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Original Article

Efficacy of Probiotics with Metronidazole Versus Metronidazole Alone for the Treatment of Bacterial Vaginosis

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Abstract

Objective: To assess the efficacy of probiotics with metronidazole versus metronidazole alone for the treatment of BV

Methods: A quasi-experimental study was carried out at Sir Ganga Ram Hospital in Lahore, from 1st October 2023 to 30th September 2024. The women diagnosed with BV (50 in each group) received either tablet metronidazole 400mg twice daily for 7 days, or the same metronidazole regimen combined with an oral probiotic twice daily for 21 days. All women were evaluated for cure, defined as complete resolution of symptoms (Amsel's criteria ≤ 1), on day 8 and 22 of treatment. Chi-square test was employed to compare the cure rates between the two treatment groups.

Results: Mean age (30.34 ± 8.51 vs. 30.10 ± 7.53 years), BMI (26.01 ± 3.74 vs. 25.80 ± 3.33 kg/m²), and proportions of primiparous (44.0% vs. 48.0%) and multiparous women (56.0% vs. 52.0%) were comparable between groups (all p-values >0.05). The cure rate in metronidazole with probiotics group was significantly higher than in metronidazole alone group at day 8 (46.0% vs. 26.0%, p-value 0.037); and day 22 of treatment (74.0% vs. 50.0%, p-value 0.013). Nausea (8.0% vs. 6.0%), vomiting (4.0% vs. 2.0%), and metallic taste (6.0% vs. 4.0%), were slightly more frequent in metronidazole alone group. Abdominal discomfort (0.0% vs. 4.0%) and allergic reactions (0.0% vs. 4.0%) occurred only in metronidazole with probiotics group. However, no statistically significant differences were found (all p-values >0.05).

Conclusion: Metronidazole combined with oral probiotics was more effective than metronidazole alone, with comparable safety in both groups. These findings support considering combination therapy as a preferred option for managing BV in sexually active women of reproductive age.

Keywords: Bacterial Vaginosis, Gynecology, Metronidazole, Probiotics

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Introduction

Bacterial vaginosis (BV) is caused by a disruption in the normal vaginal microbiota, which is normally dominated by Lactobacillus species. In BV, pathogenic bacteria such as Gardnerella vaginalis, Mobiluncus spp., Prevotella spp., and Atopobium spp. proliferate, forming a polymicrobial biofilm.[1,2] This shift reduces antimicrobial compounds from Lactobacilli, leading to elevated vaginal pH and lower lactic acid levels.[3] BV is a frequent vaginal condition in reproductive-age women, with a 59.7% prevalence in Pakistan.[4] It typically presents with a fishy odor and grey-white or milky discharge. Factors like douching, pregnancy, smoking, multiple partners, and intrauterine devices can disrupt vaginal microbiota and contribute to BV.[5,6] Its complications include increased risk of preterm birth, membrane rupture, chorioamnionitis, miscarriage, infertility, endometritis, HIV infection, and urinary tract infections.[2]

The primary treatment for BV involves antibiotics, most commonly metronidazole, administered orally or as a vaginal gel; alternatives include clindamycin and tinidazole.[6] Although initial cure rates range from 70-80% after one month, recurrence remains a major challenge, with rates reaching 40% at three months and up to 60% at six months. This high relapse rate is largely attributed to the inability of antibiotics to fully eliminate biofilm-

associated bacteria and their failure to restore the protective vaginal microbiota, leading to repeated treatments and increased risk of antibiotic resistance.[7] Given these limitations, there is growing interest in adjunctive therapies that not only target pathogenic bacteria but also promote microbiota restoration. Probiotics, particularly Lactobacilli, have shown promise in this regard.[8] These beneficial bacteria contribute to vaginal health by producing antimicrobial compounds, restoring pH balance, disrupting biofilms, and preventing pathogen colonization. They may also enhance mucosal immunity and inhibit pathogen adhesion through collagen-binding biosurfactants. Importantly, long-term probiotic use does not contribute to antibiotic resistance, making them a sustainable therapeutic option.[9]

