-arm randomized clinical trial evaluated the clinical effects of *L. rhamnosus* SP1 administered once a day for 3 months or azithromycin plus SRP in periodontitis stage III generalized grade B. The present study predominantly revealed: i) a significant improvement of PPD and PI irrespective of the treatment modality and without significant differences between the groups; ii) no added benefit of probiotics or azithromycin in terms of CAL; iii) a significant reduction in the number of sites and teeth with PPD \geq 5, \geq 6 and \geq 7 mm in all groups at 12 months follow-up without differences between the treatment regimes.

This is the first study evaluating and comparing the use of probiotics and antibiotics, in this case azithromycin, in the treatment of periodontitis stage III generalized grade B with 1-year follow-up. In general, all treatment groups revealed a significant improvement in PPD, BOP, CAL and PI however without significant differences between the treatment modalities. Hence, these results failed to exhibit an added benefit of probiotics and azithromycin. With respect to probiotics, the present results are in line with previous reports using probiotics as an adjunct therapy to SRP for the management periodontitis. The administration of *Lactobacillus reuteri* DSM-17938 + ATCCPTA 5289 [27], *Streptococcus oralis* KJ3 + *Streptococcus uberis* KJ2 + *Streptococcus rattus* JH145 [28] or *L. rhamnosus* SP1 [29] in conjunction with SRP did not enhance the clinical outcomes. Our observations are further supported by a very recent RCT which failed to demonstrate an additional clinical efficacy by the use of probiotics [30]. In that RCT, patients received *L. reuteri* ATCC PTA5289 twice a day in addition to SRP for 28 days and the patients were recalled at 3 and 6 months. The use of probiotics failed to provide a clinical benefit compared to SRP alone. Our study revealed a reduction in the percentage of patients, teeth and sites with PPD \geq 5 mm, \geq 6 mm and \geq 7 mm in all groups, however without inter-group differences. These observations are supported by previous reports indicating a lack of effect of probiotics [29, 30]. Overall, these findings in

addition to the results of the present study suggest that probiotics may not provide an added benefit to SRP at least in this type of patient.

Our findings, on the other hand are in contrast to previous reports showing an added benefit of probiotics. Patients that received *L. reuteri* DSM-17938 + ATCCPTA 5289 in conjunction to SRP showed a significantly higher PPD reduction along with a higher CAL gain at 12 months follow-up. Moreover, the probiotic group revealed a higher reduction of sites and patients with ≥ 6 mm [31] which could not be found in the present study. Outcomes from another report showed that patients who received *L. reuteri* ATCC 55730 + ATCCPTA 5289 exhibited a higher reduction of CAL, PPD and BOP [32]. Similarly, the intake for 8 weeks of *Lactobacillus salivarius* WB21 by patients with periodontitis significantly enhanced the reduction of PPD at two months follow-up [33]. Furthermore, outcomes from a more recent RCT revealed a higher reduction of PPD and BOP by the use of *L. reuteri* lozenges [34]. These positive results were corroborated by another group using *Bifidobacterium animalis* subsp. *lactis* HN019- showing improved PPD and CAL at 3 months follow-up [35]. This notable discrepancy with our findings might be attributed to the probiotic itself [36]. One might speculate that not all probiotics produce the same effect, particularly in addition to SRP. Moreover, other factors such as strain, concentration, vehicle and administration time of the probiotic might account for these divergent results.

As for the use of azithromycin, the present results in general failed to show a clear clinical advantage over SRP and placebo. These findings are in accordance with previously published data where a clinical benefit of azithromycin in conjunction with SRP could not be determined [22, 37, 38]. This lack of additional benefit of azithromycin is in direct contrast with the conclusions of a recent systematic reviews with meta-analysis [39]. These differences might be attributed to the higher potential of meta-analysis to estimate an overall mean effect. Indeed, we found a significantly reduction in the number of patients with PPD ≥ 7 mm in the azithromycin group, however this difference was not robust enough to show a significant benefit compared to the other groups. It has been suggested that azithromycin produces some minor benefits. In this regard, it should be noted that the inclusion of 3 treatment groups along with the corresponding correction for multiple comparison may have influenced the power to find minor differences between the groups. Thus, azithromycin may produce some benefits but they could not be detected by our clinical trial. A recent systematic review underlined that the reported clinical advantage of azithromycin should be interpreted with caution since the major effect derived from a single study [39] with a high risk of bias.

We recognize that this study has a number of limitations. First, the small sample size. Although a sample size calculation was performed, a larger sample size would allow to detect smaller differences between the adjunctive therapeutic agents. However, it should be noted that there is no consensus from which point a statistical difference is clinically relevant. Second, microbiological and samples were not taken, therefore it is unclear whether the probiotics triggered a microbial shift. In this sense, whether the probiotic bacteria actually colonized the oral cavity remains to be elucidated. Third, since the present study only patients with periodontitis stage III grade B, the effect of probiotics or azithromycin on other

stages and grades of periodontitis has yet to be determined. Future studies should include larger populations in different stages and grades of periodontitis.

