ORIGINAL ARTICLE

Metronidazole With or Without Probiotics for Prevention of Recurrent Bacterial Vaginosis: A Comparative Study

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ABSTRACT

Introduction: Bacterial vaginosis is one of the most common vaginal infections affecting women of reproductive and also post-menopausal age groups worldwide. It is characterized by a decrease in number of good bacteria like, lactobacilli and an overgrowth of pathological anaerobic bacteria, leading to symptoms such as abnormal foul smelling vaginal discharge. Till date metronidazole, ornidazole, tinidazole and clindamycin are the standard antibiotic treatment, at a same time recurrence rates have been found to be high. Probiotics have emerged as a potential adjunct therapy to restore and maintain a healthy vaginal microbiome, leads to reducing bacterial vaginosis recurrence. **Aims:** To evaluate the efficacy of metronidazole alone versus metronidazole added with oral probiotics in preventing bacterial vaginosis recurrence. **Methods**: A randomized comparative study was carried out at Nepalgunj Medical College Teaching Hospital from October 2022 to September 2023. Seventy-two non-pregnant women diagnosed with bacterial vaginosis were divided into two groups: Group A (metronidazole alone) and Group B (metronidazole with probiotics). Primary outcomes, including vaginal discharge, odor, vaginal pH, Nugent score, and bacterial vaginosis recurrence, were assessed at 8, 30, and 60 days post-treatment. **Results:** At the 8th day follow-up, Group B (metronidazole + probiotics) demonstrated a statistically significant reduction in abnormal vaginal discharge compared to Group A (p=0.013). By Day 60, Group B maintained superior outcomes across all measured parameters, including vaginal discharge (p=0.089), odor (p=0.230), pH (p=0.009) and Nugent scores (p<0.001). The recurrence rate of bacterial vaginosis was consistently minimum in Group B throughout the study period. **Conclusion:** The addition of probiotics to metronidazole therapy significantly prevent recurrence of bacterial vaginosis.

Keywords: Bacterial Vaginosis, Metronidazole, Probiotics

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INTRODUCTION

Bacterial vaginosis (BV) is a common vaginal infection affecting up to 30% of women of reproductive age globally. It arises from an imbalance in the vaginal microbiota, characterized by a reduction in beneficial lactobacilli and an overgrowth of anaerobic bacteria. Lactobacilli are essential for maintaining an acidic vaginal pH, which inhibits the proliferation of harmful bacteria. When lactobacilli levels decline, pathogenic anaerobes can flourish, leading to BV symptoms such as a fishy odor, abnormal discharge, and irritation.[1] Diagnosis of BV typically involves clinical criteria, such as Amsel's criteria or laboratory methods like Gram staining, with the latter considered the gold standard. Standard treatment includes antibiotics like metronidazole or clindamycin, administered orally or vaginally. However, recurrence rates remain high, with studies indicating that 50% to 80% of women experience a recurrence within a year of treatment. Factors contributing to recurrence include sexual activity, use of intrauterine devices, smoking and practices like vaginal douching.[2,3,4,5] Given the high recurrence rates and potential complications—such as increased susceptibility to sexually transmitted infections and adverse pregnancy outcomes-there is a need for improved preventive strategies.[6] Recent research has explored the use of probiotics, particularly strains like Lactobacillus crispatus, to restore the natural vaginal flora and reduce recurrence rates. Probiotics can be administered orally or vaginally and have shown promise in re-establishing a healthy microbiome. Combining probiotics with antibiotic therapy may enhance treatment efficacy and reduce the likelihood of recurrence.[7] This study aims to evaluate the effectiveness of metronidazole (500 mg) with or without the addition of oral probiotics in preventing the recurrence of bacterial vaginosis.

