

Original Research Article

Efficacy of Lactobacillus live capsules in combination with metronidazole for the treatment of bacterial vaginosis

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Abstract

Purpose: To evaluate the effectiveness of metronidazole in combination with Lactobacillus live capsules for the treatment of bacterial vaginosis (BV).

Methods: A retrospective study of 100 BV patients was conducted between June 2020 and February 2022 at Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, China. Patients were assigned to control (48 patients received metronidazole only) and study groups (52 patients received metronidazole and Lactobacillus live capsules). Short-term efficacy, changes in vaginal flora distribution, recurrence rates, and occurrence of adverse effects were investigated.

Results: The study group showed significantly higher overall efficacy compared to control group ($p < 0.05$). After treatment, vaginal flora analysis revealed a more balanced microbiota in the study group, indicating a positive effect of combined therapy. However, recurrence rates at one and three months after treatment did not significantly differ between the two groups ($p > 0.05$). Both treatment regimens were generally well-tolerated, with only a single report of mild adverse reactions in the study group.

Conclusions: The combined therapy of metronidazole and Lactobacillus live capsules enhances short-term therapeutic effectiveness and promotes a healthier vaginal microbiota. Although, the combined therapy does not significantly impact recurrence rates, it demonstrates a favorable safety profile. The lack of attention to non-bacterial constituents of the vaginal flora and potential long-term adverse effects of Lactobacillus live capsules represent an area for future study.

Keywords: Bacterial vaginosis, Metronidazole, Lactobacillus, Combination therapy, Therapeutic efficacy

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INTRODUCTION

Bacterial vaginosis (BV) is an infection characterized by overgrowth of harmful bacteria, primarily *Gardnerella vaginalis* and various anaerobic species with negative impact on women's health worldwide [1,2]. The bacterial imbalance disrupts typical vaginal microbiota, often resulting in an abnormal increase in vaginal discharge. Presence of pathogenic bacteria is confirmed through microscopic examination of

the discharge smear. Importantly, BV is also transmitted through sexual intercourse, thereby extending its implications beyond the affected individual. Clinical manifestations of BV vary from mild to severe, causing significant discomfort to patients. Predominant symptoms include vulvar itching, a burning sensation, and an abnormal greyish-white vaginal discharge with a distinct fishy odor. These symptoms often intensify following menstrual cycles or sexual intercourse, thereby causing significant physical discomfort

and psychological distress to affected individuals [3,4]. Metronidazole (an antibiotic) is the cornerstone of BV treatment in current clinical practice. Its effectiveness in reducing severity of symptoms and managing BV has been validated in numerous clinical studies [5,6]. However, despite its acknowledged efficacy, persistence of clinical symptoms in many patients following treatment still exist. This highlights the need for a more comprehensive, patient-centric therapeutic strategy that not only treats the infection but also enhances patient comfort and well-being. In the vaginal ecosystem, Lactobacillus species are dominant and vital for maintaining vaginal health producing lactic acid and other substances that inhibit growth of pathogenic organisms [7]. Administering exogenous Lactobacillus using Lactobacillus live capsules has shown efficacy in managing Candida-associated vaginitis during pregnancy [8,9]. As a result, a combined therapeutic approach incorporating both metronidazole and Lactobacillus live capsules becomes necessary for BV treatment [10]. Also, the high prevalence of BV, coupled with its significant impact on women's health, necessitates a more comprehensive treatment approach that mitigates not just the immediate infection but also long-term recurrence and patient discomfort [11]. This study presents an innovative approach to BV treatment, emphasizing the critical balance between eradication of pathogenic bacteria and restoration of a healthy vaginal microbiota. Furthermore, this study provides potential benefits of a combined antibiotic-probiotic treatment to improve patient outcomes, and significantly contribute to existing knowledge on BV management. Thus, this study was aimed at investigating the efficacy of Lactobacillus live capsules in combination with metronidazole for the treatment of BV.

METHODS

Patients

This study was a retrospective study of 100 patients diagnosed and treated for bacterial vaginosis between June 2020 and February 2022. This study was approved by the Ethics Committee of Zhejiang University School of Medicine (approval no. 20201326-15), and conducted in accordance with the Declaration of Helsinki [12].

Inclusion criteria

Presence of white, viscous, non-purulent discharge; fishy odour of the discharge exacerbated upon addition of 10 % potassium

hydroxide, vaginal pH between 5.0 and 5.5, presence of clue cells in vaginal fluid, patients aged 20 – 60 years with good treatment compliance, no previous history of BV treatment, and normal cardiac, hepatic, and renal functions.

Exclusion criteria

Pregnant or lactating women, patients with prior surgeries involving the uterus and appendages, individuals with sexually transmitted diseases such as syphilis or HIV infection, antibiotic usage within one week before admission, and severe allergic reactions to the medications.

Patients were divided into control (48 patients received metronidazole only) and study (52 patients received metronidazole in combination with Lactobacillus live capsules) groups.