Conclusion

In conclusion and within the limitations of the present study the administration of *L. rhamnosus* SP1 or azithromycin in the treatment of periodontitis stage III generalized grade B failed to produce additional beneficial effects when compared to the SRP on its own. Given the lack of benefits and the conflicting data in the literature, the benefits of probiotics and azithromycin as an adjunct to SRP in the treatment of periodontitis remains unclear.

Abbreviations

BOP

bleeding on probing

CAL

Clinical attachment loss

PPD

Probing pocket depth

SD

Standard deviation

SRP

Scaling and root planing

PI

Plaque accumulation

NSPT

non-surgical periodontal therapy

Declarations

Ethics approval and consent to participate:

The study and protocol were approved by an independent bioethical committee of the Faculty of Medicine of the University of Chile according to legal regulations (Project number 1070431). The study protocol was explained to all patients, and informed consent forms were signed prior to entry in the study.

Consent for publication:

Consent for publication was obtained by the ethical committee of the Faculty of Medicine of the University of Chile, Chile according to legal regulations

Availability of data and material:

The datasets used and/or analysed during the current study are available from the corresponding authors on reasonable request.

Competing interests:

The authors declare that they have no competing interest.

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Author contributions:

JG* and AM conceived the idea for the study and came up with a design and concept and wrote the manuscript. RC, JB, PC, NS, FJS collected the data, analysed the data, did the statistical analysis and proofread the manuscript draft. All authors critically revised and approved the final manuscript.

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Tables

Table 1. Baseline data of patients in the treatment groups, intra- and inter- group comparisons of clinical parameters at baseline, 3-, 6-, 9- and 12-months follow up

	Baseline (a)	3 months (b)	6 months (c)	9 months (d)	12 months (e)	p- value (intra- group)	Post- hoc (Bonferroni adjustment)
Age (years)							
Probiotic group (n=16)	46.5 ± 9.3						
Antibiotic group (n=16)	49.0 ± 7.9						
Placebo group (n=15)	52.8 ± 7.5						
p- value (Inter-group)	0.1171						
Gender (M/F) (%)							
Probiotic group (n=16)	50.0 / 50.0						
Antibiotic group (n=16)	63.5 / 37.5						
Placebo group (n=15)	53.3 / 46.7						
p- value (Inter-group)	0.8150						
Smokers (%)							
Probiotic group (n=16)	43.8						
Antibiotic group (n=16)	18.8						
Placebo group (n=15)	40.0						
p- value (Inter-group)	0.3440						
CAL (mm)							
Probiotic group (n=16)	3.8 ± 0.7	3.4 ± 0.6	3.5 ± 0.6	3.5 ± 0.7	3.7 ± 0.6	0.0001	a > b (p=0.0013) a > c (p=0.0151) a > d (p=0.0072) a > e (p=0.3520)
Antibiotic group (n=16)	4.4 ± 0.9	3.8 ± 0.8	4.0 ± 1.0	4.1 ± 1.0	4.1 ± 1.1	0.0001	a > b (p=0.0013) a > c (p=0.0013) a > d (p=0.0262) a > e (p=0.0262)
Placebo group (n=15)	4.7 ± 1.5	4.1 ± 1.4	4.2 ± 1.4	4.3 ± 1.5	4.4 ± 1.5	0.0001	a > b (p=0.0013) a > c (p=0.0019) a > d (p=0.0092) a > e (p=0.0031)
p- value (inter-group)	0.0823	0.2821	0.3254	0.1589	0.4271		
PPD (mm)							
Probiotic group (n=16)	2.7 ± 0.6	2.2 ± 0.4	2.3 ± 0.4	2.2 ± 0.3	2.3 ± 0.3	0.0001	a > b (p=0.0007) a > c (p=0.0032) a > d (p=0.0008) a > e (p=0.0061)
Antibiotic group (n=16)	2.9 ± 0.4	2.2 ± 0.3	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.3	0.0001	a > b (p=0.0006) a > c (p=0.0004) a > d (p=0.0004) a > e (p=0.0008)
Placebo group (n=15)	3.2 ± 0.9	2.4 ± 0.5	2.4 ± 0.5	2.5 ± 0.6	2.4 ± 0.55	0.0001	a > b (p=0.0007) a > c (p=0.0030) a > d (p=0.0023) a > e (p=0.0008)
p- value (inter-group)	0.2436	0.5916	0.4425	0.5391	0.8799		
BOP (%)							
Probiotic group (n=16)	49.3 ± 18.1	39.2 ± 14.9	42.1 ± 13.6	42.4 ± 14.6	43.0 ± 12.3	0.0001	a > b (p=0.0386) a > c (p=0.1961) a > d (p=0.0703) a > e (p=0.0494)
Antibiotic group (n=16)	57.4 ± 10.2	41.9 ± 10.9	44.1 ± 13.5	48.1 ± 14.1	42.3 ± 13.3	0.0005	a > b (p=0.0022) a > c (p=0.0052) a > d (p=0.0437) a > e (p=0.0023)
Placebo group (n=15)	52.5 ± 12.6	40.8 ± 13.3	42.3 ± 15.3	45.2 ± 13.1	40.8 ± 11.5	0.0001	a > b (p=0.0026) a > c (p=0.0107) a > d (p=0.1981) a > e (p=0.0026)
p- value (inter-group)	0.2744	0.8560	0.9035	0.5170	0.8703		
PI (%)							
Probiotic group (n=16)	54.6 ± 18.8	24.7 ± 11.3	25.2 ± 13.1	28.1 ± 14.6	25.1 ± 12.8	0.0003	a > b (p=0.0004) a > c (p=0.0004) a > d (p=0.0006) a > e (p=0.0011)
Antibiotic group (n=16)	58.6 ± 18.8	25.2 ± 14.0	32.6 ± 15.7	31.8 ± 14.8	32.7 ± 14.0	0.0001	a > b (p=0.0007) a > c (p=0.0005) a > d (p=0.0004) a > e (p=0.0008)
Placebo group (n=15)	56.1 ± 9.4	32.4 ± 13.9	27.6 ± 12.5	26.8 ± 13.3	35.8 ± 18.3	0.0030	a > b (p=0.0012) a > c (p=0.0015) a > d (p=0.0010) a > e (p=0.0018)
p- value (inter-group)	0.7774	0.2022	0.4261	0.6122	0.1789		

