A comparative study of synbiotic as an add-on therapy to standard treatment in patients with aggressive periodontitis

Gangadevi Murugesan, Kulur Mukhyaprapana Sudha, Malathi Krishnamurthy Subaramoniam,1 Trayambak Dutta,2 Karukkupalayam Ramasamy Dhanasekar2

Abstract:

Context: The role of synbiotic in the management of aggressive periodontitis (AP) is not well established. Aim: We designed this study to evaluate the efficacy and safety of synbiotic as an add-on therapy in the management of AP. Settings and Design: This was a randomized, double-blind, placebo-controlled study. Materials and Methods: Sixty patients with AP were randomized to two groups of 30 each. Study group received standard treatment, i.e., scaling and root planing along with doxycycline 100 mg twice daily for the 1st day (loading dose) followed by 100 mg once daily for 1 week and synbiotic lozenge twice daily for 8 weeks, whereas control group received standard treatment for 1 week and placebo lozenge for 8 weeks. Clinical parameters were recorded at baseline, 4th, 8th, and 12th weeks. Statistical Analysis Used: Pearson’s Chi-square test was applied to measure gingival bleeding index. Results: On comparison at 12 weeks, there was a statistically significant reduction (P < 0.01) in probing depth, clinical attachment loss, oral hygiene index, and bleeding on probing in study group. No Adverse drug reactions were noted. Conclusion: Co-administration of synbiotic lozenge along with standard therapy is highly efficacious in improving periodontal health in patients with AP.

Key words: Aggressive periodontitis, clinical attachment loss, probing depth, synbiotic

INTRODUCTION

Periodontitis is a chronic inflammatory disease of infectious origin that leads to destruction of supporting tissues of tooth. It is one of the major causes of tooth loss which is characterized by rapid destruction of periodontal attachment.[1] Aggressive form of the disease commonly affects systemically healthy individuals <30 years. It can be subdivided into localized and generalized aggressive periodontitis (AP). The localized form does not involve more than two teeth. First molar and incisors are commonly affected. In generalized form, at least three permanent teeth are involved other than first molars and incisors. The etiology of aggressive disease is very complex. Pathogenic bacteria are the primary etiologic agents in the pathogenesis or periodontitis. Aggregatibacter actinomycetemcomitans and Porphyromonas gingivalis are common infective agents that cause high prevalence of AP in people age <30 years.[2,3] Apart from this, contributing factors include genetics, environment, and host factors. The main symptoms are pain and loosening of teeth in the affected areas. Gum bleeding may occur spontaneously or upon stimulation. The most common and conventional treatment for AP is scaling and root planing (SRP) under the coverage of systemic antibiotics. Among all the antibiotics, the most efficacious in treating AP is doxycycline. However, the overuse and misuse of antibiotics over time have led to the emergence of drug-resistant microorganisms. The use of antibiotics may also disturb the indigenous microflora of the body which includes lactobacilli in the oral cavity. Hence, it is better to avoid the use of antibiotics that are highly active against lactobacilli. Recently, the trend has shifted toward the usage of synbiotics. Synbiotic is a mixture of pre- and probiotics and commonly includes Streptococcus faecalis,
**Materials and Methods**

