ORIGINAL ARTICLE

Evaluation of Efficacy and Safety of Oral Fixed-dose Combination of Probiotics in Bacterial Vaginosis

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Abstract

Aim: To evaluate the efficacy and safety of the vaginal-specific lactobacilli strain in management of bacterial vaginosis (BV).

Materials and methods: A nonrandomized, open-labeled, noncomparative, multicentric study was conducted in a total of 58 female patients suffering from BV. Each patient was administered a combination of four strains of lactobacilli. Vaginal pH, discharge, odor, itching, and painful urination were performed at baseline, week 2, and week 4 as assessment parameters.

Results: At the end of the study, data were extractable in only 56 females (mean age was 34.57 ± 11 years). Associated BV symptoms like vaginal discharge, odor, and painful urination reduced significantly at week 4 as compared to baseline. The most frequently encountered symptoms were vaginal discharge, vaginal pH, odor, and itching. With a shift in pH < 4.5, at the end of week 4 all females showed improvement in the vaginal microbiota. Tolerability of fixed-dose combination was found to be good and none of the subjects discontinued the treatment.

Conclusion: Probiotic combination of vaginal-specific probiotic strains was found to be effective and safe for use in females who suffer from BV.

Clinical significance: Lactobacilli have been found in very low numbers in women suffering from BV. After supplementing probiotic, mere fall in pH < 4.5 indicates probable colonization of the vagina with a specific strain of lactobacilli has helped in production of lactic acid and restoration of the vaginal microflora.

Keywords: Bacterial vaginosis, *Lactobacillus*, Microbiota restoration, Probiotic.

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Introduction

Infections of the vagina and outer female genitals include conditions caused by bacteria, viruses, cancer, noncancerous tumors and tissue growths, foreign bodies, or fistulas (abnormal passages between organs or an organ and a body cavity that allow fluids to pass from one to the other). These infections include:[1]

- Bacterial vaginosis (BV), which represents about 60% of all vaginal infections.
- Yeast infections, which account for 30–35% of vaginal infections.
- Trichomonas vaginitis, which is responsible for 5–10% of vaginal infections.[1]

Bacterial vaginosis is the most common cause of abnormal vaginal discharge among women of childbearing age and is associated with adverse obstetric and gynecologic outcomes. Prevalence of BV among women of the reproductive age group is around 31.5%.[2]

Vulvovaginal infections are associated with decrease or absence of protective lactobacilli, which are normally present in the vagina. Lactobacilli produce lactic acid from glycogen, maintaining the vagina's acidic pH (<4.5). The acid environment inhibits the growth of other bacterial species found in the vagina in low levels. When lactobacilli are lacking, overgrowth of bacteria, such as *Haemophilus* spp., *Gardnerella vaginalis*, *Bacteroides* spp., *Mycoplasma hominis*, *Mobiluncus* spp., peptostreptococci, *Ureaplasma*, and other anaerobes can occur.[3]

Common symptoms are inclusive of increased vaginal discharge (white or gray in color) that often smells like fish, burning with urination and mild itching.

Lactobacilli in Vaginal Flora

More than 20 species have been detected in the vagina. The healthy vaginal microflora does not contain high numbers of many different species of *Lactobacillus*. The main hydrogen peroxide-producing strains of lactobacilli are *L. crispatus* and *L. jensenii*. *L. iners* and *L. gasseri* are also among the dominant species of the vaginal microflora.[4]

Role of Lactobacilli in Vaginal Flora

The main mechanism of lactobacilli in the vaginal flora is to prevent the overgrowth of pathogenic and opportunistic organisms. The presence of lactobacilli in vaginal epithelium is responsible for maintaining the vaginal pH < 4.5, which makes the condition unfavorable for the pathogen growth and sustainability.[5]

Bacterial vaginosis may coexist with candidiasis. In a study conducted by McClelland et al., it was observed that 26.9% of women with vulvovaginal candidiasis (VVC) had concurrent BV.[5]

Probiotics can be an effective treatment for dysbiotic conditions. Probiotic therapy addresses the cause of dysbiosis by restoring the ecological equilibrium of the urogenital tract. They

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may represent a superior approach to treating BV during pregnancy, especially since antibiotic therapy has been determined to be neither useful nor warranted.

Although *lactobacilli* spp. are most commonly administered through vaginal suppositories, oral substitution represents a patient-friendly concept for the restitution of a normal vaginal microbiota. In this study, we aimed to determine whether there is an effect of an orally administered preparation of four *Lactobacillus* spp. (*L. crispatus*, *L. rhamnosus*, *L. gasseri*, *L. jensenii*) on the vaginal microbiota of women suffering from BV.[6]

Materials and Methods

Design and Participants

A nonrandomized, open-labeled, noncomparative, multicentric study was conducted to determine the effectiveness of probiotic combination for 4 weeks. A total of 58 female patients, reporting to gynecologists, were screened for vaginal pH, discharge, odor, itching, and painful urination.

Inclusion Criteria

Females were screened on the basis of vaginal pH and discharge odor. A pH strip with a narrow range of 3.5–6.0 manufactured by Analab Scientific India was used to determine the vaginal pH during screening. All females having history of vaginal discharge, vaginal pH >4.5, and fishy or unpleasant odor were enrolled in the study.

