

A COMPARATIVE OBSERVATIONAL STUDY ON EFFECTIVENESS OF PROBIOTICS AND ANTIBIOTICS IN BACTERIAL VAGINOSIS**Sowmya B¹, Dattatreya Kar², Rajashree Panigrahy³, Basanta Kumar Pati^{1*}**¹Department of OBG, IMS & SUM Hospital, Siksha O Anusandhan (Deemed to be University), Bhubaneswar-751003, Odisha, India.²Department of Medical Research, IMS & SUM Hospital, Siksha O Anusandhan (Deemed to be University), Bhubaneswar-751003, Odisha, India.³Department of Microbiology, IMS & SUM Hospital, Siksha O Anusandhan (Deemed to be University), Bhubaneswar-751003, Odisha, India.

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Email: basantapati@soa.ac.in**ABSTRACT**

Introduction: Bacterial vaginosis is a common vaginal dysbiosis in women of reproductive age. Bacterial vaginosis is a dysbiosis characterized by a reduction of Lactobacillus species, such as *L. crispatus*, *L. gasseri*, and *L. Jensenii*. Anti-microbial resistance of BV pathogens and low long-term cure rates have been increasing in the few years. **Aim:** Probiotics are proposed as an alternative treatment for BV applying live micro-organisms with the capacity to confer health benefits to the patient. **Methods:** Patients with white discharge per vagina with or without foul smell, and itching visiting Obstetrics and Gynecology OPD are subjected to Amsel criteria. Those test positive for 3 out of 4 are diagnosed to have bacterial vaginosis and were enrolled in the study. **Result:** Highest prevalence of bacterial vaginosis was at the age group of 26-30 years (28%), with the lowest prevalence (16%) above 40 years of age. Among group A (probiotics), 68% and 32% of women were in not working and working groups, respectively, when compared with group B (antibiotics), 64% and 36% of women were in not working and working groups. Nulligravida (28% and 32%), Singleton Pregnancy (32% and 16%) in Group A and Group B. We observed that patients treated with both antibiotics (50%) and probiotics (50%) had similar recurrence rates of BV. **Conclusion:** Hence it would be prudent to prefer probiotics in patients with BV, as they colonize other normal commensals and have similar efficacy as that of antibiotics. The other beneficial factors of probiotics include acceptability to patients and nil side effect profile.

Keywords: Antibiotics; Bacterial Vaginosis; Contraceptives; Probiotics**INTRODUCTION**

Bacterial Vaginosis (BV) is a polymicrobial disorder characterized by altered normal vaginal flora, with loss of Lactobacillus species and predominated by Gardnerella species, Prevotella species, and Atopobium species, etc., affecting mainly the women of reproductive age group (Melo et al., 2008). The prevalence of Bacterial Vaginosis ranges between 5% - 58% of women globally highest in Southern Africa, and low in western Europe (DiFonzo and Bordia, 1998; Melo et al., 2008). A population-based prevalence study by Bhalla et al. (2007) in

Delhi found that the highest prevalence was found in the urban slum (38.6%), rural (28.8%), and urban community (25.4%) (Bhalla et al., 2007).

The overall reproductive health of the women is depicted by the vaginal health which is influenced by varying extraneous and native factors which include medications, hormonal changes, stress conditions, cigarette smoking, black ethnicity, high use of vaginal douches, early age at first intercourse, unprotected sexual intercourse and so on (Cherpes et al., 2008; Schlosser and Mirowski, 2010; Waigwa et al., 2018; Seña et al., 2021). Also, Changes in vaginal pH during

different phases of the menstrual cycle make it more prone during menstruation (Eschenbach et al., 2000).

The shift in the vaginal microbiota allowing the overgrowth of pathogens has to be heralded by considerable disturbances in the *Lactobacillus* population. The involvement of Bacteriophages in the etiology explains the higher recurrence rate in women/partners treated by antibiotics (Figure 1) (Pavlova et al., 1997; Blackwell, 1999).