Note: Data presented as mean ± SD or number (%). CAL: Clinical attachment loss. PPD: Probing pocket depth. BOP: Bleeding on probing. PI: Plaque index
 Intra- group comparison by Friedman test ($p < 0.05$) and Bonferroni- corrected Wilcoxon signed rank test ($p < 0.0125$). Statistical significant in bold
 Inter- group comparison by Fisher's exact test, ANOVA and Kruskal Wallis test ($p < 0.05$)

Table 2. Intra- and inter- group comparisons of clinical parameters at baseline, 3-, 6-, 9- and 12-months follow up

	Effect size ($\Delta 3$ months-BL) ^a	Effect size ($\Delta 6$ months-BL) ^b	Effect size ($\Delta 9$ months-BL) ^c	Effect size ($\Delta 12$ months-BL) ^d	$\Delta 3$ months-BL	$\Delta 6$ months-BL	$\Delta 9$ months-BL	$\Delta 12$ months-BL
CAL (mm)								
Probiotic group (n=16)	-0.4 ± 0.3	-0.3 ± 0.4	-0.3 ± 0.3	-0.1 ± 0.3	-0.4 ± 0.4	-0.3 ± 0.4	-0.3 ± 0.4	-0.1 ± 0.3
Antibiotic group (n=16)	-0.4 ± 0.3	-0.4 ± 0.4	-0.3 ± 0.4	-0.3 ± 0.4	-0.5 ± 0.4	-0.4 ± 0.4	-0.3 ± 0.4	-0.3 ± 0.5
Placebo group (n=15)	-0.6 ± 0.4	-0.5 ± 0.4	-0.4 ± 0.4	-0.4 ± 0.3	-0.6 ± 0.5	-0.6 ± 0.4	-0.4 ± 0.5	-0.4 ± 0.4
<i>p</i> - value (inter-group)					0.2628	0.2906	0.6268	0.1217
PPD (mm)								
Probiotic group (n=16)	-0.2 ± 0.1	-0.2 ± 0.2	-0.2 ± 0.1	-0.1 ± 0.2	-0.5 ± 0.4	-0.5 ± 0.5	-0.5 ± 0.4	-0.4 ± 0.5
Antibiotic group (n=16)	-0.2 ± 0.2	-0.2 ± 0.1	-0.2 ± 0.1	-0.2 ± 0.1	-0.7 ± 0.5	-0.6 ± 0.3	-0.6 ± 0.3	-0.6 ± 0.4
Placebo group (n=15)	-0.3 ± 0.2	-0.3 ± 0.2	-0.2 ± 0.2	-0.3 ± 0.2	-0.8 ± 0.5	-0.8 ± 0.6	-0.7 ± 0.6	-0.7 ± 0.5
<i>p</i> - value (inter-group)					0.2774	0.2266	0.4099	0.1511
BOP (%)								
Probiotic group (n=16)	-0.2 ± 0.3	-0.1 ± 0.4	-0.1 ± 0.3	-0.1 ± 0.2	-10.0 ± 16.6	-7.1 ± 19.1	-6.9 ± 13.5	-6.3 ± 11.2
Antibiotic group (n=16)	-0.3 ± 0.2	-0.2 ± 0.3	-0.2 ± 0.3	-0.3 ± 0.2	-14.7 ± 11.1	-13.2 ± 14.9	-9.2 ± 15.0	-15.0 ± 12.6
Placebo group (n=15)	-0.2 ± 0.2	-0.2 ± 0.3	-0.1 ± 0.3	-0.2 ± 0.2	-11.8 ± 11.2	-10.2 ± 13.3	-6.7 ± 16.9	-11.7 ± 10.0
<i>p</i> - value (inter-group)					0.6122	0.5741	0.8760	0.0990
Plaque accumulation (%)								
Probiotic group (n=16)	-0.5 ± 0.3	-0.5 ± 0.4	-0.5 ± 0.3	-0.5 ± 0.4	-29.9 ± 17.2	-29.3 ± 20.4	-26.5 ± 19.4	-29.4 ± 21.2
Antibiotic group (n=16)	-0.6 ± 0.3	-0.5 ± 0.3	-0.5 ± 0.3	-0.5 ± 0.3	-32.6 ± 16.5	-26.0 ± 15.0	-26.9 ± 14.4	-26.0 ± 16.3
Placebo group (n=15)	-0.4 ± 0.3	-0.5 ± 0.2	-0.5 ± 0.3	-0.4 ± 0.3	-23.7 ± 15.7	-28.9 ± 13.9	-29.1 ± 15.3	-20.3 ± 16.6
<i>p</i> - value (inter-group)					0.3197	0.8377	0.8951	0.3817