Participants in the age group of 18–30 years who attended the outpatient department of periodontics were included in the study. Institutional Ethics Committee approved this study and it was monitored in accordance with Declaration of Helsinki and Good Clinical Practice (ICH-GCP) guidelines. The treatment period was 8 weeks along with posttreatment follow-up period of 4 weeks per patient. The sample size was calculated on the basis of the type of study design and as per that the data analysis was done. Sixty participants were assigned to control and study groups using simple randomization. Patients with generalized interproximal attachment loss affecting the permanent teeth other than first molar and incisors were included in the study. Patients having no past medical history with rapid attachment loss and bone destruction were also included in the study. The control group \((n = 30)\) received standard therapy and placebo, whereas the study group \((n = 30)\) received standard therapy along with synbiotics. Both males and females, patients recently diagnosed with AP, participants willing to give written informed consent, and patients adhering to oral hygiene instructions were evaluated for the study. Smokers and alcoholics, pregnant and lactating women, patients treated with synbiotics in the past 1 month, participants allergic to synbiotics, and patients with diabetes mellitus, chronic liver diseases, and heart, kidney, and HIV infection/AIDS were excluded from the study. The participants were recruited once they submitted written informed consent. The demographic details of the participants were recorded. Complete medical/dental history, clinical and oral examination, and laboratory investigations were done. Doses of the synbiotic lozenges were decided on the basis of clinical features, signs, and symptoms of the patients who fulfill the eligibility criteria in this study. Study group received standard treatment, i.e., SRP along with doxycycline 100 μg twice daily for the 1st day (loading dose) followed by 100 μg once daily for 1 week and synbiotic lozenge twice daily for 8 weeks, whereas control group received standard treatment twice daily for 1 week and placebo lozenge twice daily for 8 weeks. SRP is performed as part of the initial therapy. It is done to remove bacterial endotoxins. The removal of necrotic cementum is an important step and this procedure uses long, moderate to light pull strokes. SRP with antibiotic therapy is done for suppression and elimination of the pathogenic periodontal flora. Dosage of synbiotic lozenges was decided based on Dhawan and Dhawan, 2013, study on the role of probiotics in oral health. As per this study, synbiotics were administered twice daily to understand their role in oral hygiene.\[^{15}\]

Doxycycline is a semi-synthetic tetracycline and was chosen as a part of the therapy in this study as it shows greater concentration in the gingival crevicular fluid. Doxycycline was further preferred over other antibiotics as one of the causative organisms of AP, i.e., *A. actinomycetemcomitans* is susceptible to it. For better patient compliance, the dosage of doxycycline was considered once daily. Bioavailability is 95% and the lipid solubility is high. The microbes involved in this type of periodontitis are quite susceptible to doxycycline therapy at a minimum inhibitory concentration of 1–2 μg/ml. Administration of doxycycline in conjunction with supragingival plaque control can arrest the progression of AP. It also has the property of anti-collagenase effect. We included synbiotic to this standard therapy to understand the clinical advantage and it has to offer in AP therapy. Each synbiotic lozenge contains prebiotics: *S. faecalis* T-110 JPC – 30 million, *C. butyricum* TO-A – 2 million, and *B. mesentericus* TO-A JPC – 1 million and probiotics: *L. sporogenes* – 50 million. Participants were instructed to place the lozenges in the oral cavity for a few minutes, allowing them to dissolve to increase its local absorption. The assessment parameters used are as follows:

1. Oral hygiene index (OHI) – calculated based on the presence of debris and calculus on exposed tooth surface
2. Gingival bleeding index (GBI) – seen as bleeding on probing (BOP) even with a gentle touch
3. Probing depth (PD) – distance from free end of gingival margin to bottom of periodontal pocket
4. Clinical attachment loss (CAL) – distance from cementoenamel junction to bottom of periodontal pocket

Adverse drug reactions (ADRs) upon being reported were documented and appropriate medical care was provided. WHO scale was used to perform causality assessment of ADRs. Severity assessment was done using Modified Hartwig and Siegel severity assessment scale.

**Results**

A total of 106 participants were screened, of which 38 participants were excluded based on eligibility criteria. Eight participants did not provide the informed consent and hence were excluded from the study. Hence, 60 participants were enrolled in the study and were randomized into either of the two groups: control group (standard therapy along with placebo lozenge) and study group (synbiotic along with standard therapy). All the enrolled participants completed the study. The mean age of participants in both the groups was 23 years. Female preponderance was more in both controls (57%) and study groups (60%). Participants with generalized AP (66%) were higher than the localized form in both the groups. The efficacy of the treatment was assessed at the 4th, 8th, and 12th weeks using standardized tables for PD, CAL, OHL, and GBI. ADR monitoring along with regular laboratory investigations was done to assess the tolerability of the study drugs. Data were collected and the results were analyzed statistically. The clinical effectiveness of synbiotic treatment was concluded by monitoring the clinical parameters such as PD, CAL, OHI, and GBI.