METHODS

This study was conducted in the Department of Obstetrics and Gynecology, Nepalgunj Medical College Teaching Hospital, Kohalpur from October 2022 to September 2023. Patients presented with complaints of vaginal discharge at the outpatient department underwent thorough clinical examinations. Vaginal samples were collected and Gram staining was performed to assess bacterial morphology. Microscopic examination, conducted with the assistance of a laboratory technician, focused on identifying clue cells—vaginal epithelial cells covered with bacteria—which are indicative of bacterial vaginosis. Additionally, the "whiff test" was performed by adding 10% potassium hydroxide to the vaginal discharge to detect a characteristic fishy odor. These assessments were conducted to fulfill Amsel's criteria[3] and to calculate the Nugent score[5] by using counts of Rhodes and cocci /high power field, both of which are standard diagnostic methods for bacterial vaginosis. After confirming the diagnosis of bacterial vaginosis through clinical examination, Amsel's criteria[3] and the Nugent scoring system[5] participants received counseling on the benefits and risks associated with metronidazole therapy, both with and without the addition of probiotics. Those who provided informed consent were subsequently enrolled in the study. Group division was performed by using the lottery method, a form of simple random sampling. In this approach, each participant was assigned a unique identifier, and these identifiers were placed into a container. The identifiers were thoroughly mixed, and then drawn at random to assign participants to one of two groups: Group A (Metronidazole alone) or Group B (Metronidazole combined with probiotics). This method ensures that each participant had an equal chance of being allocated to either group, thereby minimizing selection bias and promoting the internal validity of the study. Diagnosis of Bacterial vaginosis (BV) was confirmed on the basis of clinical examination, presence of at least three of Amsel's clinical criteria and a Nugent score >7.

Amsel's criteria include: (1) homogeneous, thin, white vaginal discharge; (2) vaginal pH > 4.5; (3) a positive "whiff" test, characterized by a fishy odor upon addition of 10% potassium hydroxide; and (4) the presence of clue cells on microscopic examination.[3] The Nugent scoring system, considered the gold standard for BV diagnosis, involves Gram staining of vaginal smears and evaluating the relative abundance of bacterial morphotypes. A score of <7 considered normal, >7 indicates BV. A score above 4 suggests an imbalance in the vaginal flora, supporting the diagnosis of BV.[5]

Inclusion Criteria: Diagnosed case of BV based on clinical examination, Amsel's criteria[3], and Nugent scoring system.[5]

Exclusion Criteria:

Diagnosed case of malignancy

Immunocompromised status

Diabetes mellitus

Planning for pregnancy in the near future

Allergy or contraindication to the study drugs

The outcomes of the study were measured at follow-up visits on days 8th, 30th and 60th, focusing on the following parameters:

- **Clinical Symptoms**: The effectiveness of the treatment was evaluated based on the resolution of clinical symptoms at each follow-up visit.
- **Recurrence Rate:** The recurrence of symptoms was documented during each follow-up to monitor the persistence or return of bacterial vaginosis.
- **Amsel's Criteria**: Diagnostic assessments were conducted using Amsel's criteria.[3]
- **Nugent Score:** Vaginal smears were analyzed using the Nugent scoring system.[5]
- These assessments were also conducted at each follow-up visit.

Sample Size Calculation:

Prevalence of BV (p) = 24.4% = 0.244. [8]

q = 1 - 0.244 = 0.756

Allowable error (L) = 10% = 0.1

Z = 1.96

Sample size (N) = $Z^2 \times p \times q / L^2 = (1.96)^2 \times 0.244 \times 0.756 / (0.1)^2 = 70.86$.

Rounding up, the required sample size was 71 participants. To facilitate equal group distribution, the total was adjusted to 72, with 36 participants in each group. Participants (N = 72) were randomly assigned to the two groups using the lottery method.

Statistical Analysis:

Data was analyzed using SPSS 26. The Student's t-test was used to compare mean symptoms pre- and post-therapy, recurrence rates by using Amsel's criteria, and Nugent scores between the two groups. A p-value < 0.05 was considered statistically significant.