Note: Data presented as mean ± SD. BL: Baseline. CAL: Clinical attachment loss. PPD: Probing pocket depth. BOP: Bleeding on probing. ^aEffect size of ($\Delta 3$ months-BL) was calculated by delta mean change from month 3 to baseline over standard deviation of baseline. ^bEffect size of ($\Delta 6$ months-BL) was calculated by delta mean change from month 6 to baseline over standard deviation of baseline. ^cEffect size of ($\Delta 9$ months-BL) was calculated by delta mean change from month 9 to baseline over standard deviation of baseline. ^dEffect size of ($\Delta 12$ months-BL) was calculated by delta mean change from month 12 to baseline over standard deviation of baseline. Inter- group comparison by ANOVA (*p*<0.05)

Table 3. Clinical attachment loss (CAL) and probing pocket depth (PPD) in moderate (4-6mm) and deep sites (≥ 7 mm) at baseline, 3- months and 12-months follow up

	Baseline (a)	3 months (b)	12 months (c)	<i>p</i> - value (intra-group)	Post- hoc (Bonferroni adjustment)	Effect size ($\Delta 3$ months-BL) ^a	Effect size ($\Delta 12$ months-BL) ^b	$\Delta 3$ months-BL	$\Delta 12$ months-BL
Moderate sites (CAL)									
Probiotic group (n=16)	5.6 ± 0.6	6.0 ± 1.0	6.1 ± 1.2	0.0238	a > b (p=0.1208) a > c (p=0.0747)	0.4 ± 0.9	0.5 ± 0.9	0.4 ± 0.9	0.5 ± 0.9
Antibiotic group (n=16)	5.9 ± 1.0	6.4 ± 1.3	6.4 ± 1.4	0.0018	a < b (p=0.0171) a > c (p=0.0340)	-0.04 ± 0.7	0.5 ± 1.0	0.7 ± 0.9	0.5 ± 1.0
Placebo group (n=15)	6.1 ± 1.3	6.0 ± 1.7	6.5 ± 1.6	0.0006	a > b (p=0.7333) a > c (p=0.1398)	0.7 ± 1.0	0.4 ± 1.0	-0.04 ± 0.7	0.4 ± 1.0
<i>p</i> - value (inter-group)	0.4031	0.6160	0.7649					0.0857	0.9483
Deep sites (CAL)									
Probiotic group (n=16)	8.4 ± 1.8	9.3 ± 2.0	10.8 ± 3.6	0.0498	a > b (p=0.7127) a > c (p=0.1756)	0.05 ± 0.9	0.8 ± 1.1	0.1 ± 1.7	1.6 ± 2.2
Antibiotic group (n=16)	9.5 ± 2.1	10.4 ± 2.4	11.2 ± 1.7	0.0498	a > b (p=0.6858) a > c (p=0.5930)	0.09 ± 0.6	0.2 ± 0.6	0.2 ± 1.1	0.4 ± 1.1
Placebo group (n=15)	9.5 ± 2.1	11.1 ± 2.0	10.6 ± 2.1	0.3386	a > b (p=0.2489) a > c (p=0.1763)	0.4 ± 1.5	0.4 ± 0.8	0.9 ± 2.9	0.8 ± 1.6
<i>p</i> - value (inter-group)	0.4837	0.3254	0.9420					0.8257	0.6535
Moderate sites (PPD)									
Probiotic group (n=16)	4.5 ± 0.3	4.4 ± 0.5	4.3 ± 0.3	0.0006	a > b (p=0.1788) a > c (p=0.0464)	-0.2 ± 1.9	-0.8 ± 1.4	-0.06 ± 0.5	-0.2 ± 0.4
Antibiotic group (n=16)	4.5 ± 0.2	4.4 ± 0.3	4.3 ± 0.2	0.0040	a > b (p=0.0287) a > c (p=0.0010)	-0.6 ± 0.8	-0.8 ± 0.7	-0.2 ± 0.2	-0.2 ± 0.2
Placebo group (n=15)	4.6 ± 0.3	4.2 ± 0.2	4.2 ± 0.3	0.0280	a > b (p=0.0007) a > c (p=0.0012)	-1.4 ± 0.9	-1.3 ± 1.2	-0.4 ± 0.2	-0.4 ± 0.3
<i>p</i> - value (inter-group)	0.6098	0.3097	0.7395					0.4489	0.3449
Deep sites (PPD)									
Probiotic group (n=16)	7.5 ± 1.0	7.4 ± 0.9	7.9 ± 1.2	0.1054	a > b (p=0.0947) a > c (p=0.5716)	-0.4 ± 0.3	-0.1 ± 0.3	-0.4 ± 0.3	-0.1 ± 0.3
Antibiotic group (n=16)	7.5 ± 0.7	7.7 ± 0.7	7.1 ± 0.2	0.1054	a > b (p=0.6845) a > c (p=0.1088)	0.1 ± 1.4	-0.2 ± 0.1	0.08 ± 1.1	-0.2 ± 0.08
Placebo group (n=15)	7.8 ± 0.7	7.6 ± 0.9	7.2 ± 0.2	0.6747	a > b (p=0.3991) a > c (p=0.0510)	-0.6 ± 1.8	-1.0 ± 1.0	-0.4 ± 1.4	-0.8 ± 0.8
<i>p</i> - value (inter-group)	0.3767	0.2995	0.1862					0.7364	0.2588