Clinical evidence supports the potential of combining probiotics with antibiotics to improve treatment outcomes. An RCT study found that combination of probiotics with antibiotic therapy demonstrated a significantly higher cure rate than antibiotics alone (83.3% vs. 36.6%; p-value <0.001).[6] In contrast, another RCT study reported that probiotics containing Lactobacilli alongside oral metronidazole were more effective (64.3% vs. 40%; p-value 0.272) than metronidazole alone, but the difference was not significant.[10] Differently, a study showed that application of Lactin-V following vaginal metronidazole significantly reduced recurrence rate of BV (30.0% vs. 45.0%; p-value 0.01) compared to placebo.[11]

The review of literature showed that BV is usually treated with metronidazole alone, but increasing antibiotic resistance has raised concerns about the long-term effectiveness of this conventional treatment. In addition, metronidazole alone does not restore the normal vaginal microbiota, which often leads to high recurrence rates. The RCT studies showed that probiotics, especially those containing Lactobacillus spp., may help recover vaginal flora and reduce recurrence. However, there are differences across studies regarding types of probiotics used, administration methods, efficacy and safety profiles. For these limitations and challenges, this study compared the effectiveness of probiotics with metronidazole versus metronidazole alone in the treatment of BV.

Methods

This quasi-experimental research was conducted in the Obstetrics and Gynecology unit at Sir Ganga Ram Hospital, Lahore, from 1st October 2023 to 30th September 2024. The study received ethical approval (No. 54-MS-Gynaecology/IRB dated 5th September 2023) from the Institutional Review Board (IRB) of Fatima Jinnah Medical University, Lahore. All volunteer participants provided informed consent.

A total of 100 women with BV were enrolled from outpatient department (OPD) Obstetrics and Gynecology by using non-probability consecutive sampling method. Other inclusion criteria were sexually active women, and of age 18-45 years. Exclusion criteria were pregnant women, breastfeeding mothers, abnormal uterine bleeding (AUB), urinary tract infections (UTIs), diabetes mellitus (DM), or malignancy, women having history of gastrointestinal tract diseases or previous surgery, women using intrauterine devices, had history of vaginal douching, or unprotected sexual intercourse within last 24 hours or on antibiotic therapy within two weeks or hypersensitive to trial medications.

Bacterial vaginosis (BV) was diagnosed when a woman met at least three of the four Amsel's criteria: (1) thin, white, homogeneous vaginal discharge; (2) vaginal pH > 4.5; (3) a fishy odor upon addition of 10% KOH (whiff test); and (4) clue cells observed on microscopic examination of a saline wet mount.[10] All women were placed in the lithotomy position and examined for vaginal discharge using a non-lubricated speculum. A homogeneous milky white discharge observed during speculum examination was considered a positive finding. Vaginal pH was assessed by placing pH paper directly on the vaginal wall. The whiff test was performed by mixing vaginal discharge collected with a sterile swab with a drop of 10% potassium hydroxide in a test tube. The presence of a fishy amine odor was considered a positive result. For microscopic analysis, vaginal discharge was collected using a sterile swab stick, spread on a glass slide, and mixed with a drop of 0.9% normal saline. This wet mount was examined for clue cells, which were identified as vaginal squamous epithelial cells heavily coated with bacteria, obscuring the peripheral borders.

The sample size was calculated using 83.3% effectiveness in antibiotic combined with probiotic group and 36.6% in antibiotic alone group,[6] 95% power of study, 99% confidence level, and 10% expected dropout. Patients were allocated in a 1:1 into two study groups i.e. A Group and B Group. The women in A Group (n=50) were given Tab metronidazole 400 mg twice daily for 7 days. While, the women in Group B (n=50) were given Tab metronidazole 400 mg twice daily for 7 days and oral probiotic capsule containing Lacticaseibacillus rhamnosus GR-1 and Limosilactobacillus reuteri RC-14 twice daily for 21 days. Probiotics were given 1-2 hours after metronidazole intake.

Before intervention, data including age, BMI, and parity were noted on a research proforma. All women were monitored up to three weeks of treatment and advised to avoid vaginal douching and unprotected intercourse during the course of treatment. The women were assessed at day-8 and day-22 for the presence of BV using

Amsel's criteria. All four parameters were rechecked and noted that how many of the patients have been cured of the disease in both groups. The cure rate defined as the proportion of patients who experience complete resolution of symptoms and have no evidence of BV (Amsel's criteria ≤ 1) on follow up testing after completing a course of treatment.