RESULTS

Out of 342 participants who presented with symptoms of vaginal discharge during the study period, 88 cases were enrolled during the first visit, while 16 cases were lost to follow-up. The remaining 72 participants met the inclusion criteria and continued with follow-up, allowing for further statistical analysis. The overall prevalence of bacterial vaginosis was 25.73%, and these cases were subsequently analyzed.

Parameter		Group A			Group B			p value
Age		33.36 ± 6.79			32 ±6.02			0.336
Parity		3.31 ± 1.36			2.14 ± 1.01			0.078
Cycle	Regular	Irregular			Regular	Irregular		
	30 (83.33%)	6 (16.66%)			31 (86.11%)	5 (13.88%)		
Residence	Rural	Urban			Rural	Urban		
	26 (72.22%)	10 (27.77%)			29 (80.55%)	7 (19.44%)		
Contraceptive	None	Barrier	LARC	Permanent	None	Barrier	LARC	Permanent
	31 (86.11%)	2 (5.55%)	2 (5.55%)	1 (2.77%)	31 (86.11%)	3 (8.34%)	1 (2.77%)	1 (2.77%)
Education	Illiterate	Lower secondary	Upper seconday	University	Illiterate	Lower secondary	Upper secnday	university
	31 (86.11%)	3 (8.34%)	1 (2.77%)	1 (2.77%)	28 (77.77%)	2 (5.55%)	3(8.34%)	3 (8.34%)
Occupation	House wife	Job holder			House wife	Job holder		
	33 (91.66%)	3 (8.34%)			33 (91.66%)	3 (8.34%)		

Table I: Demographic characteristics

The table above presents the baseline characteristics of participants in both study groups. The mean age in Group A (metronidazole alone) was 33.36 years, while in Group B (metronidazole with probiotics), it was 32 years. The p-value for age comparison was 0.336, indicating no statistically significant difference. Regarding parity, Group A had a higher mean parity of 3.31 compared to 2.14 in Group B; however, this difference was not statistically significant (p = 0.078). Most participants in both groups reported regular menstrual cycles. In terms of educational attainment, Group A had a slightly lower education level compared to Group B. The majority of participants in both groups resided in rural areas. Occupationally, both groups had similar distributions, with the majority being housewives. Mean with student T-test used for data analysis.

Parameters	Group A	Group B
Vaginal discharge at time of enrollment		
Present	34	34
Absent	2	2
p Value	0.693	
On Day 8th follow up visit		
Present	13	4
Absent	23	32
p Value	0.013*	
On Day 30th follow up visit		
Present	14	5
Absent	22	31
p Value	0.016*	
On Day 60th follow up visit		
Present	11	5
Absent	25	31
p Value	0.089	
Smell at time of enrollment		
Present	36	35
Absent	0	1
p Value	0.314	
On Day 8th follow up visit		
Present	35	34
Absent	1	2
p Value	0.555	
On Day 30th follow up visit		
Present	22	18
Absent	14	18
p Value	0.343	
On Day 60th follow up visit		
Present	24	12
Absent	19	17
p Value	0.230	

Table II: Clinical examination

The table above presents the clinical outcomes observed during the study period.

Abnormal Vaginal Discharge: At enrollment, all participants exhibited abnormal vaginal discharge. By day 8, Group B (metronidazole with probiotics) demonstrated a significant reduction in abnormal discharge compared to Group A (metronidazole alone), with a p-value of 0.013. This improvement persisted through day 30 (p = 0.016) and day 60 (p = 0.089), indicating a consistent trend favoring the combination therapy, though the difference on day 60 was not statistically significant

Foul Odor of Vaginal Discharge: Initially, all participants reported a foul odor associated with their discharge. By day 8, both groups showed improvement, with Group B exhibiting a slightly greater reduction; however, this difference was not statistically significant (p = 0.555). By day 60, the distinction between the groups became more pronounced, with Group B showing better outcomes (p = 0.230), though still not reaching statistical significance. Mean with student T-test used for data analysis.