Internationally, BV has been evaluated that, increase in the risk of HIV transmission 2-4 fold (Taha et al., 1998). It has also been shown that BV increases the risk of obstetrical complications which includes preterm labor and delivery, chorioamnionitis, and post-cesarean endometritis (Sweet, 2000; Ugwumadu, 2002; Anahtar, 2015; McClelland et al., 2018). Indeed many cases were found to be asymptomatic. Among symptomatic individuals, the most commonly noted include profuse vaginal discharge, rotten fish vaginal odor, and pelvic pain (Koumans et al., 2007; Narasimha Rao and Chandini, 2017). The recent guidelines given by Centers for Disease Control and Prevention for the treatment of symptomatic individuals includes, metronidazole 2g single dose or 400mg twice a day for five days orally a more effective regimen. Alternatives include metronidazole gel, tinidazole 1g/2g oral dose, clindamycin cream/ tablets/ ovules (Workowski, 2015; Amegashie et al., 2017; Pang et al., 2018).

Pavlova et al also speculated that these exogenous resistant lactobacilli would give an advantage over the endogenous vaginal lactobacilli, allowing long-term colonization (Pavlova et al., 1997). Many Randomized trials have come suggesting Probiotics as an alternate treatment to BV by enhancing the concentrations of habitual microflora. These are the live microorganisms when introduced in sufficient amounts offers health benefit to the host. Apart from only probiotics, the

mixture of both prebiotics and probiotics practically add to the functional attributes of strains (Brocklehurst et al., 2013; Sheehy et al., 2015). The present study aimed to evaluate the effectiveness of probiotics and antibiotics in bacterial vaginosis.

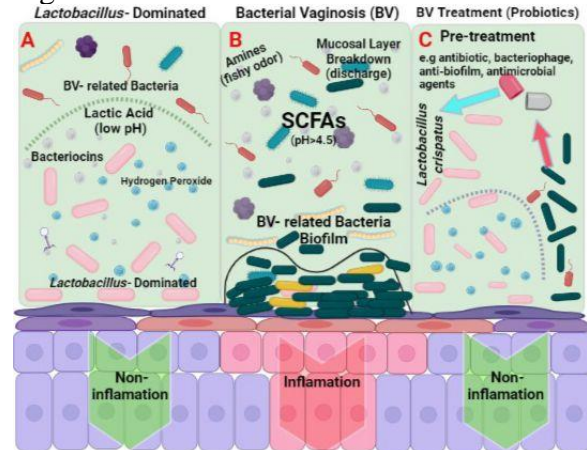


Figure 1. Diagrammatical representation of the cause of bacterial vaginosis (BV) and its treatment. This figure was created with biorender.com (Accessed on 24 November 2022)

METHODS

A prospective comparative observational study was conducted at the Department of Obstetrics and Gynecology, in collaboration with the Department of Microbiology of IMS & SUM Hospital, Bhubaneswar. This study protocol was approved with Ref.no/DMR/IMS.SH/SOA/180379 by the Ethical Committee and Review Board of the institution for rights and safety of the research subjects. Written informed consent was taken from all the study participants.

As many as 414 patients with symptoms of white discharge per vagina with or without foul smell, and itching visiting Obstetrics and Gynecology OPD are subjected to Amsel criteria. 126 women who test positive for three out of four are diagnosed to have bacterial vaginosis and were enrolled in the study. Randomized

allocation was done in two groups' i.e. Group A probiotics (50) and Group B antibiotics (50). Non-probability convenient sampling was done and as many as consenting patients attending the O&G OPD were included in the study conducted over 1.5 years. The inclusion criteria are 1. Thin homogenous gray-white vaginal discharge; 2. pH > 4.5; 3. Presence of clue cells; 4. Positive whiff test (Amine test) and the exclusion criteria are 1. Any other active infection; 2. Immunocompromised state; 3. Pregnancy; 4. PID; 5. Cervical erosion or ectropion

After implementing the informed consent process, a detailed patient history and examination were done. A complete history was taken for each study subject in the O&G OPD including: Occupation, Socioeconomic status, Clinical symptoms of BV, Menstrual history, Obstetric history, H/O Contraceptive usages. Past history of Diabetes Mellitus, Tuberculosis, Pelvic Inflammatory Diseases, Immuno compromised state, H/O prolonged steroid intake were also taken into consideration. Personal History like Cigarette smoking, alcohol intake, pan or guthkha intakes were also taken. Family history like presence of diabetes mellitus in partner was also taken for the study.