Note: Data presented as mean ± SD; BL: Baseline. CAL: Clinical attachment loss. PPD: Probing pocket depth. ^aEffect size of ($\Delta 3$ months-BL) was calculated by delta mean change from month 3 to baseline over standard deviation of baseline. ^bEffect size of ($\Delta 12$ months-BL) was calculated by delta mean change from month 12 to baseline over standard deviation of baseline. Intra- group comparison by Friedman test (*p*<0.05) and Bonferroni- corrected Wilcoxon signed rank test (*p* < 0.025). Statistical significant in bold Inter- group comparison by ANOVA and Kruskal Wallis test (*p* < 0.05)

Table 4. Follow-up of moderate (4-6mm) and deep pockets (≥ 7 mm) detected at baseline and pocket closure at 3- and 12- months follow up

	3 months	12 months
Follow-up of moderate pockets detected at baseline (%)		
PPD ≤ 3 mm		
Probiotic group (n=16)	68.5 \pm 16.4	80.3 \pm 18.3
Antibiotic group (n=16)	74.0 \pm 13.7	77.8 \pm 18.9
Placebo group (n=15)	77.0 \pm 14.7	77.2 \pm 14.5
<i>p</i> - value (inter-group)	0.2877	0.6950
PPD 4-6mm		
Probiotic group (n=16)	30.3 \pm 15.9	18.8 \pm 17.6
Antibiotic group (n=16)	25.6 \pm 13.0	20.9 \pm 17.1
Placebo group (n=15)	21.5 \pm 13.1	21.5 \pm 13.4
<i>p</i> - value (inter-group)	0.2391	0.7886
PPD ≥ 7 mm		
Probiotic group (n=16)	1.2 \pm 2.0	0.9 \pm 2.3
Antibiotic group (n=16)	0.4 \pm 1.4	1.3 \pm 2.6
Placebo group (n=15)	1.5 \pm 3.8	1.3 \pm 3.8
<i>p</i> - value (inter-group)	0.2861	0.8539
Follow-up of deep pockets detected at baseline (%)		
PPD ≤ 3 mm		
Probiotic group (n=16)	16.5 \pm 28.5	42.4 \pm 41.3
Antibiotic group (n=16)	33.0 \pm 39.9	41.7 \pm 43.9
Placebo group (n=15)	43.3 \pm 38.7	38.8 \pm 31.5
<i>p</i> - value (inter-group)	0.2087	0.9798
PPD 4-6mm		
Probiotic group (n=16)	73.4 \pm 30.9	47.0 \pm 43.6
Antibiotic group (n=16)	50.2 \pm 37.3	50.0 \pm 41.6
Placebo group (n=15)	38.1 \pm 28.1	45.9 \pm 28.6
<i>p</i> - value (inter-group)	0.1019	0.9715
PPD ≥ 7 mm		
Probiotic group (n=16)	10.1 \pm 17.7	10.6 \pm 18.2
Antibiotic group (n=16)	16.8 \pm 21.1	8.3 \pm 18.0
Placebo group (n=15)	18.6 \pm 26.6	15.3 \pm 16.3
<i>p</i> - value (inter-group)	0.6924	0.3030
Pocket closure (%)		
Probiotic group (n=16)	65.3 \pm 17.9	78.1 \pm 20.0
Antibiotic group (n=16)	71.9 \pm 14.4	76.7 \pm 19.7
Placebo group (n=15)	73.3 \pm 18.1	74.4 \pm 16.8
<i>p</i> - value (inter-group)	0.3790	0.6660

Note: Data presented as mean \pm SD. PPD: Probing pocket depth.