Parameters	Group A	Group B
Vaginal pH in enrolment		
<4.5	0	0
>4.5	36	36
p Value	Not applicable	
On Day 8th follow up visit		
<4.5	27	28
>4.5	9	8
p Value	0.0781	
On Day 30th follow up visit		
<4.5	23	31
>4.5	13	5
p Value	0.029*	
On Day 60th follow up visit		
<4.5	24	33
>4.5	12	3
p Value	0.009*	
Nugent's scoring[5] at time of enrollment		
<7	0	0
>7	36	36
p Value	Not applicable	
On Day 8th follow up visit		
<7	32	34
>7	4	2
p Value	0.737	
On Day 30th follow up visit		
<7	19	30
>7	17	6
p Value	0.006*	
On Day 60th follow up visit		
<7	19	2
>7	17	34
p Value	<0.001*	

Table III: Labarotory parameters

The table above presents findings from the examination of vaginal discharge, including pH measurement, the Whiff test (addition of potassium hydroxide to detect fishy odor), microscopic identification of clue cells for Amsel's criteria[3] and Gram staining for Nugent scoring.[5]

Vaginal pH: At enrollment, all participants had a vaginal pH >4.5. By the second follow-up on day 8th, both groups showed improvement, with Group B demonstrating a more significant reduction in pH (p = 0.0781), though this was not statistically significant. By day 60, Group B had a significantly lower pH compared to Group A (p = 0.009).

Whiff Test: All participants tested positive at enrollment. By day 8, Group B showed a more notable reduction in positive Whiff test results (p = 0.045), which was statistically significant. At the final follow-up on day 60, Group B continued to show better improvement, though the difference was not statistically significant (p = 0.966).

Nugent Score: Both groups had similar scores at enrollment. By day 8, Group B showed greater improvement (p = 0.737), though this was not statistically significant. However, this difference became statistically significant at the subsequent follow-ups on day 30 (p = 0.006) and day 60 (p < 0.001). Mean with student T-test used for data analysis.

DISCUSSION

The prevalence of bacterial vaginosis (BV) in the present study was found to be 25.73%, which is comparable to the findings of Ranjit E. et al[8] who reported a prevalence of 24.4%, Recine N. et al[9] also reported a prevalence of 24 %, similarly, Peebles K. et al[10] concluded a prevalence of 23% in Central Asia. Singh et al[11] reported a slightly higher prevalence of 31.5%, while Bitew A. et al[12] documented a prevalence of 39.5%, possibly due to the inclusion of pregnant women with HIV as a study population. Singh A. et al and Singh S et al reported 20% a prevalence of 20% may be due to geographical variation.[13,14] Regarding participant demographics, the mean age in Group A was 33.36 ± 6.79 years, and in Group B, it was 32 ± 6.02 years. Singh et al reported a mean age of 29.5 ± 5.5 years in their study population.[11] This slight age difference is unlikely to have significantly impacted the study outcomes, as all participants were within the reproductive age range (15–49 years), where BV is most commonly observed. Additionally, the p-value of 0.336 indicates that the age difference between groups was not statistically significant.

Regarding parity, Group A had a higher mean parity (3.31± 1.36) compared to Group B (2.14 ± 1.01). Parity is a known risk factor for bacterial vaginosis, as higher parity is associated with changes in the vaginal flora, increasing susceptibility to infections, as reported by Ajani et al, Verstraelen H et al, Thoma ME et al., and Gibbs RS et al.[15,16,17,18] However, the study design included randomization, which likely helped to balance this factor between the groups. Conversely, studies by Kenyon C et al, Schmidt RM et al and Bautista C et al[19,20,21] reported that parity does not significantly affect BV prevalence. Similarly, Peebles K et al and Bradshaw CS et al[10,22] concluded that parity differences are unlikely to meaningfully impact study outcomes, especially when groups are randomized and other risk factors such as sexual activity and hygiene are balanced. In the present study, the p-value for parity was 0.078, indicating that the difference was not statistically significant. Regarding the menstrual cycle, most participants in both groups had a regular cycle. Hormonal fluctuations during the menstrual cycle can influence vaginal pH and microbiota, potentially affecting BV recurrence. However, as menstrual cycle regularity was similar between the two groups in this study, this factor is unlikely to have biased the results, as also reported by Russo R et al.[23]