**Discussion**

AP is characterized by rapid destruction of the periodontal ligament and alveolar bone around the affected teeth with increased PD formation and CAL. The standard therapy is SRP along with systemic antibiotics which lead to drug resistance. Synbiotic is a combination of pre- and probiotics.\[^{16}\] Synbiotic can be co-administered as they repopulate the beneficial microflora...
and reduce the pathogenic bacteria. Probiotics produce different antimicrobial components which include hydrogen peroxide, organic acids, low-molecular-weight antimicrobial substances, and bacteriocins which kill micro-organisms. They modulate the pro-inflammatory pathways induced by pathogens, thereby modifying the host immune response by inducing cytoprotective protein expression on cell surfaces. As per Shah et al., 2013, the use of probiotics significantly improved periodontal health of participants with AP.\[4\]

No significant difference was noted in mean age and gender distribution in both control and study groups. Participants with generalized AP were higher than the localized form in both the groups. A previous study conducted by Lye and Brown also had a similar distribution.\[7\] According to Figure 1, there was a statistically significant reduction in the mean PD in the study group 3.10 (0.30) mm than the control group 3.60 (0.49) mm at 8 weeks as compared to the findings at baseline (P < 0.01). The findings are comparable to that of the study conducted by Shimauchi et al., 2008, and Vivekananda et al., 2010, in which statistically significant reduction in the PD was observed.\[8,9\] According to Figure 2, the CAL in the study group showed a significant reduction which was 5.00 (0.53) mm when compared to the control group 5.37 (0.72) mm at the 8th week (P < 0.01). This correlates well with the studies conducted by Mayanagi et al., 2009, and Vivekananda et al., 2010, which also showed a statistically significant reduction in the CAL.\[9,10\]

According to Figure 3, our study showed a statistically significant decrease (P < 0.01) in the mean OHI in the study group 1.38 (0.12) than the control group 1.51 (0.18) at 8 weeks as compared to the findings on day 0. This was similar to the study done by Krasse et al., 2006,\[11\] Kang et al., 2006,\[12\] and Riccia et al., 2007,\[13\] which also showed a statistically significant reduction in the OHI. According to Table 1, the mean GBI as measured by BOP was positive in 20% of participants in the control group at the end of 8 weeks as compared to none in the study group. There was a statistically significant reduction in the GBI (P < 0.01) in the study group at 8 weeks as compared to the findings on day 0. Our finding correlates with the studies conducted by Krasse et al., 2006,\[11\] Riccia et al., 2007,\[13\] Tsubura et al., 2009,\[14\] and Vivekananda et al., 2010,\[9\] which also showed similar results.

Addition of symbiotic to standard treatment showed a statistically significant reduction in mean PD, mean CAL, mean OHI, and GBI when compared to standard therapy. This correlates well with the studies conducted by Shah et al., 2013.\[14\] There was no significant difference in the hemoglobin levels, total white blood cell count, and blood sugar in both the control and study groups at the end of treatment period which asserts that addition of symbiotic does not affect hematological and biochemical laboratory parameters. No serious adverse events (SAEs) were reported in our study. Abdominal pain, bloating, and nausea were common adverse events (AEs) reported during the study period in both the groups. Other AEs noted were diarrhea and headache. All the ADRs recorded were categorized as possible under WHO causality assessment scale. As per the modified Harwig and Siegel severity assessment scale, all the ADRs reported were mild. This suggests that addition of symbiotic is not associated with increase in incidence of any AE, thereby showing the safety of symbiotic. Similarly, the safety of symbiotic was well established in a study done by Chatterjee et al., 2011.\[15\] Thus, symbiotic can be used in patients with AP and its use can improve the periodontal health.\[14\] Symbiotic was not associated with any SAE and hence can be safely used in the management of AP.
CONCLUSION

