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Research Article

**SAFETY AND EFFICACY OF COMBINED ANTIBIOTIC AND
PROBIOTIC THERAPY IN TREATMENT OF BACTERIAL
VAGINOSIS**Fakharunissa Waheed¹, Roshan Ara Kazi² and Qamarunissa Muhabat³Dept. of Obstetrics & Gynecology – Indus Medical College, T.M.K^{1,2},Dept. of Obstetrics & Gynecology – Aga Khan University Hospital, Karachi³

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Abstract:

Background: Bacterial vaginosis is a common condition and the associated disease burden is rising every year. As successful as the traditional antibiotic is, supplementation with modern approach may help lessen the disease burden. One such approach is oral or vaginal instillation of probiotic which stems from the observed dominance of lactobacilli in healthy vaginal microbiota and its depletion in bacterial vaginosis (BV).

Objective: To determine the safety and efficacy of combined antibiotic and probiotic therapy in the management of bacterial vaginosis.

Methodology: This prospective cohort was conducted upon a sample of 100 premenopausal women diagnosed with BV. The study subjects were treated with oral metronidazole (500 mg) twice daily from days 1 to 7, and randomized to receive oral probiotic (lactobacillus) or placebo twice daily from days 1 to 30. Primary outcome was cure of BV as determined by normal Nugent score, negative sialidase test and no symptoms or signs of BV at day 30. The data obtained was recorded onto a structured questionnaire and analyzed using SPSS v.21 & Microsoft Excel 2016.

Results: The mean age of the women mothers stood at 33 (SD ± 6). The success (achievement of cure of BV as determined by normal Nugent score, absence of clue cells, negative sialidase test, no symptoms or signs and no discharge or odor at day 30) rate of the treatment stood at 88% for the combined treatment group and 40% for the antibiotic/placebo group ($p < 0.001$).

Conclusion: After careful consideration, it can be concluded that combined therapy is safe and more efficacious than lone antibiotic. Thus use of probiotics should be routinely employed for the treatment of BV.

Key Words: Bacterial Vaginosis, Lactobacillus, Metronidazole, Probiotic & Antimicrobial.

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INTRODUCTION:

Bacterial vaginosis (BV) is one of most frequently vaginal infections among women, with prevalence ranges from 5 % in Australia to 58.3 % in sub-Saharan Africa. ^[1, 2] Evidence from the studies have shown that BV is regarded as a mild disease but even when asymptomatic it has been associated with some complication, such as a high incidence of endometritis or pelvic inflammatory disease (PID), and it may also leading to premature rupture of the membranes, abortion and premature delivery. ^[3-5]

Moreover, either symptomatic or asymptomatic BV was strongly associated with many sexually transmitted infections (STIs), including Chlamydia trachomatis, Neisseria gonorrhoeae, HSV-1 and 2 infections, and an increased high risk of HIV-1 transmission. ^[6-8] A meta-analysis has also shown a positive association between BV and uterine cervical human papillomavirus (HPV) infection. ^[9]

In recent decades, many pharmacologic interventions have been used to treat the development of BV. Among these interventions, antibiotic therapy is the main measure to treat BV. The mechanism of the dramatic treatment effects of antimicrobials might be through directed at altering the abnormal flora by killing Gardnerella vaginalis and some anaerobes.

This change is accompanied by the disappearance of signs and symptoms characteristic of BV. In spite of clindamycin preparations and metronidazole were effective for BV. However, both of them often associated with failure and high rates of recurrences, as well as side effects, including drug resistance, are also common ^[10, 11]. Thus, the best strategies to treat BV remain to be established.

Although the pathogenesis of BV is not clearly understood, a number of studies have demonstrated that BV has been strongly associated with absence of lactobacilli and the presence of G. vaginalis and some anaerobes (such as Prevotella species, and Atopobium species). The overgrowth of these bacteria and the subsequent suppression of lactobacilli leads to a rise in pH and disorder of the ecological environment. ^[12]

Further research has demonstrated that some bacterial biofilms are increasingly identified as a source of many recalcitrant bacterial infections. Swidsinski et al. ^[13] have documented that BV is not only an overgrowth condition, but also involves the presence of a dense, adherent bacterial biofilm on the vaginal mucosa, which is an obligate finding in bacterial

vaginosis, and is absent among healthy control subjects.

