Original Article

Indian Journal of Obstetrics and Gynecology
Volume 12 Number 2, April – June 2024
DOI: http://dx.doi.org/10.21088/ijog.2321.1636.12224.3

Can Probiotics Play a Major Role as an Adjunctive Therapy in Treatment of Bacterial Vaginosis?

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How to cite this article:

Bandana Sharma, Pavika Lal, Rashmi Yadav *et al*. Can Probiotics Play a Major Role as an Adjunctive Therapy in Treatment of Bacterial Vaginosis?. Indian J Obstet Gynecol. 2024;12(2):63-69.

Abstract

Background: Bacterial Vaginosis is one of the most common causes of abnormal vaginal discharge in women of reproductive age, which can have a major impact on quality of life. Although the treatment course of oral metronidazole for 7 days results in curative rate of 70%–80% at four weeks of treatment, but is associated with high rates of recurrence occurred within twelve months, reaching up to 40%–50%.

Methods: A Randomized Prospective Interventional Study was done on 1000 reproductive age group females (pregnant or non-pregnant) diagnosed with bacterial vaginosis from November 2020 to October 2022 at department of Obstetrics & Gynaecology, Kanpur. The study group were divided into two subgroups - Group 1 were given metronidazole 500 mg for 7 days and probiotics for 14 days and group 2 were given metronidazole 500 mg for 7 days and placebo for 14 days. The patients were followed after 3 months to know the recurrence.

Results: Majority of patients belonged to rural background (63.1%) with lower socioeconomic (46.6%) and belong to age group 20-35 years. It was observed that there was significant change in Amsel's criteria and Nugent's scoring in Group 1 as compared to Group 2. The rate of recurrence at the end of the treatment for Amsel's criteria in group 1 were 1.03 as compared to group 2 was 1.68 and for Nugent's scoring, the rate of recurrence at the end of treatment in group 1 was 3.17 as compared to group 2 was 4.78.

Conclusion: Probiotics can be considered as one the adjuvant therapy for treating bacterial vaginosis and re-establishing equilibrium in the vaginal microflora thus, preventing the recurrences.

Keywords: Bacterial Vaginosis; Reproductive age group females; Probiotics; Recurrence.

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Received on: 30.04.2024

Accepted on: 26.05.2024

INTRODUCTION

Vaginal discharge is a very common ailment in women of reproductive age which many a time can be attributed to bacterial vaginosis (BV). This condition is often linked to various complications, such as post-hysterectomy vaginal infections and adverse pregnancy outcomes, including premature rupture of membranes, preterm labour, chorioamnionitis, and postpartum endometritis. Additionally, BV increases the risk of contracting human immunodeficiency virus (HIV). Treatment typically involves a 7-day course of oral

metronidazole, with cure rates ranging from 70% to 80% after 4 weeks.[1] However, the recurrence rateis as high as 40%-50% within twelve months.[2]

The vaginal flora is primarily composed of Lactobacillus species, such as L. crispatus, L. jensenii, L. iners, and L. gasseri,[3-5] which help maintain a healthy vaginal environment by producing lactic acid and other antimicrobial substances. However, in bacterial vaginosis (BV), this balance is disrupted. There is a significant shift in the vaginal microbiota, characterized by a decrease in lactobacilli and an overgrowth of various anaerobic bacteria. These include Gardnerella vaginalis, Mycoplasma hominis, Prevotella, Peptostreptococcus, Mobiluncus, and Bacteroides species. This imbalance can lead to various symptoms and complications associated with BV.

The primary recommended first-line treatment for bacterial vaginosis (BV) involves either oral or vaginal administration of metronidazole or clindamycin.[6] These antibiotics, despite having different spectra of activity, have been found to have comparable short-term efficacy. Studies indicate that cure rates range from 80% to 90% within one month after treatment.[7] However, the treatment of BV is complicated by a high relapse rate. Up to 30% of women experience a recurrence of symptoms within one month of completing therapy. This recurrence is particularly notable among those who were treated with topical antibiotics compared to those who received systemic (oral) antibiotics.[8,9] The reasons for the higher relapse rates with topical treatments are not fully understood but may be related to differences in how the drugs distribute and act within the body.

