

GENERAL GYNECOLOGY

Efficacy of vaginal probiotic capsules for recurrent bacterial vaginosis: a double-blind, randomized, placebo-controlled study

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OBJECTIVE: We assessed the effectiveness of vaginal probiotic capsules for recurrent bacterial vaginosis (BV) prevention.

STUDY DESIGN: One hundred twenty healthy Chinese women with a history of recurrent BV were assigned randomly to daily vaginal prophylaxis with 1 capsule (Probiac Vaginal; Nicar Laboratories, Inc, Blainville, Quebec, Canada) that contained 8 billion colony-forming units of *Lactobacillus rhamnosus*, *L acidophilus*, and *Streptococcus thermophilus* (n = 58 women) or 1 placebo capsule (n = 62 women) for 7 days on, 7 days off, and 7 days on.

RESULTS: Probiotic prophylaxis resulted in lower recurrence rates for BV (15.8% [9/57 women] vs 45.0% [27/60 women]; $P < .001$) and

Gardnerella vaginalis incidence through 2 months (3.5% [2/57 women] vs 18.3% [11/60 women]; $P = .02$). Between the 2- and 11-month follow-up period, women who received probiotics reported a lower incidence of BV and *G vaginalis*. Aside from vaginal discharge and malodor, no adverse events were reported in either study group.

CONCLUSION: Short-term probiotic prophylaxis is well tolerated and reduces BV recurrence and *G vaginalis* risk through 11 months after treatment.

Key words: bacterial vaginosis, *G vaginalis*, probiotic

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Bacterial vaginosis (BV) is the most common vaginal infection in women of childbearing age, with a prevalence of 19-42%.¹⁻⁴ This infection occurs when the normal *Lactobacillus* bacteria in the vagina are disrupted and subsequently replaced by predominantly anaerobic bacteria such as *Gardnerella vaginalis* and, to a lesser extent, *Mycoplasma hominis*, *Prevotella*, and *Peptostreptococcus*.^{5,6} Although most in-

fectured women are asymptomatic,^{1,7} BV increases the risk for pelvic inflammatory disease, mid-trimester miscarriage, preterm delivery, and other gynecologic complications.⁸⁻¹¹

The standard of care for BV treatment is oral or vaginal metronidazole or vaginal clindamycin.¹² However, treatment success rates as low as 52%¹³ and recurrence rates of >50% within 6-12 months are common.¹³⁻¹⁵ The study of Swidsinski et al¹⁶ suggests that antibiotic treatment reduces vaginal bacteria metabolic activity, although a *G vaginalis*-rich biofilm persists, which likely contributes to BV relapse. Furthermore, a recent trial reported that all *G vaginalis* strains develop resistance to metronidazole in recurrent BV cases.¹⁷ Given the mediocre efficacy of antibiotic treatment for BV, there is a clear need to explore new BV therapies.

Lactobacilli are an alternative option for BV prevention and treatment because they produce acetic acid and hydrogen peroxide, thereby hindering pathogenic bacteria growth. Vaginal probiotic capsules are particularly appealing because of their ease of use and

high satisfaction rates vs creams, gels, and oral yogurt consumption.¹⁸ Several trials have studied the efficacy of vaginal probiotic capsules on BV.^{18,19} However, no known trial has studied the prophylactic use of these capsules in women with a history of recurrent BV.

Therefore, the purpose of this study was to determine the efficacy of vaginal probiotic capsules for BV prophylaxis in healthy women with a history of recurrent BV. We hypothesized that women who are treated with vaginal probiotic capsules would have a lower incidence of BV and *G vaginalis* compared with treatment with placebo.

MATERIALS AND METHODS

This single-center, double-blind, randomized, placebo-controlled trial was conducted at Yuyao/Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (Shanghai, China). Enrollment occurred between December 2008 and January 2009. The research practices that were used in this trial were in accordance with the Declaration of Helsinki. The institutional review board at Yuyao/Xinhua Hospital

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approved this protocol (study no. 08-SC-NIC-01), and all subjects provided informed consent before any research activities were initiated.

Inclusion criteria for study participation were healthy women who were 18-55 years old, were currently free from BV, had had ≥ 2 BV episodes in the previous year, had had no antibiotic treatment within 1 week of study participation, and who were willing to refrain from other intravaginal products (eg, douche or spermicide). Exclusion criteria included the presence of other causes of vulvovaginitis (eg, candidiasis or *Chlamydia trachomatis*), pregnant or lactating, history of daily fermented milk and/or yogurt consumption, allergy to study product ingredients, immunosuppressed state, systemic or intravaginal antibiotic or antifungal therapy within 7 days of study participation, intraepithelial neoplasia or cervical carcinoma that required treatment, and urogenital infection within 21 days of participation.