A detailed general and systemic pelvic examination was done for every patient. On pelvic examination, the normal color and contour of the vagina and cervix, the color and quality of the discharge was noted. Using Litmus paper, pH of the discharge was found. Using three sterile swab sticks, high vaginal sample was taken from the lateral vaginal wall and posterior vaginal fornix for gram stain, culture and sensitivity, 10% KOH for amine test. The samples were placed in a dry and clean container and sent to microbiology laboratory as soon as possible. Additional investigations including complete blood count, erythrocyte sedimentation rate, fasting and post prandial blood sugar for both partners to exclude other active infections and immuno-compromised state

was also done. Once the diagnosis of bacterial vaginosis was made using Amsel criteria, patients were being treated with antibiotics or probiotics or antibiotics and probiotics in O&G department. Patients who were treated with only vaginal probiotics (Evanew, Zuventus pharmaceuticals) starting on Day 8 of menstrual cycle to Day 16 at bedtime for three months and only antibiotics (Tab. Metronidazole 500mg twice daily for seven days, according to CDC) are included in our study. Patients were informed about sexual abstinence and avoidance of vaginal douching during the course of treatment. After treatment, patients were asked to report any new symptoms, regression of existing symptoms and were subjected to pH and response to treatment was noted.

Hemoglobin, packed cell volume, differential count (neutrophils, lymphocytes, monocytes, basophils), total leukocyte count, fasting blood sugar, 2 hr post prandial blood sugar, pH of vaginal swab, amine test, microscopy of vaginal swab (presence of clue cells), vaginal swab culture and sensitivity, colony characteristics for biochemical and enzymatic test and antibiotic susceptibility testing like investigations were performed.

The statistical analyses were carried out using software like Microsoft Excel version 16 and statistical software SPSS version 20.0. Percentage calculation was used to assess all the variations.

RESULT

In our study, we found that highest prevalence of bacterial vaginosis was at the age group of 26-30 years (28%), with lowest prevalence (16%) above 40 years of age, rest being 18% at the age group 21-25 years and 31-35 years, 20% at 36-40 years of age (Table 1). Among group A (probiotics), 68% and 32% of women were in not working and working group, respectively, when compared with group B (antibiotics), 64% and 36% of women were

in not working and working group. Among group A, 68% and 32% of women were in not working and working group, respectively, when compared with group B, 64% and 36% of women were in not working and working group.

We found that 80% of women were in married group and 20% were in unmarried group, 68% in married and 32% of women in unmarried group among Group A and Group B, respectively. In this study, prevalence of bacterial two or more pregnancies, including abortion, of about 40% and 52% in Group A and Group B, respectively, when compared to Nulligravida (28% and 32%), Singleton Pregnancy (32% and 16%) in Group A and Group B. The prevalence of bacterial vaginosis were high in women with regular menstrual cycle of 60% and 84%, when compared with 40% and 16% in women with irregular menstrual cycle, in probiotic and antibiotic group, respectively. Among married group of women, 46% of women were not using any type of contraceptives, while 16.2% were using oral contraceptive pills and 12.6% with intrauterine copper device, 21.6% were using barrier contraceptives. In unmarried 38.5% were not using any method of contraception, while the remaining 61.5% used barrier contraception.

Among 100 women with bacterial vaginosis, 18% had prevalence of diabetes mellitus in married group. No significant history could be documented regarding other predisposing factors for BV. In our study we found few proportions of married women in both probiotic and antibiotic group, had history of husband diagnosed with diabetes mellitus of about 20% and 23.5%, respectively. Unmarried women enrolled in our study did not give any significant history regarding their partner. In our study among 100 BV, 48% of women were moderate anemia, 18% had mild anemia, 2% had severe anemia, while 32% of women had no anemia (Table 1).