From our study, we conclude that co-administration of probiotic along with standard therapy is more efficacious than SRP and doxycycline in the treatment of AP. We also found that probiotic is safe as it does not produce any SAE. Therefore, probiotic can be used in the routine management of AP. Synbiotic has a great potential in arena of periodontics in terms of altering anaerobic bacteria colonization, improvement of pocket depth, gingival bleeding, and CAL. Synbiotics can be used as an adjunct to SRP in AP patients. They can be used as an effective adjunctive therapy to conventional nonsurgical periodontal treatment in AP patients as it has an anti-inflammatory and antimicrobial property which prevents and safeguards against destruction of periodontal attachment apparatus and loss of alveolar bone.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Riep B, Edesi-Neuss L, Claessen F, Skarabis H, Ehmke B, Flemmig TF, et al. Are putative periodontal pathogens reliable diagnostic markers? J Clin Microbiol 2009;47:1705-11.
2. Niklaus L, Mark B, Mary C, Marjorie J, Andrea M, Shinya M, et al. Consensus report: Aggressive periodontitis. Ann Periodontol 1999;4:33.
3. Chahboun H, Arnau MM, Herrera D, Sanz M, Ennibi OK. Bacterial profile of aggressive periodontitis in Morocco: A cross-sectional study. BMC Oral Health 2015;15:25.
4. Shah MP, Gujari SK, Chandrasekhar VS. Evaluation of the effect of probiotic insersan alone, combination of probiotic with doxycycline and doxycycline alone on aggressive periodontitis - A Clinical and Microbiological Study. J Clin Diagn Res 2013;7:595-600.
5. Dhawan R, Dhawan S. Role of probiotics on oral health: A randomized, double-blind, placebo-controlled study. J Interdiscip Dent 2013;3:71-8.
6. Pandey KR, Naik SR, Vakil BV. Probiotics, prebiotics and synbiotics – A review. J Food Sci Technol 2015;52:7577-87.
7. L20 H, Brown LJ. Early onset periodontitis in the United States of America. J Periodontol 1991;62:608-16.
8. Shimauchi H, Mayanagi G, Nakaya S, Minamibuchi M, Ito Y, Yamaki K, et al. Improvement of periodontal condition by probiotics with Lactobacillus salivarius WB21: A randomized, double-blind, placebo-controlled study. J Clin Periodontol 2008;35:989-905.
9. Vivekananda MR, Vandana KL, Bhat KG. Effect of the probiotic Lactobacilli reuteri (Prodentis) in the management of periodontal disease: A preliminary randomized clinical trial. J Oral Microbiol 2010;2:5344.
10. Mayanagi G, Kimura M, Nakaya S, Hirata H, Sakamoto M, Benno Y, et al. Probiotic effects of orally administered Lactobacillus salivarius WB21-containing tablets on periodontopathic bacteria. A double-blinded, placebo-controlled, randomized clinical trial. J Clin Periodontol 2009;36:506-13.
11. Krasse P, Carlsson B, Dahl C, Paulsson A, Nilsson A, Sinkiewicz G, et al. Decreased gum bleeding and reduced gingivitis by the probiotic Lactobacillus reuteri. Swed Dent J 2006;30:55-60.
12. Kang MS, Chung J, Kim SM, Yang KH, Oh JS. Effect of Weissella cibaria isolates on the formation of Streptococcus mutans biofilm. Caries Res 2006;40:418-25.
13. Riccita DN, Bizzini F, Perilli MG, Polimeni A, Trinchieri V, Amicosante G, et al. Anti-inflammatory effects of Lactobacillus brevis (CD2) on periodontal disease. Oral Dis 2007;13:376-85.
14. Tsubura S, Mizumuma H, Ishikawa S, Oyake Y, Okabayashi M, Kato K, et al. The effect of Bacillus subtilis mouth rinsing in patients with periodontitis. Eur J Clin Microbiol Infect Dis 2009;28:1353-6.
15. Chatterjee A, Bhattacharya H, Kandwal A. Probiotics in periodontal health and disease. J Indian Soc Periodontol 2011;15:23-38.
16. Roshna T, Nandakumar K. Generalized aggressive periodontitis and its treatment options: Case reports and review of the literature. Case Rep Med 2012;2012:535321.