Subjects who met all study entry criteria and who provided informed consent were assigned randomly to BV prophylaxis (test group) with a proprietary vaginal probiotic capsule (Probiacac Vaginal; Nicar Laboratories, Inc, Blainville, Quebec, Canada) or a placebo capsule (control group) for 7 days on, 7 days off, and 7 days on. The randomization sequence that was used in this trial was generated by a computerized random-number generator (SAS, release 9.2; SAS Institute Inc, Cary, NC). Study products were delivered to the investigative site in identical containers that were labeled only with the lot number and a sequentially numbered patient identification code.

Probiacac Vaginal is a pharmaceutical grade probiotic complex that is produced with 3 DNA-certified proprietary lactic acid bacteria strains. Mother cultures were kept at -80°C to prevent any mutation of probiotic characteristics. Each strain was fermented individually then filtered, lyophilized, and ground into a powder before being blended into the final probiotic complex. Each probiotic vaginal capsule contained 8 billion colony-forming units of live lactic bacteria that included *L rhamnosus* (6.8 billion

stabilized lactic ferments), *L acidophilus* (0.4 billion stabilized lactic ferments), and *Streptococcus thermophilus* (0.8 billion stabilized lactic ferments) and lactose. Placebo capsules were of identical appearance, smell, and texture and contained only lactose. Study products were kept secured and double verification was used to ensure correct product administration to study subjects.

Baseline evaluations included a physical examination, vaginal swabs, medical history, concomitant medication use, blood pressure, height, and weight. Each subject received instruction regarding appropriate use of the vaginal capsules. The study product was dispensed in a box that contained 7 vaginal capsules and a vaginal applicator. The women used the study product for 1 week and returned 1 week later to pick up the second box that contained a 1-week supply of capsules. The women returned for follow-up visits at 30 and 60 days after treatment. Follow-up evaluations included the collection of vaginal swabs, an assessment of vaginal flora, and a report of adverse events. The women were contacted by telephone at 10.8 ± 0.2 months after treatment and were asked to confirm or deny the presence of BV symptoms, diagnosis of BV or *G vaginalis*, and adverse events over the 2- to 11-month follow-up period. If a subject reported a diagnosis of BV, the research staff confirmed this diagnosis with the subject's treating physician at Yuyao/Xinhua Hospital.

The primary endpoint of this study was BV that was diagnosed at any time during the 2-month follow-up period. BV was diagnosed in the presence of positive results with the Amsel Criteria,²⁰ which confirms BV in the presence of at least 3 of the following 4 criteria: (1) vaginal pH >4.5 , (2) clue cells on microscopy of saline solution wet mount, (3) release of fish amine odor on addition of 10% potassium hydroxide to a drop of vaginal discharge, and (4) characteristic thin, homogenous vaginal discharge. Vaginal swabs were collected and cultured on 5% blood agar, eosin methylene blue agar, and Sabouraud dextrose agar. The plates were evaluated after 24-48

hours incubation at 37°C in microaerophilic conditions.²¹

This study was conducted with triple-blinding procedures. The study product was packaged and labeled by the manufacturer according to the study identification number and treatment assignment. Women were blinded to the treatment that was being received throughout the trial. Investigators and all involved clinicians were blinded to the treatment allocation throughout the course of the study. The blind was broken to investigators, but not patients, in cases of a positive BV diagnosis. Test subjects who experienced BV during the supplementation period continued using the study product. If the infection persisted for >1 week, treatment was supplemented with antibiotics at the physician's discretion. Control subjects who had BV discontinued the placebo treatment and began a course of antibiotics at the physician's discretion.