In terms of education level, Group A had a slightly lower education level compared to Group B. Education can influence health-seeking behavior, understanding of treatment importance, and awareness of preventive measures, as reported by Bitew A et al. While lower education levels may contribute to poor health outcomes in some studies, the minimal difference in education levels in the present study is unlikely to have significantly impacted the results.[12]

Most participants in both groups were from rural areas, which aligns with the study setting, where a significant portion of the population resides in rural regions. According to Vicariotto F et al, limited healthcare access in rural areas could influence BV prevalence and recurrence rates. However, since both groups had similar distributions, this factor was controlled for in the present study.[24]

Both groups exhibited similar occupational profiles, predominantly comprising housewives, reflecting Nepal's sociocultural context where many women are homemakers. Occupation can influence exposure to bacterial vaginosis (BV) risk factors, such as stress and hygiene practices, as reported by Romeo M et al.[25] However, since both groups were comparable in this regard, occupation is unlikely to have affected the study outcomes. At enrollment, all participants presented with abnormal vaginal discharge, a classical symptom of BV. This aligns with the diagnostic criteria for BV, which include the presence of thin, grayish-white, homogeneous discharge, as reported by Amsel R.et al[3] By the first follow-up visit on day 8th, Group B (metronidazole + probiotics) showed a significant reduction in abnormal discharge compared to Group A (metronidazole alone) (p = 0.013). This suggests that probiotics may enhance the efficacy of metronidazole in resolving BV symptoms by restoring the vaginal microbiome, as similarly reported by Wang Z et al, Recine N et al and Russo R et al.[7,9,23]

However, a study conducted by Hemalatha R. et al[26] did not support early improvement between these groups, possibly due to differences in probiotic strains used. By the second and third follow-up visits on day 30 and day 60, the trend of improvement continued, with Group B consistently showing better outcomes (p = 0.016 and p = 0.089, respectively). However, the difference observed at the longer follow-up (day 60) was not statistically significant compared to the earlier visit on day 30. This aligns with previous studies conducted by Wang Z JM et al, Recine N et al and Bohbo et al[7, 9, 27] which concluded that probiotics effectively maintain a healthy vaginal flora and prevent the overgrowth of pathogenic bacteria over shorter periods. However, Mastromarino P et al failed to demonstrate a significant difference in outcomes between the two groups, possibly due to variability in anaerobic bacterial strains.[28]

At enrollment, all participants presented with foul-smelling vaginal discharge—a classical symptom of bacterial vaginosis (BV)—commonly described as a "fishy odor" caused by amines produced by anaerobic bacteria, as reported by Spiegel CA et al.[4] By the first follow-up visit on day 8, both groups showed improvement, with Group B demonstrating a slightly greater reduction in odor (p = 0.555), though this difference was not statistically significant. This improvement is likely attributable to the combined effect of metronidazole, which targets anaerobic bacteria, and probiotics, which help restore the vaginal microbiome. These findings are consistent with studies by Recine N et al, Vicariotto F et al, and Anukam et al.[7,24,29] However, studies by Hemalatha R et al and Mastromarino et al[26,28] did not show significant improvement in vaginal odor, possibly due to differences in the anaerobic bacterial strains used or variations in probiotic formulations. By the second follow-up visit on day 60, the difference between the groups became more pronounced, with Group B showing better outcomes (p = 0.230); however, this result also failed to reach statistical significance.