The exact reasons for recurrences of bacterial vaginosis (BV) remain unclear, whether recurrences are due to the failure to fully eradicate the causative organisms during initial treatment or reinfection from sexual partners.[10] Despite the ambiguity, several studies suggest that adjunctive treatment with oral or vaginal probiotics could potentially reduce recurrence rates by restoring the natural balance of the vaginal microbiota. However, this approach has not yet been incorporated into the guidelines of major professional bodies such as the American College of Obstetricians and Gynecologists (ACOG) and the Royal College of Obstetricians and Gynaecologists (RCOG).Given the promising but not yet conclusive evidence, our study aims to investigate the role of probiotics in reducing the recurrence rate of BV. By conducting a detailed analysis, we hope to provide more definitive answers regarding the efficacy of probiotics as an adjunctive treatment, which could potentially inform future guidelines and offer new strategies for managing this common and troublesome condition.

Probiotics, particularly those containing Lactobacillus strains, can help in the following ways:

1. Restoring Lactobacillus Dominance: Probiotics introduce beneficial Lactobacillus bacteria into the vagina, helping to re-establish a healthy microbial balance.
2. Producing Lactic Acid: Lactobacillus bacteria produce lactic acid, which lowers the vaginal pH, creating an acidic environment that is inhospitable to harmful bacteria.
3. Producing Antimicrobial Substances: These beneficial bacteria produce substances like hydrogen peroxide and bacteriocins, which inhibit the growth of pathogenic bacteria.
4. Enhancing Immune Response: Probiotics can enhance the local immune response, helping the body to better fight off infections.
5. Biofilm Disruption: Some probiotics can disrupt biofilms formed by pathogenic bacteria, making them more susceptible to the body's defenses and treatments.

METHODS & MATERIALS

Setting: This was a randomized prospective interventional study conducted in department of obstetrics and gynaecology, GSVM Medical college, Kanpur, Uttar Pradesh, India, over period of two years. All non-pregnant females between age group of 18-45 years, who fulfil ¾ Amsel's criteria and willing to participate were enrolled for the study. Those patients who were under 18 or over 45 years of age, those with diabetes or other chronic illnesses, and those taking oral contraceptive pills were excluded from the study.

After obtaining written and informed consent and ethical clearance from the institutional ethics committee in Kanpur, a total of 1000 females who attended the gynecological OPD with complaints of vaginal discharge were recruited. Vaginal smears were collected for Gram staining, and Nugent's classification was performed only if BV was diagnosed on the basis of Amsel's criteria. The patients were equally divided into two groups: Group 1 received oral metronidazole 400 mg twice daily for 7 days along with oral probiotics capsule Florita twice daily for 14 days, while

Group 2 received oral metronidazole 400 mg twice daily for 7 days along with placebo for 14 days. Post-treatment, patients were followed up after 3 months to assess recurrence of symptoms, and Amsel's criteria and Nugent's score were repeated for objective assessment.

RESULTS

Rural areas were where most of the patients were located, with mostly being 18-25 years old, having low socio-economic status, having primary education. Most of the patients were not pregnant when the study was conducted. (Table 1)

Table 1: Distribution of the Participants in Terms of 'sociodemographic factors'

Socio-demographic factors	Group		
	Group 1	Group 2	Total
Age Group			
18-25 Years	237 (47.4%)	250 (50.0%)	487 (48.7%)
26-35 Years	253 (50.6%)	225 (45.0%)	478 (47.8%)
>35 Years	10 (2.0%)	25 (5.0%)	35 (3.5%)
Socioeconomic - Status			
Upper	106 (21.2%)	106 (21.2%)	212 (21.2%)
Middle	161 (32.2%)	161 (32.2%)	322 (32.2%)
Lower	233 (46.6%)	233 (46.6%)	466 (46.6%)
Residence			
Rural	320 (32.0%)	311 (31.1%)	631 (63.1%)
Urban	180 (18.0%)	189 (18.9%)	369 (36.9%)
Level of Education			
Illiterate	65 (6.5%)	67 (6.7%)	132 (13.2%)
Primary Level	233 (23.3%)	236 (23.6%)	469 (46.9%)
Middle level	144 (14.4%)	135 (13.5%)	279 (27.9%)
Secondary level	58 (5.8%)	62 (6.2%)	120 (12.0%)
Currently Pregnant			
Yes	186 (37.2%)	188 (37.6%)	374 (37.4%)
No	314 (62.8%)	312 (62.4%)	626 (62.6%)

