

Evaluation of Efficacy & Safety of Oral Fixed Dose Combination of Probiotics in Bacterial Vaginosis

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Abstract

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

Method: A non-randomized, open labeled, non-comparative, multi-centric, study was conducted in total of 58 female patients suffering from bacterial vaginosis. 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.

Result: At the end of study data was 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 symptom was vaginal discharge, vaginal pH, odor and itching. With a shift in $\text{pH} < 4.5$, 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 were found to be effective and safe for use in females who suffer from bacterial vaginosis.

Key words: Bacterial vaginosis (BV); Lactobacillus; Microbiota restoration; Probiotic

Introduction

Infections of the vagina and outer female genitals include conditions caused by bacteria, viruses, cancer, non-cancerous 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 to 35 % of vaginal infections
- Trichomonas vaginitis is responsible for 5-10% of vaginal infections [1]

Bacterial Vaginosis (BV) is the most common cause of abnormal vaginal discharge among women of child bearing age and is associated with adverse obstetric and gynecologic outcomes. Prevalence of BV among women of 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.

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Lactobacilli produce lactic acid from glycogen, maintaining the vagina's acidic pH (<4.5). 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*, urea plasma and other anaerobes can occur [3].

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

Lactobacilli in vaginal flora: >20 species have been detected in the vagina. 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 vaginal microflora [4].

Role of Lactobacilli in vaginal flora: The main mechanism of lactobacilli in 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].

BV may co-exist 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 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 4 *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 non-randomized, open labelled, non-comparative, multi-centric, 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. 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.

Results

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

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 pH

Table 1: Baseline and follow up evaluation of effect of probiotic in bacterial vaginosis (BV).

Parameters	Baseline (Day 0)	Week 2 (Day 14)	Week 4 (Day 28)
	(%) N=58	(%) N=58	(%) N=56
Homogenous 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
Odour	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

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 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 to 19.0% and at week 4, only 3.6% females had pH>4.5 Figure 2.

The change in vaginal pH enlightens the fact of restoring vaginal microflora by probiotic supplement which is responsible for maintaining the pH <4.5.

79.3% of females had complaint of itching which reduced at week 2 to 13.8% and at week 4 only 1.8% had complained of itching Figure 3.

At the end of study visit global assessment was done by investigators by rating efficacy and safety as excellent, good or poor Table 2.

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, bacterial vaginosis, and urinary tract infection remain a major medical problem in terms of the number of women afflicted each year [7].

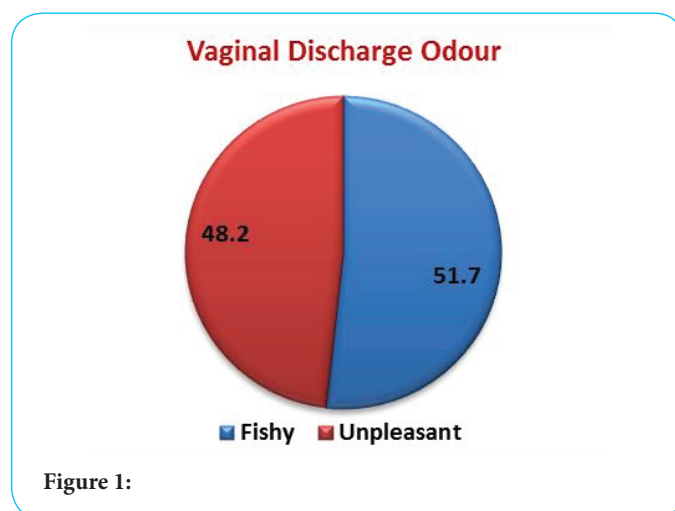


Figure 1:

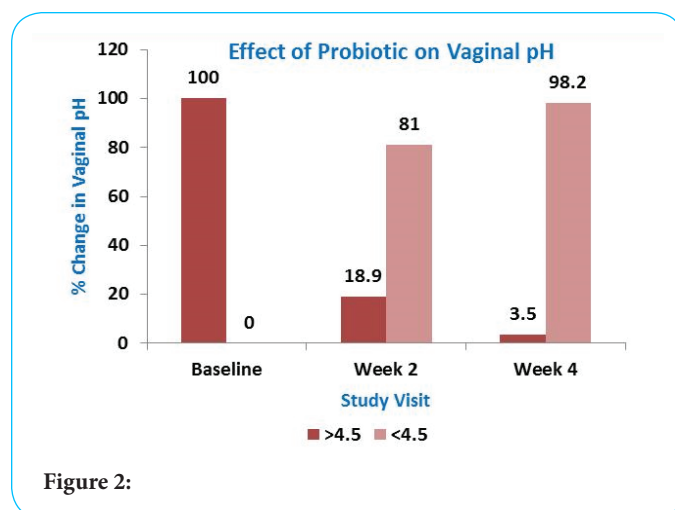


Figure 2:

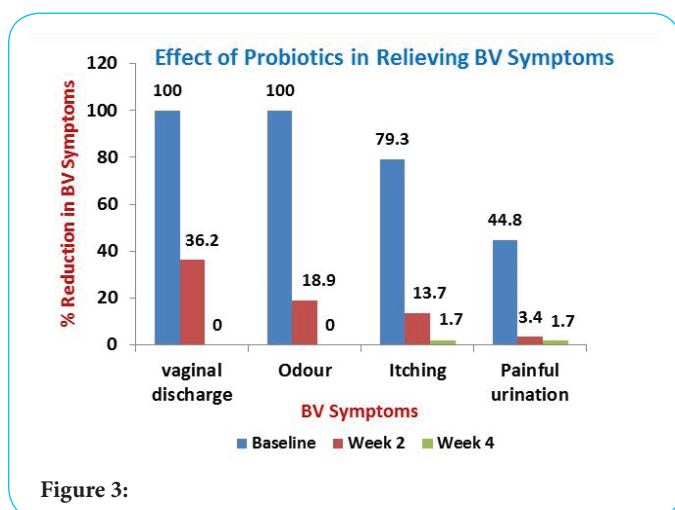


Figure 3:

Table 2: Global Assessment done by investigators.

	Excellent	Good	Poor
Efficacy	71.40%	28.60%	None
Safety	60.30%	39.70%	None

When vaginal flora is examined, it is known that microorganisms of *Lactobacillus* spp. are dominant bacteria and form urinary micro biota which demonstrates antimicrobial activity [8].

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 or symptomatic episodes. Bacterial vaginosis is the most common associated infection with candidiasis [10].

Treatment of recurrent vaginal infections require long-term antimicrobial prophylaxis which results in increase emergence of antimicrobial resistance, this suggests 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 re-colonisation with *Lactobacilli* [11].

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

Same has been demonstrated in earlier studies conducted in females suffering from BV using vagino specific probiotic increases the lactobacilli count within one 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 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 antibiotic were used concomitantly.

Conclusion

Probiotic supplement with vaginal specific lactobacilli strain have shown improvement in symptoms associated with bacterial vaginosis and also decrease the chances of recurrence by restoring the microflora of 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.

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