Inter-group comparison by ANOVA and Kruskal Wallis test ($p < 0.05$)

Table 5. Teeth and sites with PPD₅ ≥6 and ≥7mm at baseline, 3- and 6-12months follow up

	Baseline (a)	3 months (b)	12 months (c)	p- value (intra-group)	Post- hoc (Bonferroni-adjustment)	Effect size (Δ3 months-BL) ^a	Effect size (Δ12 months-BL) ^b	Δ3 months-BL	Δ12 months-BL
Teeth with PPD ≥5mm (%)									
Probiotic group (n=16)	33.3 ± 25.3	13.9 ± 12.5	9.7 ± 10.5	0.0040	a > b (p=0.0009) a > c (p=0.0008)	-0.7 ± 0.7	-0.9 ± 0.8	-19.4 ± 18.1	-23.5 ± 21.6
Antibiotic group (n=16)	42.3 ± 24.1	12.7 ± 11.7	11.6 ± 11.6	0.0008	a > b (p=0.0007) a > c (p=0.0005)	-1.1 ± 0.6	-1.1 ± 0.7	-28.5 ± 16.0	-30.7 ± 18.9
Placebo group (n=15)	46.4 ± 32.6	15.0 ± 21.1	15.2 ± 19.1	0.0034	a > b (p=0.0007) a > c (p=0.0008)	-1.2 ± 0.9	-1.2 ± 0.9	-31.4 ± 25.3	-31.2 ± 23.8
p- value (inter-group)	0.4163	0.8307	0.8075					0.1978	0.4069
Teeth with PPD ≥6mm (%)									
Probiotic group (n=16)	15.9 ± 15.4	6.4 ± 7.3	4.9 ± 6.2	0.0184	a > b (p=0.0165) a > c (p=0.0089)	-0.5 ± 0.7	-0.6 ± 0.7	-9.6 ± 12.6	-11.1 ± 13.8
Antibiotic group (n=16)	16.7 ± 12.6	6.4 ± 8.2	5.5 ± 8.1	0.0014	a > b (p=0.0009) a > c (p=0.0007)	-0.5 ± 0.5	-0.6 ± 0.5	-10.2 ± 8.8	-11.2 ± 9.0
Placebo group (n=15)	26.6 ± 25.8	8.4 ± 13.7	8.5 ± 12.2	0.0054	a > b (p=0.0025) a > c (p=0.0043)	-1.0 ± 0.9	-1.0 ± 1.0	-18.2 ± 7.6	-18.2 ± 18.4
p- value (inter-group)	0.6056	0.9650	0.6213					0.3702	0.2921
Teeth with PPD ≥7mm (%)									
Probiotic group (n=16)	8.3 ± 11.0	2.3 ± 2.9	1.8 ± 2.6	0.0490	a > b (p=0.0738) a > c (p=0.0145)	-0.4 ± 0.7	-0.5 ± 0.7	-6.0 ± 9.7	-6.5 ± 9.2
Antibiotic group (n=16)	7.6 ± 7.6	3.0 ± 5.2	2.4 ± 4.7	0.0049	a > b (p=0.0015) a > c (p=0.0077)	-0.4 ± 0.4	-0.4 ± 0.5	-5.1 ± 5.5	-5.2 ± 7.1
Placebo group (n=15)	16.1 ± 19.7	5.7 ± 8.9	5.1 ± 6.9	0.0469	a > b (p=0.0122) a > c (p=0.0143)	-0.7 ± 0.9	-0.8 ± 1.1	-10.4 ± 13.1	-11.0 ± 14.7
p- value (inter-group)	0.6573	0.8204	0.3481					0.6055	0.8091
Sites with PPD ≥5mm (%)									
Probiotic group (n=16)	10.9 ± 10.2	3.4 ± 3.6	2.4 ± 2.9	0.0043	a > b (p=0.0013) a > c (p=0.0011)	-0.6 ± 0.6	-0.7 ± 0.7	-7.6 ± 7.9	-8.5 ± 9.1
Antibiotic group (n=16)	14.1 ± 8.9	3.6 ± 4.3	3.3 ± 4.0	0.0005	a > b (p=0.0007) a > c (p=0.0005)	-0.8 ± 0.4	-0.8 ± 0.5	-10.2 ± 5.7	-10.8 ± 6.6
Placebo group (n=15)	20.0 ± 18.6	4.8 ± 7.2	4.3 ± 6.1	0.0019	a > b (p=0.0007) a > c (p=0.0007)	-1.1 ± 1.1	-1.2 ± 1.1	-15.2 ± 14.6	-15.7 ± 14.9
p- value (inter-group)	0.3755	0.8940	0.8700					0.2328	0.3160
Sites with PPD ≥6mm (%)									
Probiotic group (n=16)	4.3 ± 4.7	1.4 ± 1.7	1.2 ± 2.0	0.0180	a > b (p=0.0215) a > c (p=0.0076)	-0.4 ± 0.5	-0.4 ± 0.5	-2.9 ± 3.7	-3.1 ± 4.1
Antibiotic group (n=16)	4.9 ± 4.4	1.6 ± 2.7	1.3 ± 2.1	0.0049	a > b (p=0.0009) a > c (p=0.0017)	-0.4 ± 0.3	0.4 ± 0.4	-3.5 ± 2.6	-3.6 ± 3.6
Placebo group (n=15)	10.2 ± 11.3	2.2 ± 3.5	2.1 ± 3.1	0.0013	a > b (p=0.0030) a > c (p=0.0011)	-1.0 ± 1.1	-1.0 ± 1.2	-8.0 ± 9.1	-8.1 ± 9.3
p- value (inter-group)	0.4818	0.9371	0.6105					0.3637	0.4272
Sites with PPD ≥7mm (%)									
Probiotic group (n=16)	1.8 ± 2.6	0.6 ± 1.0	0.6 ± 1.4	0.0407	a > b (p=0.0738) a > c (p=0.0195)	-0.3 ± 0.5	-0.3 ± 0.5	-1.2 ± 1.9	-1.2 ± 1.9
Antibiotic group (n=16)	1.9 ± 2.1	0.6 ± 1.3	0.6 ± 1.2	0.0042	a > b (p=0.0016) a > c (p=0.0043)	-0.4 ± 0.4	-0.3 ± 0.4	-1.4 ± 1.6	-1.4 ± 1.7
Placebo group (n=15)	4.7 ± 6.8	1.4 ± 2.4	1.1 ± 1.8	0.0423	a > b (p=0.0198) a > c (p=0.0169)	-0.8 ± 1.4	-0.9 ± 1.5	-3.3 ± 5.5	-3.6 ± 6.0
p- value (inter-group)	0.5671	0.8492	0.4180					0.5396	0.7226