Statistical Package for Social Sciences (SPSS) version 25.0 was used for data entry and statistical analysis. Quantitative variables including age and BMI were presented as mean and standard deviation. Independent sample t-test used to compare the means between the groups. Qualitative variables like age categories, BMI classes, parity, and efficacy were described as frequency and percentages. Chi-square test was used to compare cure rates between groups, with a p-value ≤0.05 considered statistically significant.

Results

Table 1 shows that means of age (30.34 ± 8.51 vs. 30.10 ± 7.53 years, p-value 0.822), and BMI (26.01 ± 3.74 vs. 25.80 ± 3.33 Kg/m2, p-value 0.757) were comparable between the two study groups. The proportions of age categories (p-value 0.826), BMI classes (p-value 0.626) and parity (p-value 0.688) were also similar in both groups.

Table 1: *Baseline characteristics of study population stratified by intervention*

		Metronidazole Alone (n=50)	Metronidazole with Probiotics (n=50)	p-value
Age (years)		30.34 ± 8.51	30.10 ± 7.53	0.822 *
	18 – 35	35 (70.0%)	36 (72.0%)	0.826 **
	36 – 45	15 (30.0%)	14 (28.0%)	
BMI (Kg/m^2)		26.01 ± 3.74	25.80 ± 3.33	0.757 *
	Normal weight	17 (34.0%)	16 (32.0%)	0.626 **
	Overweight	24 (48.0%)	28 (56.0%)	
	Obese	09 (18.0%)	06 (12.0%)	
Parity	Primiparous	22 (44.0%)	24 (48.0%)	0.688 **
	Multiparous	28 (56.0%)	26 (52.0%)	

**Independent sample t -test, **Chi square test, significant p -value ≤0.05*

Table 2 shows that 13 (26.0%) women in metronidazole alone group and 23 (46.0%) in metronidazole with probiotics group were cured at day 8 of treatment, and this difference was statistically significant (p-value 0.037). The cure rate was further improved across both groups (25, 50.0% vs. 37, 74.0%) at day 22, and a statistically significant difference was observed, as indicated by the p-value 0.013.

Table 2: *Efficacy of probiotics with metronidazole versus metronidazole*

Variable		Metronidazole Alone (n=50)	Metronidazole with Probiotics (n=50)	p-value
Efficacy at day-8	Cured	13 (26.0%)	23 (46.0%)	0.037 **
	Not cured	37 (74.0%)	27 (54.0%)	
Efficacy at day-22	Cured	25 (50.0%)	37 (74.0%)	0.013 **
	Not cured	25 (50.0%)	13 (26.0%)	

***Chi square test, significant p -value ≤0.05*

Figure 1 shows that incidence of nausea (4, 8.0% vs. 3, 6.0%), vomiting (2, 4.0% vs. 1, 2.0%), metallic taste (3, 6.0% vs. 2, 4.0%), and bloating (4, 8.0% vs. 3, 6.0%) was slightly higher in metronidazole alone group. Abdominal discomfort (0, 0.0% vs. 2, 4.0%) and allergic reaction (0, 0.0% vs. 2, 4.0%) were observed only in metronidazole with probiotics group. However, these differences between the two groups remained insignificant (all p-values >0.05).

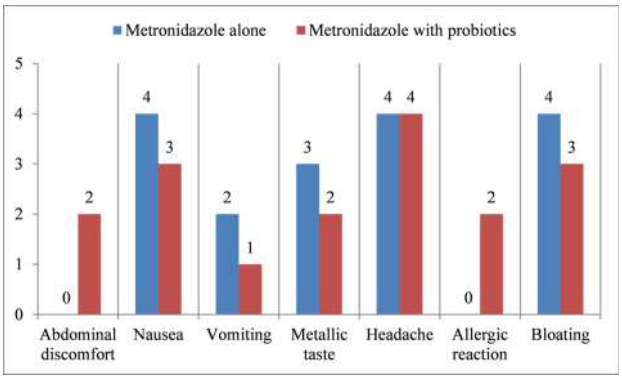

Figure 1: *Incidence of sign and symptoms in both groups*

Discussion

BV is a common infection caused by a disruption in the balance of normal vaginal bacteria, impacting millions of women worldwide.[1] It is usually treated with metronidazole alone, but increasing antibiotic resistance has raised concerns about the long-term effectiveness of this conventional treatment.[12] In addition, metronidazole alone does not restore the normal vaginal microbiota, which often leads to high recurrence rates.[9] These limitations have prompted interest in combining it with probiotics to improve outcomes. In the present study, the combination of metronidazole with oral probiotics demonstrated greater efficacy in women with BV compared to metronidazole alone. These findings are in