In this study, 64% of women had their main complaint as white discharge,

10% had vaginal itching or pain abdomen, while the remaining 16% had both white discharge and itching. Using Nugent score, 72 women were diagnosed with bacterial vaginosis, while 12 were intermediate and 16 were normal flora, respectively (Table 2). In our study, 78 women were positive for whiff test, while the remaining 22 women were negative for whiff test (Table 3). During treatment married women of about 80% and 68% were randomized into Group A and Group B, while only 20% and 32% of unmarried women were randomized into Group A and B, respectively (Table 4). Our study did not find any significant values of remission and recurrence rates among Group A and Group B. In Group A, among married women, 18 had recurrence of symptoms, while 22 had remission of symptoms. In unmarried group, four had recurrence of symptoms, while six had symptom cure after probiotic treatment. In the antibiotic group, 37.5% of unmarried women had recurrence of symptoms while 62.5% of women were free of symptoms; 47% of married women had recurrence while 53% had no recurrence after treatment.

DISCUSSION

In our study among 100 bacterial vaginosis patients, 50 were randomly assigned to receive probiotic treatment (Group - A) and 50 were to get antibiotic treatment (Group - B). In our study the prevalence rate of BV in the age group 21-25 years was found out to be 18%, 26-30 years was 28%, 31-35 years was 18%, 36-40 years was 20%, >40 years was about 16%. Highest prevalence was found between age group of 26-30 years and the lowest prevalence was between the age group >40 years. This was as compared with another study by Vani et al, (2018) which found that the highest prevalence of BV was found in the age group between 28-32 years. Similar study by Ronald et al. showed highest prevalence was among 20-24 years age group (Gray et al., 2009).

Bitew et al. (2021) found that high prevalence of BV was found in 31-35 years.

Table 1. A detailed patient history based on different factors.

Age	Frequency (n)	Percentage (%)		
21-25	18	18%		
26-30	28	28%		
31-35	18	18%		
36-40	20	20%		
>40	16	16%		
Occupation				
Not working	Working			
Group A	34(68%)	16(32%)		
Group B	32(64%)	18(36%)		
Marital Status				
Married	Unmarried			
Group A	40(80%)	10(20%)		
Group B	34(68%)	16(32%)		
No. of Pregnancies				
Nulligravida (0)	No. of Pregnancy (1)		2 or more	
Group A	14(28%)	16(32%)	20(40%)	
Group B	16(32%)	8(16%)	26(52%)	
Menstrual History				
Regular(0)	Irregular(1)			
Group A	30(60%)	20(40%)		
Group B	42(84%)	8(16%)		
Contraceptive Types				
	Married Frequency(n)	Married Percentage (%)	Unmarried Frequency(n)	Unmarried Percentage (%)
No usage(0)	34	45.9%	10	38.5%
OCP (1)	12	16.2%		
Barrier (2)	16	21.6%	16	61.5%
IUCD (3)	12	16.2%		
Medical History				
H/O DM	Frequency (n)	Percentage (%)		
Yes(1)	18	18%		
No(0)	82	82%		
H/O Diabetes Mellitus in Husband/Partner				
	Married	Unmarried		
Group A	20% (diabetic) 80% (nondiabetic)	0		
Group B	23.5% (diabetic) 76.5% (non-diabetic)	0		
Nutritional Status				
Hb	Frequency (n)	Percentage (%)		
>12(0)	32	32%		
11-11.9(1)	18	18%		
8-10.9(2)	48	48%		
<8(3)	2	2%		

Table 2. Nugent Score

Nugent score	0-3(0)	4-6(1)	7-10(2)
Group A	10(20%)	2(4%)	38(76%)
Group B	6(12%)	10(20%)	34(68%)