Data analysis

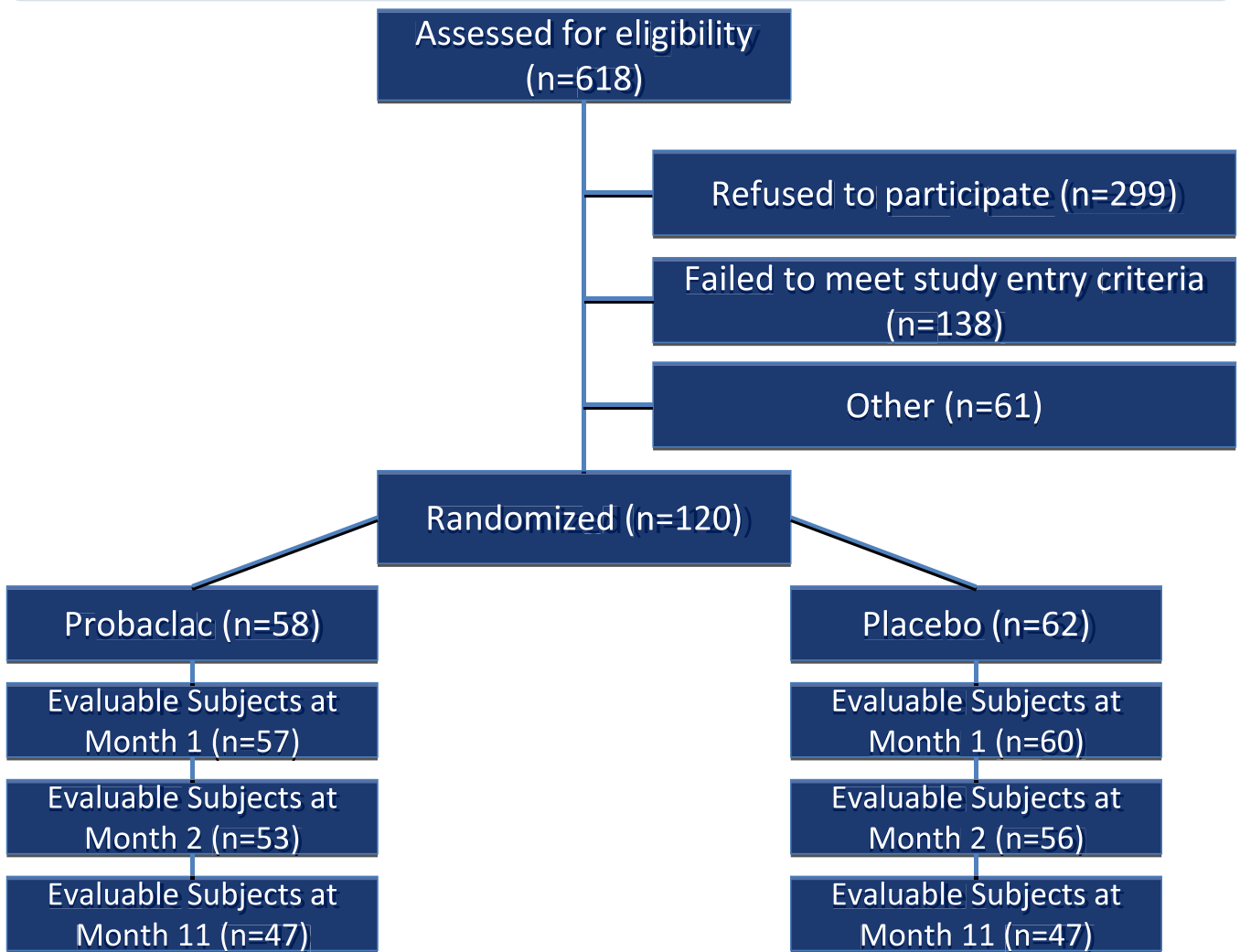
All data were recorded on case report forms, double-entered into a database, verified, and monitored independently for accuracy by Sprim China Ltd. (Shanghai, China). Clinical monitors and biostatisticians were blinded to treatment allocation throughout the entire clinical study and until after all analyses were completed.

Patient randomization was stratified by age (18-30, 31-40, 41-55 years) to minimize confounding age effects between groups. Sample size for this trial was estimated by assuming a 35% BV incidence in the control group, an anticipated 30% BV risk reduction in the test group, 90% statistical power, alpha level of .05, and a 17% attrition rate. Overall, 120 women (60 per group) were planned for enrollment.

Statistical analyses were performed with SAS/STAT software (release 9.2; SAS Institute Inc, Cary, NC). Baseline variables were analyzed with independent *t* tests to assess between-group differences. χ^2 and the Fisher's exact test were used to compare BV and *G vaginalis* incidence between test and control groups. Odds ratios were calculated by logistic regression. Data are reported as

FIGURE 1

Consolidated Standards of Reporting Trials (CONSORT) flow diagram



Probaclac Vaginal; Nicar Laboratories, Inc, Blainville, Quebec, Canada.