In Group: 1 the mean Amsel's Criteria decreased from a maximum of 3.42 at the start of treatment to a minimum of 1.03 at follow-up period whereas, in Group: 2, the mean Amsel's Criteria decreased from a maximum of 3.43 at the start of treatment to a minimum of 1.68 at follow up period. The overall change in Amsel's Criteria overtime compared in the two groups using the Generalized Estimating Equations method. There was a significant difference in the trend of Amsel's Criteria at the end of follow up between the two groups (p= <0.001). (Table 2)

Table 2: Comparison of the two study Groups with respect to change in Amsel's Criteria over time

Amsel's Criteria	Group		P-value for comparison of the two groups at each of the timepoints (Wilcoxon-Mann-Whitney Test)
	Group I	Group II	
	Mean (SD)	Mean (SD)	
Baseline	3.42 (0.55)	3.43 (0.55)	0.783
Follow-Up	1.03 (1.05)	1.68 (1.54)	<0.001
P Value for change in Amsel's Criteria over time within each group (Wilcoxon Test)	<0.001	<0.001	–
Overall P Value for comparison of change in Amsel's Criteria over time between the two groups (Generalized Estimating Equations)	<0.001		

The following line diagram depicting the change in Amsel's Criteria from the start of treatment to at the end of follow up period in between the two groups. This line diagram shows that there is more decrease in Amsel's criteria in group1as compare to group 2. (Fig. 1)

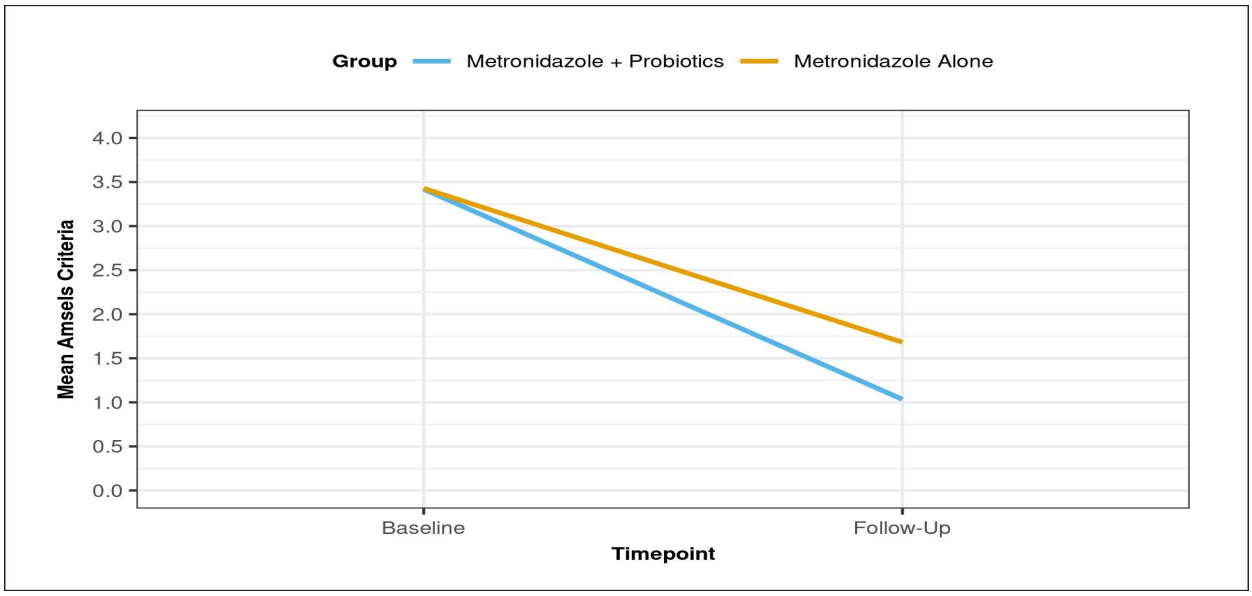

Fig. 1: Change in Amsel's Criteria Over Time

In Group 1, the mean Nugent's Scoring decreased from a maximum of 8.45 at the treatment to a minimum of 3.17 at the Follow-Up period whereas, in Group: 2, the mean Nugent's Scoring decreased from a maximum of 8.46 at the start of the treatment to a minimum of 4.78 at the Follow-Up period. The overall change in Nugent's Scoring overtime was compared in the two groups using the Generalized Estimating Equations method. There was a significant difference in the trend of Nugent's Scoring at the end of follow up between the two groups (p=<0.001). (Table 3)

Table 3: Comparison of the two study Groups with respect to change in Nugent's Scoring over time