This suggests that probiotics may have a sustained effect in preventing the recurrence of BV symptoms, including foul-smelling discharge, as reported by Recine R et al, Bohbot JM et al, and Reznichenko H et al.[9,27,30] However, Mastromarino et al[28] failed to demonstrate a similar effect, possibly due to variations in anaerobic bacterial strains within the study population and the use of different probiotic strains. At enrollment, all participants had a vaginal pH greater than 4.5, which is a diagnostic criterion for BV, as reported by Nugent et al. A high vaginal pH indicates a reduction in lactobacilli, which are essential for maintaining an acidic vaginal environment. By the first follow-up on day 8, both groups showed improvement, with Group B exhibiting a more notable reduction in pH (p = 0.0781), though this difference did not reach statistical significance.

This aligns with the role of probiotics in restoring lactobacilli and lowering vaginal pH, as similarly reported by, Recine N et al, Anukam et al, and Muñoz-Cruz MR et al.[9, 29, 31] However, studies by Hemalatha R et al and Mastromarino P et al failed to demonstrate a similar effect, possibly due to differences in the probiotic strains used for BV management.[26, 28] By the second visit on Day 60, Group B had a significantly lower pH compared to Group A (p = 0.009). This finding supports the use of probiotics as a long-term strategy to maintain a healthy vaginal pH and prevent BV recurrence, as reported by Bradshaw CS et al.[22]

At enrollment, all participants had a positive Whiff test, indicating the presence of amines and confirming the diagnosis of BV, as reported by Muñoz-Cruz MR et al.[31] By the first follow-up visit on day 8, Group B showed a more significant reduction in positive Whiff tests. This was accompanied by a reduction in vaginal pH to < 4.5, suggesting improved vaginal health. According to Nugent RP et al[5] this improvement may reflect the enhanced effectiveness of the combined treatment with metronidazole and probiotics in reducing the production of amines by anaerobic bacteria. By the second and third follow-up visits on day 30 and day 60, respectively, Group B continued to show greater improvement (p = 0.029 and p = 0.009), with these differences found to be statistically significant. These findings further support the potential role of probiotics in maintaining a healthy vaginal environment and preventing BV recurrence, as also supported by Nugent RP and Muñoz-Cruz MR et al[5,31]

At enrollment, both groups had similar Nugent scores, indicating comparable severity of BV at baseline. By the first follow-up visit on day 8, Group B showed greater improvement

in Nugent scores (p = 0.737); however, this difference was not statistically significant. This suggests that probiotics may aid in the restoration of normal vaginal flora, as reflected by the Nugent score—a microscopic assessment of vaginal bacteria—supported by Nugent RP et al.[5] By the second follow-up visit on day 60, Group B had a significantly lower Nugent score compared to Group A (p < 0.001). This finding aligns with previous studies conducted by Muñoz-Cruz MR et al[31], demonstrating that probiotics help maintain a healthy vaginal microbiome and reduce the likelihood of BV recurrence. Throughout all follow-up visits, Group B consistently showed lower recurrence rates compared to Group A.

This is a critical observation, as recurrent BV remains a major clinical challenge, with up to 50% of women experiencing recurrence within 12 months of treatment, as reported by Muñoz-Cruz MR et al.[31] The addition of probiotics to metronidazole therapy appears to reduce the risk of recurrence restoring and sustaining a healthy vaginal microbiome, as supported by Bradshaw CS et al.[22]

Clinical Implications:

The results of this study suggest that probiotics should be considered as an adjunct to metronidazole therapy in the prevention of recurrent BV. Probiotics help restore the vaginal microbiome, reduce symptoms, and prevent recurrence, potentially reducing the need for repeated antibiotic courses. This approach may be particularly beneficial in low-resource settings, where access to healthcare is limited, and recurrent BV is a significant burden.

LIMITATIONS

The study had a relatively small sample size (72 participants), which may limit the generalizability of the findings. The follow-up period was limited to 60 days and longer-term studies are needed to assess the sustained benefits of probiotics in preventing BV recurrence.

CONCLUSION

The addition of probiotics to metronidazole significantly prevented the recurrence of bacterial vaginosis, with improvements observed in abnormal vaginal discharge, foul odor, vaginal pH, and Nugent scores. Group B (metronidazole + probiotics) consistently showed a lower recurrence rate.

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