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mean \pm SD or n (%). Statistical significance was set at a probability value of $\leq .05$.

RESULTS

Subject retention through the 2-month follow-up visit was 91% (53/58 women) in the test group and 90% (56/62 women) for the control group. All withdrawals were due to personal reasons and unrelated to the study. At the 11-month telephone follow-up interview, 81% of the test group (47/58 women) and 76% of the control group (47/62 women) were contacted (Figure 1). No between-group differences in baseline characteristics were detected (Table 1).

All subjects reported either none or 1 sexual partner within the previous year. Most of the women (85%) were non-smokers; 15% of them reported smoking 1-15 cigarettes each day.

The test group experienced lower BV recurrence rates through 2 months (15.8% vs 45.0%; odds ratio [OR], 0.23; 95% confidence interval [CI], 0.10–0.55; $P < .001$). BV incidence at each fol-

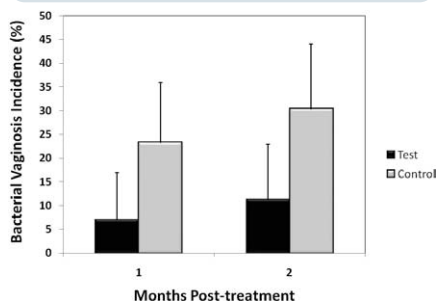
TABLE 1
Baseline subject characteristics

Variable	Test (n = 58)	Control (n = 62)	P value
Age, y	37.4 \pm 10.6	37.2 \pm 10.9	.92
Height, cm	161.9 \pm 8.2	160.7 \pm 8.4	.43
Weight, kg	56.1 \pm 7.2	56.1 \pm 7.2	.99
Body mass index, kg/m ²	21.4 \pm 2.7	21.7 \pm 2.8	.55

There was no significant difference between groups for any variable.

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FIGURE 2
Bacterial vaginosis incidence through 2 months after treatment



Error bars represent 95% confidence intervals.

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low-up visit is presented in Figure 2. *G vaginalis* incidence was lower in the test group over the 2-month follow-up period (3.5% vs 18.3%; OR, 0.16; 95% CI, 0.02–0.88; $P = .02$; Figure 3). *G vaginalis* incidence at each follow-up visit is presented in Figure 3.

The percentage of women who reported a confirmed diagnosis of BV between the 2-month visit and the 11-month follow-up interview remained lower in the test group vs the control group (10.6% vs 27.7%; OR, 0.31; 95% CI, 0.11–0.93; $P = .04$). A similar beneficial probiotic effect was observed between the 2-month visit and the 11-month follow-up visit for *G vaginalis* (0% vs 6.4%; $P = .08$).

Through 2 months after treatment, probiotic prophylaxis was effective in reducing discharge, lowering vaginal pH, and reducing presence of clue cells; however, little effect on malodor was ob-

served (Table 2). Subject-reported incidence of vaginal discharge and malodor between 2 and 11 months after treatment were 3-fold higher in the control group.

Adverse events were defined as any untoward occurrence in a subject, regardless of the relationship with the treatment. Aside from vaginal discharge and malodor, no adverse events were reported in either study group during the course of the trial.

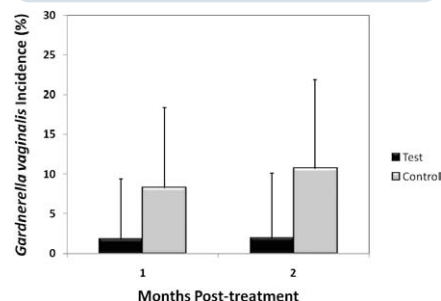
COMMENT

Probiotic prophylaxis with vaginal capsules is well tolerated and yields dramatic reductions in BV recurrence and *G vaginalis* risk through 11 months after treatment in women with history of recurrent BV.

Strengths of this clinical study included the prospective, randomized, placebo-controlled, triple-blinded design along with stringent data monitoring, entry, and analysis standards. A limitation of this study was that 11-month outcomes were collected with telephone follow-up interview. The frequency of BV and *G vaginalis* diagnosis and associated symptoms over the 2- to 11-month follow-up period may have been underreported. Regardless, the fact that treatment allocation remained blinded to all subjects and investigators suggests that reporting bias was consistent between test and control groups.