Nugent's Scoring	Group		P-value for comparison of the two groups at each of the time points (Wilcoxon-Mann-Whitney Test)
	Metronidazole + Probiotics	Metronidazole Alone	
	Mean (SD)	Mean (SD)	
Baseline	8.45 (0.52)	8.46 (0.53)	0.781
Follow-Up	3.17 (2.42)	4.78 (3.10)	<0.001
P Value for change in Nugent's Scoring over time within each group (Wilcoxon Test)	<0.001	<0.001	
Overall P Value for comparison of change in Nugent's Scoring over time between the two groups (Generalized Estimating Equations)	<0.001		

The following line diagram depicting the change in Nugent's Scoring from the start of treatment to at the end of follow upper iodin between the two groups. This line diagram shows that there is more decrease in Nugent's Scoring in group 1 as compare to group 2. (Fig. 2)

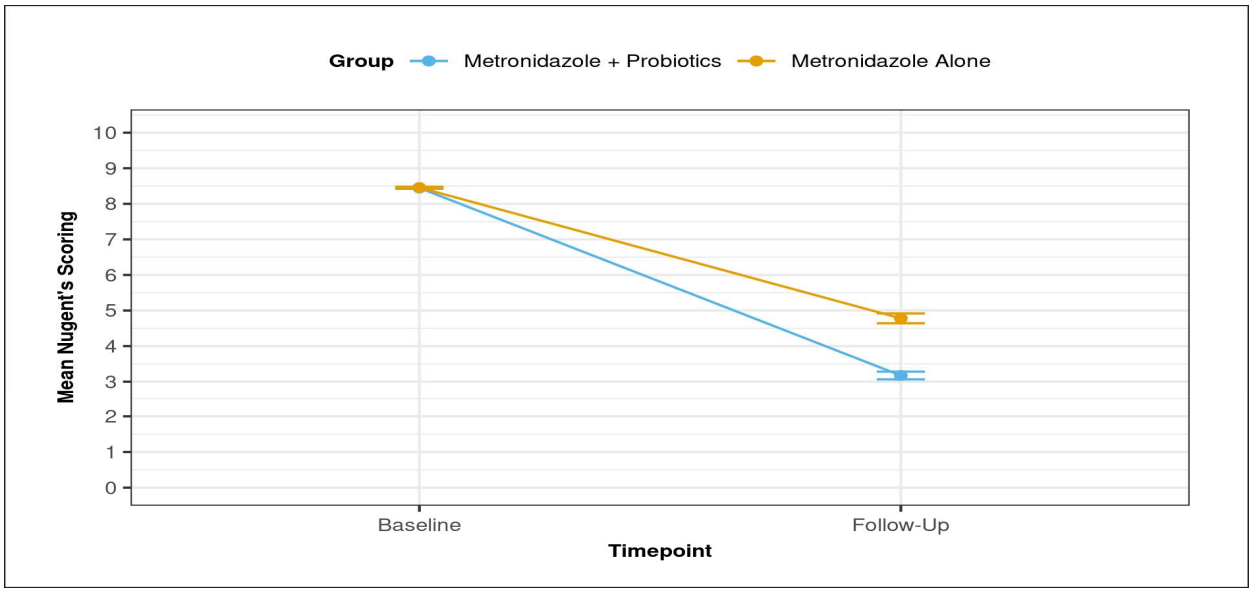

Fig. 2: Change in Nugent's Scoring Over Time

DISCUSSION

In our study, the majority of patients fell within the age group of 20-35 years, with a mean age of 26.4 years. This finding aligns with the research by Mtebe V. Majigo *et al*[11], which reported a median age of 29 years for BV. Although Bacterial vaginosis is not considerd as a STD but it is more prevalent in this age group due to their increased frequency of sexual activity.

In our study, majority of patients belonged to rural areas (63.1%) and had primary level education (46.9%), with poor personal hygiene practices. Yiewou Marguerithe Kamga *et al*[12] demonstrated that bacterial vaginosis was significantly more prevalent in women from rural areas compared to urban areas (29.5% vs. 24.5%, $\chi 2 = 8.609$, $p = 0.014$). Additionally, they found that bacterial vaginosis was more common among individuals with a primary level of education (33.3%) compared to those with higher education level. This finding was also observed in our study, possibly indicating increased awareness and adherence to personal hygiene practices among individuals with higher education level.