Table 3. KOH

KOH	Present (1)	Absent(0)
Group A	38	12
Group B	40	10

Table 4. Treatment Percentage

	Married Frequency (n)	Married Percentage (%)	Unmarried Frequency (n)	Unmarried Percentage (%)
Group A	40	80%	10	20%
Group B	34	68%	16	32%

In our study we found that 74% of people were married and the remaining 26% were unmarried. Though many studies had shown significant numbers in married women, presently increasing unprotected sexual activity is on the rise, thus future research should focus on sexually active people rather than focusing on married and unmarried people. 66 women in our study were in not under working group when compared with 34 working women. Bitew et al. (2021) found that 45.8 % among BV were housewives. There are contradictory views among the prevalence of disease in working group and housewives.

Though we did not have significant number of people enrolled in this group, further studies should focus on this point of view, as there is changing socio-cultural and environmental factors such as co habitation, women job empowerment in different sectors, usage of common lavatories probably might increase the disease incidence. Priestley et al. (1997) also found that BV and Candida species were present more during the first week of menstrual cycle. In our study, 60% and 40% had regular and irregular cycle, respectively, in Group A when compared to 84% and 16%. With more regular menstrual cycle, there is decrease in vaginal pH in more number of days, increased usage of vaginal tampons increasing the occurrence of BV.

On comparing our study with Bitew et al. (2021) 18% and 5.3% of women with BV had diabetes mellitus. Many studies have mentioned about high risk of acquisition of HIV, Herpes simplex virus

associated with Bacterial Vaginosis. As we all know India is a diabetic country, we should decrease the incidence of diseases which increases the risk of diabetes mellitus, passing on to next generation. Priestley et al. (1997) found that among nine patients with intermittent BV, all had unprotected sex . Our study did not have any conclusive evidence regarding unprotected sexual intercourse. We suggest more number of people would have been affected, should volunteer for further investigations and treatment. It would be of great use for future researchers toward this group of people.

In our study, we tried to find out people using different types of contraception method. Among which 54% of married women were using either of one type of contraception, which includes 16.2% were using oral contraceptive pills and Intrauterine Copper device, 21.6% of them were using barrier methods . Among 61.5% of unmarried sexually active women using contraceptive methods, everyone utilized barrier method as a choice, as it is available at low cost, easily available. Theories suggest that use of Intrauterine copper device, Oral combined oral contraception might increase the risk of acquiring disease through changes in cervical mucous pattern, thread into vagina another source of ascending infection. Our study wants to throw light regarding the usage of barrier contraceptives, which would not only prevent sexually transmitted disease but prevent localization of pathogenic organisms in vagina without disturbing the local microenvironment 20% of women in Group A and 23.5% of

women in Group B had significant history of diabetes mellitus in the partner, while unmarried group of women were not ready to reveal any history about the partner.

In our study among 100 bacterial vaginosis patients, prevalence of anemia was found out to be 68%, among which 18% were mildly anemic, 48% were moderately anemic, 2% were severely anemic, while 32% were not at all anemic. Hence importance to health in terms of nutritional elements should be taken care of, to prevent other diseases. In a study by Katare et al. (2020), they concluded that cure rate of BV was high in patients taking probiotic treatment (n=42/44) when compared with antibiotic treatment (n=34/46). Contradictorily, our study found no difference in cure rate among both groups (56%). Lin et al. (2021) found significant improvement in color or odor of the vagina, itching, and reduced vaginal discharge in subjects taking probiotics at two and four weeks of treatment.

The recurrence rate of BV in Group A and group B was found to be 44% and also no significant difference in recurrence rate among married (45%) and unmarried people (40%). Faruqui and Chitra (2020) also showed that significant improvements in odor of vaginal discharge, itching, and pH after two weeks and four weeks of treatment. Vani et al. (2018) found that patients treated with probiotics in addition has shown better improvement (9.09% recurrence) than patients treated with only antibiotic group (66.66 % had recurrence). Though our study did not include probiotics and antibiotics treated patients, similar studies shows that probiotics offers significant benefit to patients. Aarti et al. also found no rate of recurrence within three months among patients taking probiotic treatment (Katare et al., 2020). Van de Wijgert et al. (2020) found that intermittent use of both antibiotics and probiotics will reduce the recurrence rate of BV. Ya, Reifer and Miller, (2010) found significant improvement in recurrence rate

(n=9/57) when compared with placebo group (n=27/60).