This clinical trial represents the first report of vaginal probiotic capsules solely for recurrent BV prevention. The study of Shalev et al²² represents a similar trial design as the current study. Although subjects who consumed yogurt

FIGURE 3
Gardnerella vaginalis incidence through 2 months after treatment



Error bars represent 95% confidence intervals.

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that contained live *Lactobacillus* bacteria had a lower incidence of recurrent BV than those who consumed only pasteurized yogurt, >80% of the women withdrew from the trial after only 2 months. The poor compliance that was associated with daily yogurt consumption precludes a recommendation for use in women with BV.

Probiotics are also an attractive alternative to metronidazole. In fact, a recent Cochrane Review reported that treatment with vaginal *Lactobacillus* tablets was more effective than metronidazole for BV.²³ Metronidazole gel is associated with a 15% BV recurrence rate through 2 months,²⁴ which is similar to that observed with vaginal probiotic capsules in the current trial. However, the adverse event incidence that is associated with metronidazole use is concerning.²⁴ Vaginal discharge and malodor were the only reported adverse events in the cur-

TABLE 2
Bacterial vaginosis symptoms through 11 months after treatment

Symptom	1 month, n		2 months, n		11 months, n ^a	
	Test (n = 57)	Control (n = 60)	Test (n = 53)	Control (n = 56)	Test (n = 47)	Control (n = 47)
Discharge	17 (29.8%)	26 (43.3%)	14 (26.4%) ^b	29 (51.8%)	5 (10.6%) ^b	13 (27.7%)
pH >4.5	16 (28.1%) ^b	32 (53.3%)	16 (30.2%)	23 (41.1%)	NA	NA
Malodor	21 (36.8%)	22 (36.7%)	21 (39.6%)	26 (46.4%)	4 (9.3%) ^b	13 (27.7%)
Clue cells	14 (24.6%) ^c	32 (53.3%)	18 (34.0%) ^b	33 (58.9%)	NA	NA

NA, data not available.

^a Follow-up data obtained by telephone; ^b $P < .05$; ^c $P < .01$.

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rent trial, with a lower incidence with probiotics vs placebo at the 11-month follow-up interview. Overall, these outcomes suggest that the benefit-to-risk profile of probiotics is favorable. Obviously, any potential benefit of probiotics vs antibiotics can be confirmed only in a double-blind, randomized, placebo-controlled clinical trial.

It is well-established that BV is associated with low concentrations of vaginal *Lactobacilli*.²⁵⁻²⁷ In vitro studies have shown that various *Lactobacillus* strains inhibit *G vaginalis* production by the production of lactic acid and, to a lesser degree, hydrogen peroxide.^{28,29} A possible reason for the positive outcomes of this trial, especially because all women had a history of recurrent BV, is that we used a probiotic dose that is 80 times greater than the *Lactobacillus* volume recommended to restore and maintain a normal urogenital flora.³⁰ Although the mechanism of action has not been elucidated fully, the probiotic load of this quantity likely overwhelms the vaginal microbiota and repopulates the vagina with adequate concentrations of *Lactobacilli*, inhibits or destroys pathogenic bacteria, and blocks the adherence of *G vaginalis*.⁶ Sexual history and smoking history did not influence BV and *G vaginalis* risk. However, these effects may have been blunted because no women reported moderate or heavy smoking or multiple sexual partners, both known risk factors for BV.

Although the cause of BV has not been elucidated fully, most studies support the notion that recurrent BV is not caused by reinfection³¹ but by relapse.³² This proposed mechanism supports the use of probiotics to prevent recurrent BV because abnormalities of the vaginal flora often persist, even in the absence of clinical symptoms.³³

Although we present no outcomes that directly compare probiotics with the standard of care (antibiotics), the risk-to-benefit profile of vaginal probiotic capsules is very favorable. Probiotic prophylaxis with vaginal capsules should be considered strongly in women with recurrent BV. Although this trial was conducted in women of only Asian descent, this probiotic blend is likely beneficial

across all racial backgrounds. However, because different probiotics have varying levels of effectiveness, the beneficial results that were observed in this trial are applicable only to the vaginal capsules under study.

Given the promising outcomes that were shown in this study, we recommend that well-designed, randomized, controlled trials that will compare probiotics to the standard of care (metronidazole) be conducted to further determine the efficacy of probiotics for the treatment and prevention of BV. ■

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