The biofilm work as a prominent virulence mechanism that enhances bacterial attachment to epithelial surfaces, allows bacteria to reach much higher concentrations than in luminal fluids, and, as an immune subversion mechanism, prevents antimicrobial agents to reach the bacteria. ^[14]

This may explain the apparent antibiotics resistance in the treatment of BV. Probiotics, as live microorganisms, have demonstrated clinical utility in reducing, or treating, or both, urogenital infections (UTIs). ^[15, 16] In vitro studies have shown that probiotics Lactobacillus reuteri RC-14 and L. rhamnosus GR-1 are able to incorporate themselves into pathogenic biofilms and cause disruption and some killing. ^[17, 18]

This process may partly explain why lactobacilli can reduce the recurrence of UTIs and induce a return to a normal microbiota from a BV state. Recently, an increasing number of randomized controlled trials (RCTs) on the efficacy of probiotics supplementation on the treatment of BV have been completed; whereas, the effectiveness of probiotics for treatment of BV is remains inconclusive.

METHODOLOGY:

This prospective cohort was conducted upon a sample of 100 premenopausal women diagnosed with BV. The study subjects were treated with oral metronidazole (500 mg) twice daily from days 1 to 7, and randomized to receive oral probiotic (lactobacillus) or placebo twice daily from days 1 to 30. Primary outcome was cure of BV as determined by normal Nugent score, negative sialidase test and no symptoms or signs of BV at day 30. The data obtained was recorded onto a structured questionnaire and analyzed using SPSS v.21 & Microsoft Excel 2016.

RESULTS:

The cumulative mean age of the women mothers stood at 33 (SD ± 6).

Maternal Age Group	Frequency
Up to 20 years	03
21 to 25 years	20
25 to 30 years	27
31 to 35 years	39
36 years and above	11

The success (achievement of cure of BV as determined by normal Nugent score, absence of clue cells, negative sialidase test, no symptoms or signs and no discharge or odor at day 30) rate of the treatment stood at 88% for the combined treatment group and 40% for the antibiotic/placebo group ($p < 0.001$).

Primary Outcome	Combined Therapy	Lone Antibiotic Therapy
Achieved*	88%	40%
Not Achieved*	12%	60%

*: Within study duration i.e. 30 days

DISCUSSION:

This study demonstrated that oral probiotic treatment augmented the efficacious treatment of BV with metronidazole. A number of studies have assessed various antibiotic protocols for the treatment of BV in Caucasian, African-American, European, Asian and Mexican women, with failure rates as high as 39%.^[19] Twice daily 500 mg metronidazole for 7 days is a standard treatment for BV, but no study on the efficacy of its use in Pakistani women has been reported.

Thus, it is difficult to assess why only 40% of subjects receiving antibiotic and placebo were cured of the condition. One explanation could be that BV is more difficult to eradicate in Pakistani women, for whatever reason. Under such a scenario, the 88% cure with antimicrobial drug and probiotic is particularly impressive. If intermediate Nugent and sialidase findings are included as cures, then the failure rate for antibiotic/placebo is 30%, which is more consistent with the literature. However, under that scenario, the antibiotic/probiotic success rate would be 100%, again 39% higher than most studies with antibiotic alone.^[20]

This study was not designed to understand the mechanisms of action of the therapies. However, it is known that antibiotics function by killing the pathogens, while probiotics are known to inhibit urogenital pathogen growth and adhesion,^[21] displace BV organisms,^[22] downregulate vaginal inflammation and enhance immune defenses all of which could explain the effectiveness of the combined treatment used in this study. The concept of replenishing the vaginal microbiota with exogenous probiotic lactobacilli has been considered for the past 25 or so years.

Under normal circumstances, the patient's own lactobacilli would return after antibiotic therapy and colonize the vagina, thereby conferring some protection from infection, as seen in the placebo group

here. The additional use of probiotics is designed to enhance this process, and as noted in the present study, this leads to improvements in disease management and recovery. Only one previous study has tested the efficacy of probiotics combined with antibiotics for BV.^[23]

CONCLUSION:

After careful consideration, it can be concluded that combined therapy is safe and more efficacious than lone antibiotic. Thus, use of probiotics should be routinely employed for the treatment of BV.

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