In our study, a significant proportion of patients were from low socio-economic status (46.6%), underscoring the disproportionate burden of bacterial vaginosis on the underprivileged segment of society. T. Ashraf-Ganjoe *et al*.[13] also found that patients with BV had significantly lower educational ($p = 0.006$) and socioeconomic ($p = 0.021$) levels. In our study, the majority of patients presented with white discharge (93.2%), followed by backache (57.4%), which aligns with the findings reported by Eriksson K *et al*.

In Group 1 (Metronidazole + Probiotics), the mean Amsel's Criteria decreased significantly from a maximum of 3.42 at the start of treatment to a minimum of 1.03 after 3 months (Wilcoxon Test: $V = 105934.0$, $p < 0.001$). Similarly, in Group 2 (Metronidazole Alone), the mean Amsel's Criteria decreased from a maximum of 3.43 at the beginning of treatment to a minimum of 1.68 at the end of treatment, showing a statistically significant change within the group (Wilcoxon Test: $V = 73571.0$, $p < 0.001$). Comparing the trend of Amsel's Criteria over time between the two groups using Generalized Estimating Equations revealed a significant difference ($p < 0.001$). These findings were consistent with a study conducted by Nadia Recine *et al*.[14] in 2015 (15), where participants were divided into Group A (standard treatment for BV—metronidazole 500 mg orally twice a day for 7 days) and Group B (same antibiotic regimen followed by vaginal tablets containing Lactobacillus rhamnosus BMX 54). The study found that vaginal flora was significantly restored in Group B patients after 2 months compared to Group A ($p = 0.014$).

In Group 1 (Metronidazole + Probiotics), the mean Nugent's Scoring decreased significantly from a maximum of 8.45 at the initiation of treatment to a minimum of 3.17 after 3 months ($p < 0.001$). Similarly, in Group 2 (Metronidazole Alone), the mean Nugent's Scoring decreased from a maximum of 8.46 at the start of treatment to a minimum

of 4.78 after 3 months, showing a statistically significant change ($p < 0.001$). Comparing the trend of Nugent's Scoring over time between the two groups revealed a significant difference ($p < 0.001$). These findings align with a study conducted by R.S. Vigneshwari *et al*. in 2014[15], where they observed significant symptomatic improvement and Nugent scoring improvement in the Metronidazole + probiotics group compared to the Metronidazole alone group ($p < 0.05$).

In our study, the recurrence of bacterial vaginosis (BV) was observed more frequently in the metronidazole alone group compared to the group receiving metronidazole along with probiotics. These findings were consistent with other studies, such as the one conducted by Wei Keong Chieng *et al*.[16], where probiotics were shown to reduce the risk of BV recurrences by 45% compared to either placebo or metronidazole (14.8% vs. 25.5%, RR: 0.55, $p = 0.03$). Similarly, H-F. Liu, N. Y *et al*.[17] found that in the subgroup analysis of antibiotic plus probiotics versus antibiotics alone, the antibiotic plus probiotics group had a significantly lower BV recurrence rate at 1-3 months (RR: 0.302, 95% CI: 0.172-0.532) and overall BV recurrence rate (RR: 0.419, 95% CI: 0.238-0.737) than the antibiotics alone group.

Strength of the study

The present study assessed a larger sample which added to the scarce literature available on use of probiotics in treatment of Bacterial Vaginosis especially in Indian population.

Limitation of the study

» The sample does not reflect the actual demographic composition of the target population which also restricts the generalizability of the findings.

CONCLUSION

- From our study, we can conclude that while conventional treatment with oral metronidazole for 7 days was effective in the majority of patients, recurrence was common even after completing the recommended course. This highlights the concern of repeated antibiotic use leading to potential resistance.
- In our study, we found that adding probiotics to the standard treatment regimen showed promising results with regard to reduction in recurrence rates of bacterial vaginosis. Furthermore, the safety profile of probiotics appeared to be favorable, as no major side effects were observed.

Indeed, incorporating probiotics into the standard antibiotic therapy for bacterial vaginosis (BV) could prove to be a valuable adjunct in reducing the frequency of recurrences. This combined approach may offer benefits in restoring and maintaining a healthy vaginal microbiota, thereby potentially improving treatment outcomes. Considering the promising results observed in various studies, the inclusion of probiotics alongside antibiotics warrants consideration as a complementary strategy for managing BV. However, further research and clinical trials are needed to validate its efficacy and establish optimal treatment protocols.

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