Each patient was administered with a combination of lactobacilli strain (*L. crispatus* 1 billion CFU, *L. rhamnosus* 1 billion CFU, *L. gasseri* 30 million CFU, *L. jensenii* 20 million CFU) for 4 weeks.

Exclusion Criteria

Included patients with any of the several conditions listed as follows: Subjects with planned surgery during the treatment course or undergone surgery prior to 3 months of enrollment.

Patients who were pregnant or planning to conceive and lactating mothers were excluded from the study.

Ethical Human Considerations

This was a postmarketing surveillance study for already marketed formulation of the fixed-dose combination of *L. crispatus* 1 billion CFU, *L. rhamnosus* 1 billion CFU, *L. gasseri* 30 million CFU, and *L. jensenii* 20 million CFU, hence only consent was taken from the patients in their vernacular language. The study was conducted in accordance with the Declaration of Helsinki and at 16 centers across the country.

Results

At the end of the visit (week 4), data were extractable in 56 females with BV. There were 2 females with loss to follow-up and hence safety evaluation has been conducted in all 58 females but the efficacy analysis was conducted in 56 females who completed the study for all visits. Percentage reduction in parameters associated with BV is represented in Tables 1 and 2; and Figures 1 to 3.

The baseline and subsequent visit data stating relief in BV symptoms are presented in Table 1. At baseline, all females had vaginal discharge with fishy or unpleasant odor and were suffering from dysbiosis, which was confirmed by the pH test. Figure 1 depicts a significant reduction in discharge odor from baseline, where all females complained of either fishy (51.7%) or unpleasant smell (48.3%), while on week 4 none of the females had either discharge or odor complaint, which concludes that the probiotic supplement

Table 1: Baseline and follow-up evaluation of the effect of the probiotic in bacterial vaginosis

Parameters	*Baseline (day 0) (%) (n = 58)*	*Week 2 (day 14) (%) (n = 58)*	*Week 4 (day 28) (%) (n = 56)*
Homogeneous vaginal discharge	100	Present = 36.2	Present = 0
		Absent = 63.8	Absent = 100
pH of vagina	>4.5 = 100	<4.5 = 81.0	<4.5 = 96.4
		>4.5 = 19.0	>4.5 = 3.6
Odor	Fishy = 51.7	Present = 18.9	Present = 0
	Unpleasant = 48.3	Absent = 81.0	Absent = 100
Itching	Absent = 20.7	Absent = 86.2	Absent = 98.2
	Present = 79.3	Present = 13.8	Present = 1.8
Painful urination	Yes = 44.8	Yes = 3.4	Yes = 1.8
	No = 55.2	No = 96.6	No = 98.2

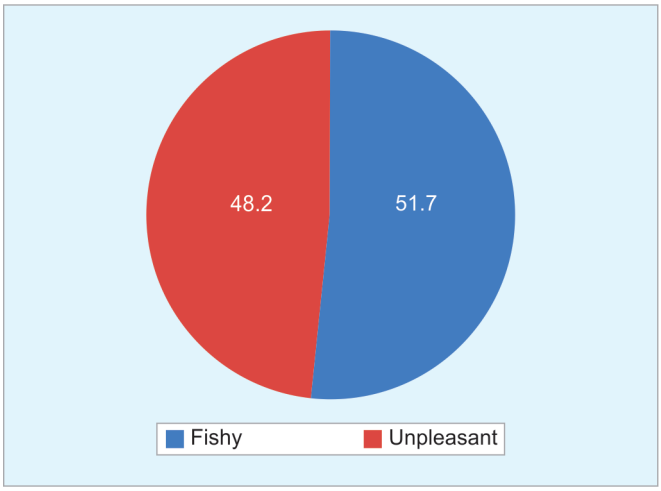

Fig. 1: Vaginal discharge odor

is effective in eradicating the major symptoms of BV. At baseline, all females were having vaginal pH > 4.5, which significantly reduced at week 2–19.0% and at week 4, only 3.6% females had pH > 4.5 (Fig. 2). The change in vaginal pH enlightens the fact of restoring the vaginal microflora by the probiotic supplement that is responsible for maintaining the pH < 4.5.

About 79.3% of females had complaint of itching, which reduced at week 2 –13.8% and at week 4 only 1.8% had complained of itching (Fig. 3).

At the end of the study visit, a global assessment was done by investigators by rating efficacy and safety as excellent, good, or poor (Table 2). About 71.4% of investigators termed that the probiotic had shown excellent results in terms of efficacy and 60.3% and 39.7% rated as excellent and good in terms of safety profile, respectively.