Note: Data presented as mean ± SD of percentages. BL: Baseline. PPD: Probing pocket depth.

^aEffect size of (Δ3 months-BL) was calculated by delta mean change from month 3 to baseline over standard deviation of baseline. ^bEffect size of (Δ12 months-BL) was

calculated by delta mean change from month 12 to baseline over standard deviation of baseline.

Intra- group comparison by Friedman test (p<0.05) and Bonferroni- corrected Wilcoxon signed rank test (p < 0.025). Statistical significant in bold

Inter- group comparison by ANOVA and Kruskal Wallis test (p < 0.05)

Table 6. Patients with PPDa5, a6 and a7mm, in risk of progression and in need for additional therapy at baseline, 3- and 12- months follow up

	Baseline (a)	3 months (b)	12 months (c)	Post- hoc (Bonferroni adjustment)
Patients with PPD ≥5mm (%)				
Probiotic group (n=16)	100	87.5	56.3	a > b (p=0.5000) a > c (p=0.0156)
Antibiotic group (n=16)	100	73.3	75.0	a > b (p=0.1250) a > c (p=0.1250)
Placebo group (n=15)	100	66.6	66.7	a > b (p=0.0625) a > c (p=0.0625)
p- value (inter-group)	1.0000	0.3900	0.5510	
Patients with PPD ≥6mm (%)				
Probiotic group (n=16)	87.5	62.5	43.8	a > b (p=0.1250) a > c (p=0.0156)
Antibiotic group (n=16)	87.5	60.0	43.8	a > b (p=0.1250) a > c (p=0.0156)
Placebo group (n=15)	80.0	46.6	60.0	a > b (p=0.0625) a > c (p=0.2500)
p- value (inter-group)	0.7760	0.7520	0.6210	
Patients with PPD ≥7mm (%)				
Probiotic group (n=16)	50.0	43.8	37.5	a > b (p=0.7055) a > c (p=0.6250)
Antibiotic group (n=16)	75.0	33.3	25.0	a > b (p=0.0156) a > c (p=0.0215)
Placebo group (n=15)	60.0	40.0	46.6	a > b (p=0.2500) a > c (p=0.5000)
p- value (inter-group)	0.3410	0.9290	0.4800	
Risk for disease progression				
Low				
Probiotic group (n=16)	31.3	62.5	62.5	a < b (p=0.1250) a < c (p=0.1250)
Antibiotic group (n=16)	6.3	56.3	75.0	a < b (p=0.0078) a < c (p=0.0010)
Placebo group (n=15)	26.7	73.3	73.3	a < b (p=0.0156) a < c (p=0.0156)
p- value (inter-group)	0.2020	0.6930	0.7840	
Moderate				
Probiotic group (n=16)	18.7	18.7	25.0	a > b (p=1.0000) a > c (p=1.0000)
Antibiotic group (n=16)	18.8	25.0	0.0	a > b (p=1.0000) a > c (p=0.2500)
Placebo group (n=15)	6.6	6.7	0.0	a > b (p=1.0000) a > c (p=1.0000)
p- value (inter-group)	0.6710	0.4920	0.0280	
High				
Probiotic group (n=16)	50.0	18.8	12.5	a > b (p=0.0625) a > c (p=0.0312)
Antibiotic group (n=16)	75.0	18.7	25.0	a > b (p=0.0039) a > c (p=0.0078)
Placebo group (n=15)	66.7	20.0	26.7	a > b (p=0.0156) a > c (p=0.0312)
p- value (inter-group)	0.3560	1.0000	0.6710	
Need for additional therapy				
0 sites				
Probiotic group (n=16)	0.0	25.0	50.0	a < b (p=0.1250) a < c (p=0.0078)
Antibiotic group (n=16)	6.3	31.3	31.2	a < b (p=0.1250) a < c (p=0.1250)
Placebo group (n=15)	0.0	40.0	40.0	a < b (p=0.0312) a < c (p=0.0312)
p- value (inter-group)	1.0000	0.6800	0.5720	
1-2 sites				
Probiotic group (n=16)	18.8	37.5	6.3	a < b (p=0.5078) a < c (p=0.6250)
Antibiotic group (n=16)	0.0	25.0	31.3	a < b (p=0.1250) a < c (p=0.0625)
Placebo group (n=15)	13.3	26.7	33.3	a < b (p=0.6875) a < c (p=0.4531)
p- value (inter-group)	0.2580	0.7840	0.1340	
≥3 sites				
Probiotic group (n=16)	81.2	37.5	43.7	a > b (p=0.0391) a > c (p=0.0312)
Antibiotic group (n=16)	93.8	43.7	37.5	a > b (p=0.0078) a > c (p=0.0039)
Placebo group (n=15)	86.7	33.3	26.7	a > b (p=0.0078) a > c (p=0.0039)
p- value (inter-group)	0.6710	0.9300	0.6930	