agreement with existing national and international literature. In a systematic review and meta-analysis, Ma and colleagues demonstrated that the combined use of antibiotic therapy alongside vaginal administration of Lactobacillus probiotics was an effective approach for improving the clinical symptoms associated with BV, while also significantly reducing the chances of its recurrence.[13] Likewise, Arooj et al. reported that combination of probiotics with antibiotic therapy demonstrated a significantly higher cure rate than antibiotics alone (83.3% vs. 36.6%; p-value <0.001).[6] Similarly, the present study observed a significantly greater cure rate in probiotics group than in metronidazole alone group (74.0% vs. 50.0%, p-value 0.013).

Few other studies from Pakistan evaluated the efficacy of probiotics and metronidazole using different combination therapies, administration routes or outcomes. In an RCT study from Quetta, Baloch and colleagues evaluated the effectiveness of intravaginal probiotics versus intravaginal metronidazole in the treatment of BV. Intravaginal probiotics demonstrated greater successful treatment than intravaginal metronidazole (90.9% vs. 60.6%, p-value 0.004). The study concluded that Intravaginal probiotics had better efficacy than metronidazole in treating BV.[14] In an RCT study from Multan, Ashraf and co-investigators also assessed the impact of probiotics with antibiotic treatment for BV. The group receiving both probiotics and antibiotics showed a significantly lower recurrence rate (8.9%) compared to the antibiotics-only group (21.4%). This difference was statistically significant (p-value <0.05). The findings suggested that probiotics improved long-term BV outcomes by supporting healthy vaginal flora.[15] In a study from Peshawar, Heema et al. compared the efficacy of oral and vaginal metronidazole for the treatment of BV. Therapeutic cure rate was significantly higher in vaginal metronidazole as compared to oral metronidazole (92.5% vs. 85.8%, p-value 0.01). The study concluded that metronidazole applied as a vaginal gel demonstrated greater effectiveness in treating BV compared to its oral administration.[16]

Metronidazole antibiotic therapy is associated with mild to moderate side effects including nausea, vomiting and metallic taste.[17] On the other hand, probiotics are generally considered as safe adjunct treatment for BV and are linked to fewer side effects.[18] Chen et al., in a systematic review and meta-analysis, concluded that probiotics may have a beneficial role in treating BV. However, further research is needed to confirm these findings. In addition, the therapeutic effect of probiotics varies with the administration route and dosage of probiotics.[19] In the present study, low incidence of adverse events including nausea (8.0% vs. 6.0%), vomiting (4.0% vs. 2.0%), metallic taste (6.0% vs. 4.0%), and abdominal discomfort (0.0% vs. 4.0%) with insignificant difference between probiotics with metronidazole and metronidazole alone groups also indicate that probiotics and metronidazole are safe to treat BV.

The study has following limitations: Its single-center design limits generalizability, non-randomized treatment allocation introduces potential bias, and the short follow-up may miss long-term outcomes. Nevertheless, the study provides valuable insights into the comparative effectiveness of treatment modalities for BV.

Conclusion:

The combination of metronidazole with oral probiotics demonstrated greater efficacy in women with BV compared to metronidazole alone. Mild side effects were observed in both groups, but the differences were not statistically significant. These findings suggest that the adjunctive use of probiotics with metronidazole may offer a more effective and safe therapeutic approach for BV in sexually active women of reproductive age.

Ethical Approval: The IRB/EC approved this study via letter no. MS/2020-FJMU-0916 dated September 05, 2023.

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Authors' Contribution

SA: Conception.

MT, NA: Design of the work.

MJ, QS, SK: Data acquisition, analysis, or interpretation.

MJ, QS, SK, MT: Draft the work.

SA, NA: Review critically for important intellectual content.

All authors approve the version to be published.

All authors agree to be accountable for all aspects of the work.

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