Discussion

Urogenital infections not caused by sexual transmission, namely yeast vaginitis, BV, and urinary tract infection, remain a major medical problem in terms of the number of women afflicted each year.[7]

When the vaginal flora is examined, it is known that microorganisms of *Lactobacillus* spp. are dominant bacteria and

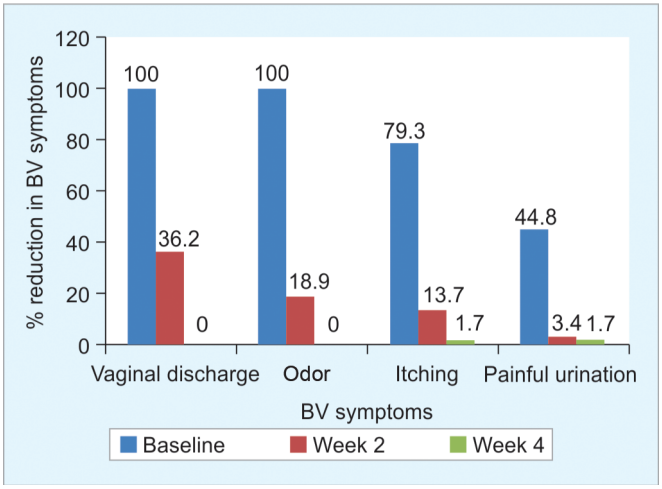

Fig. 2: Effect of probiotics in relieving bacterial vaginosis symptoms

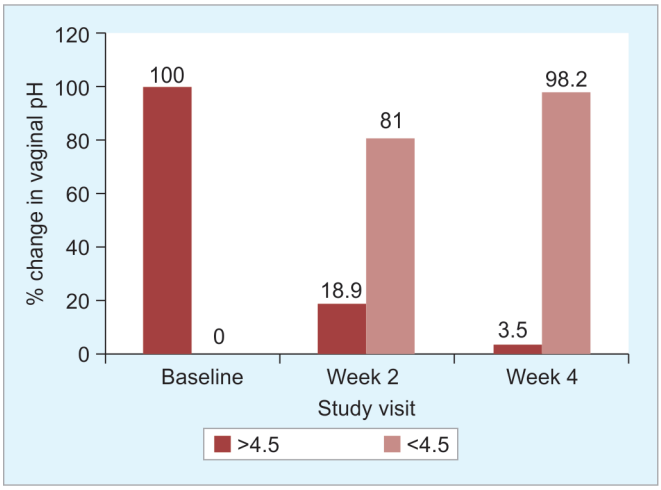

Fig. 3: Effect of probiotic on vaginal pH

Table 2: Global assessment done by investigators

	Excellent (%)	*Good (%)*	*Poor*
Efficacy	71.4	28.6	None
Safety	60.3	39.7	None

form the urinary microbiota that demonstrates antimicrobial activity.[8]

The recurrence rate of BV remains high with use of antimicrobials and such treatments are not designed to restore the lactobacilli. Antimicrobial drug resistance remains a root cause for BV recurrence.[9]

Women with recurrent BV are at high risk of acquiring candida superinfection, both in the form of asymptomatic and symptomatic episodes. Bacterial vaginosis is the most common associated infection with candidiasis.[10]

Treatment of recurrent vaginal infections requires long-term antimicrobial prophylaxis, which results in increase in emergence of antimicrobial resistance; this suggests the need of natural alternatives for its treatment. Clinical studies have demonstrated that oral administration of *Lactobacillus* can demonstrate its effects after reaching the vagina.[8]

Probiotics do not cause antibiotic resistance and may offer other health benefits due to vaginal recolonization with lactobacilli.[11]

This study further strengthens the fact that supplementation of the vaginal-specific probiotic addresses the root cause of BV and its associated complications. The mere fall in pH < 4.5 indicates probable colonization of the vagina with specific strain of lactobacilli has helped in production of lactic acid and therefore enabling a fall in pH and restoration of the vaginal microflora.

Same has been demonstrated in earlier studies conducted in females suffering from BV using vaginal-specific probiotic increases the lactobacilli count within 1 week.[12,13]

Probably in future, probiotics can become the mainstay of therapy either alone or in combination with oral/topical antibiotic as antibiotics alone can only take care of opportunistic pathogens but do not have the ability to restore the vaginal microflora.

Although the study addresses the usefulness of the probiotic in management of BV, but certain limitations cannot be ruled out. The major limitations of this study was that it was not recorded whether subjects enrolled had recurrent BV with or without mixed infections and thereby the author did not take into consideration whether concomitant topical/oral antibiotics were used concomitantly.

Conclusion

The probiotic supplement with vaginal-specific lactobacilli strain has shown improvement in symptoms associated with BV and also decreases the chances of recurrence by restoring the microflora of the vaginal epithelium. Thus, either alone or in combination with antibiotics, vaginal-specific probiotics can be a preferred choice for correcting vaginal dysbiosis and its associated conditions.

Clinical Significance

Lactobacilli have been found in very low numbers in women suffering from BV. After supplementing probiotic, mere fall in pH < 4.5 indicates probable colonization of the vagina with the specific strain of lactobacilli has helped in production of lactic acid and restoration of the vaginal microflora.

Manufacturer Name

The probiotic supplement used in this study consisted of four strains of lactobacilli (*L. crispatus* and *L. jensenii*, *L. iners*, and *L. gasseri*) was manufactured by Mascot Health Series Pvt. Ltd., Plot No. 79, 80, Sec-6A, IIE, Sidcul, Haridwar—249403.

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