Note: Data presented as mean ± SD of percentages. PPD: Probing pocket depth.
 Intra- group comparison by Bonferroni- corrected Mc Nemar test (p < 0.025). Statistical significant in bold
 Inter- group comparison by Fisher's exact test (p < 0.05). Statistical significant in bold

Figures

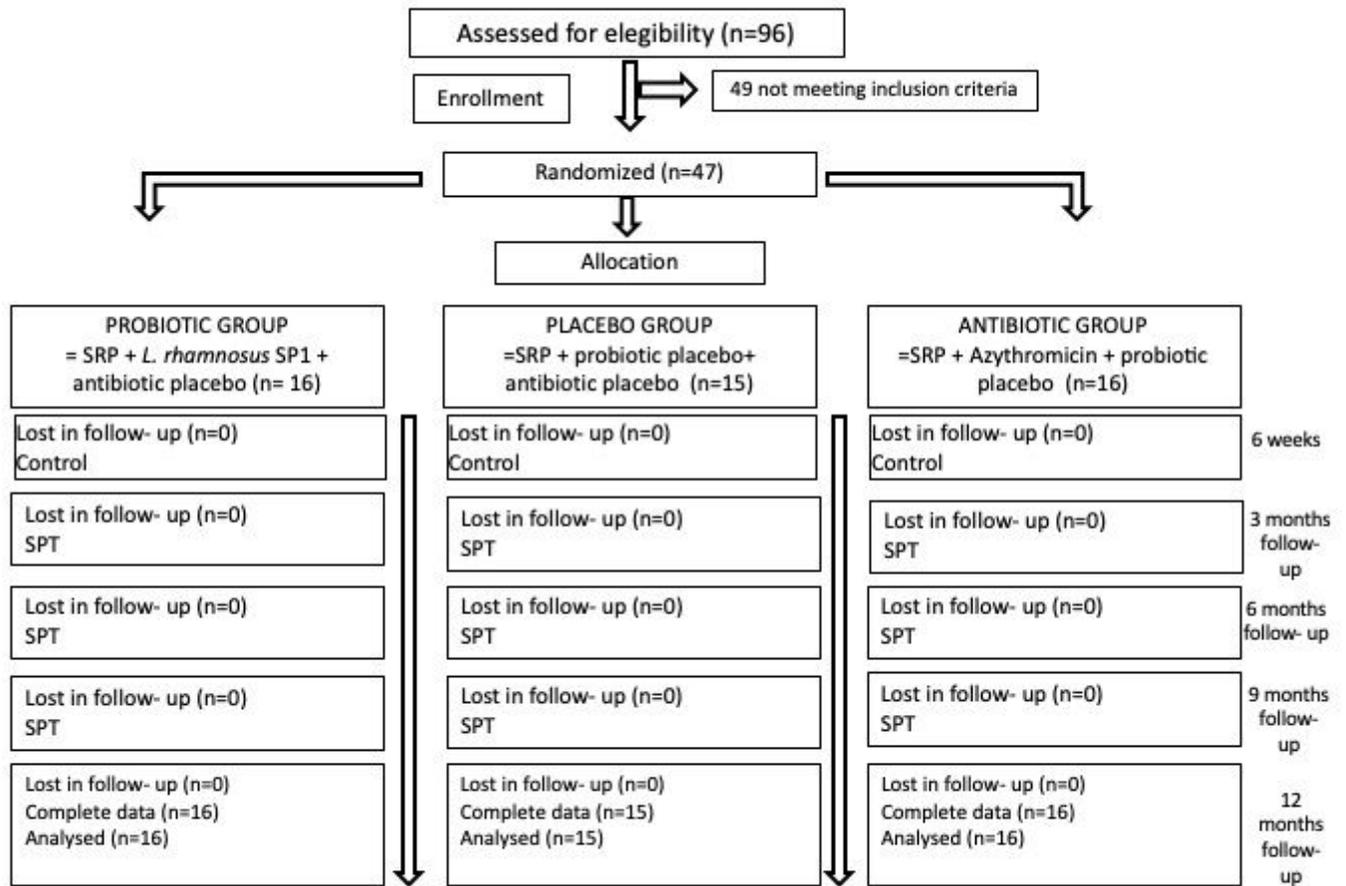


Figure.1 Flow chart of the study design.

Figure 1

Flow chart of the study design.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CONSORT2010ChecklistProbioticsBMCOraIHealth.doc](#)