In our study, 94% and 34% of people had alkaline pH before and after treatment with antibiotics or probiotics group, suggesting significant improvement in vaginal pH. But found no statistical improvement among probiotic (36%) and antibiotic group (32%) after treatment. Bitew et al. (2021) also found four times significant improvement with pH in patients taking probiotic group. Heczko et al. (2015) found improvement in Nugent score and pH after one week of intravaginal probiotic capsule. Faruqui and Chitra (2020) also showed that number of lacobacillus in the vaginal flora had increased after probiotics supplement when compared with antibiotics and probiotics supplements after two and four weeks of treatment.

In our study, 20%, 4%, 76% of them had negative, intermediate, confirmatory score for bacterial vaginosis according to Nugent criteria in Group A when compared to Group B 12%, 20%, 68% had negative, intermediate, confirmatory score, respectively. Though we did not correlate Nugent score before and after treatment with probiotics and antibiotics, many studies have positive results with probiotic treatment.

Lin et al. (2021) found significant improvement in Nugent score in subjects taking probiotics at two and four weeks of treatment. Van de Wijgert et al. (2020) also found more number of Lactobacillus colonization thereby direct improvement in Nugent scoring in group taking metronidazole. Heczko et al. (2015) found improvement in Nugent score after one week of vaginal probiotic capsules (Heczko et al., 2015). Ehrstorm et al. (2010) found high colonization of lactobacillus in patients taking probiotic group of 89% when compared to placebo group (0%). Russo Karadja and De Seta (2019) found oral supplementation of probiotics also increased the vaginal colonization of lactobacillus with

improvement in vaginal odor, discharge and itching. Nugent score also improved after 15 days (Russo, Karadja and De Seta, 2019). Vujic et al. (2013) found significant improvement of 61.5% in vaginal microbiota after 6 weeks of treatment with probiotic capsule when compared with placebo group about 26.9%

Though our study did not have any positive correlation with probiotic group, many studies have found significant improvement in vaginal pH, lactobacilli colonization in vagina, rate of improvement in symptoms, recurrence rate among probiotic supplementation group. The improvement in medical knowledge among public lead to usage of over the counter medications. Use of broad spectrum antibiotics at initial onset of symptoms also has more harm than benefit which includes, depletion of normal commensal bacteria in our body precipitating more pathogenic bacterial entry in all ways possible. Our study concludes in view of using probiotics supplement as a better option to maintain not only a healthy vaginal microbiota, but a healthy living.

CONCLUSIONS

Previously done studies have contradictory findings regarding the recurrence rates and treatment modalities for bacterial vaginosis. In our study, we observed that patients treated with both antibiotics and probiotics had similar recurrence rates of BV.

Today, multi-drug resistance has become a global threat to the inadvertent use of antibiotics as they have the potential to demolish normal commensal bacteria of our body thereby increasing the risk of acquiring other infections. Hence it would be prudent to prefer probiotics in patients with BV, as they colonize other normal commensals and have similar efficacy as that of antibiotics. The other beneficial factors of probiotics include acceptability to patients and nil side effect profile.

The women of today have evolved and have become empowered due to better education than in previous times. They are well-informed and come forward to seek treatment at an earlier stage. This provides us a good opportunity to educate all women regarding the prevalence, outcome, and recurrence rates of bacterial vaginosis which would indirectly reduce the prevalence of HPV infection, as both share common risk factors.

A significant number of sexually active unmarried women have started seeking specialist care for their medical needs. Therefore, it is important to educate young women regarding the use of barrier contraceptives that would prevent unwanted pregnancies, vaginal infections, and other sexually transmitted infections. Our study suggests future researchers to focus on probiotics and its implications for a healthy living.

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