Treatment protocol

Therapeutic protocol for the control group consisted of metronidazole (manufacturer: Henan Furen Pharmaceutical; approval number: National Drug Approval H20073322; specification: 0.2 g/tablet), a widely used antibiotic for treating bacterial vaginosis. The dosage regimen was standardized across all patients in this group, with two tablets administered orally thrice daily for one-week. Study group followed the same metronidazole regimen.

However, one week following metronidazole treatment, Lactobacillus live capsules (manufacturer: Inner Mongolia Shuangqi Pharmaceutical; approval no. National Drug Approval S20030005; specification: 0.25 g/capsule) was administered. The capsules were inserted intravaginally once daily for ten days. All participants were asked to abstain from sexual activities during treatment period and were prohibited from using any other antibiotics to avoid potential interference with the medications.

Evaluation of parameters/indices

Short-term efficacy

Short-term efficacy of the treatment was measured one-week after treatment. This was evaluated based on the improvement or disappearance of patient's clinical signs and symptoms. Primary outcome was divided into four categories: cured, markedly effective, effective, and ineffective. Total effective rate was computed as sum of cured, markedly effective, and effective rates.

Distribution of vaginal microflora

Samples of vaginal discharge were taken from the vaginal fornix using sterile swabs. These samples were cultured and classified into *Lactobacillus*, *Bacillus*, *E. coli*, *Candida albicans*, and *Mycoplasma* species.

Recurrence rates

Recurrence rates provide essential insights into long-term effects and sustainability of the treatment regimen. Recurrence rates at one and three months after treatment were recorded.

Incidence of adverse reactions

Adverse reactions such as skin rash, nausea, vomiting, dizziness, headaches, vaginal bleeding, arrhythmias, and potential damage to liver and kidney functions were evaluated and recorded.

Statistical analysis

Data were analyzed using Statistic Package for Social Science (SPSS) version 20.0 (IBM, Armonk, NY, USA). Categorical data, such as treatment response and occurrence of adverse events were presented in frequencies and percentages. Chi-square test was employed to compare categorical data between control and study groups. Continuous data such as age, levels of different bacteria in the vaginal flora, outcomes were expressed as mean \pm standard deviation (SD). Independent t-test was employed for inter-group comparison while paired t-test was used for comparisons within a group. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of patients

There was no significant difference in baseline characteristics of patients in both control and study groups ($p > 0.05$; Table 1).

Treatment response

Overall efficacy rate was significantly higher in study group compared to control group ($p < 0.05$; Table 2).

Vaginal flora

At baseline, there was no significant difference in the distribution of vaginal flora in both groups ($p > 0.05$). However, after treatment, there was significant difference in the distribution of vaginal flora between the two groups ($p < 0.05$) suggesting a more significant shift towards a healthier and more balanced vaginal microbiota following combined metronidazole and *Lactobacillus* live capsules treatment (Table 3).

Recurrence rate

Rate of bacterial vaginosis recurrence was analyzed one- and three-months following treatment. There was no significant difference in recurrence rate between control and study groups after one to three months after treatment ($p > 0.05$). These findings suggest that while the inclusion of *Lactobacillus* live capsules enhances immediate treatment response, it does not significantly impact the likelihood of bacterial vaginosis recurrence after three months (Table 4).

Table 1: Baseline characteristics of patients

Characteristic	Control (n=48)	Study (n=52)	χ^2/t -value	P-value
Age (years)	46.01 \pm 8.77	45.97 \pm 8.34	0.102	0.448
Duration of disease (months)	3.17 \pm 0.43	3.20 \pm 0.45	0.334	0.389
Vaginal cleanliness III	32	35	0.105	0.746
Vaginal cleanliness IV	16	17	0.254	0.614
Delivery history (never vs. ever)	13 vs. 35	16 vs. 36	0.229	0.632

Table 2: Treatment response

Efficacy	Control (n = 48)	Study (n = 52)	χ^2 -value	P-value
Number of patients	48	52		
Cured	11 (22.92%)	22 (42.31%)		
Markedly effective	13 (27.08%)	20 (38.46%)		
Effective	16 (33.33%)	8 (15.38%)		
Ineffective	8 (16.67%)	2 (3.85%)		
Total effective rate	40 (83.33%)	50 (96.15%)	5.238	0.022

Table 3: Vaginal microbiota distribution (mean ± SD, cfu/mL)

Bacteria type	Before treatment		P-value	After treatment		P-value
	Control	Study		Control	Study	
Lactobacillus	5.88±0.91	5.91±0.90	0.448	6.86±0.73 [#]	7.33±0.81 ^{**}	0.008 [*]
Bacillus sp.	4.96±0.55	4.94±0.52	0.434	4.30±0.51	3.84±0.40 ^{**}	<0.001 [*]
E. coli	4.73±0.57	4.71±0.61	0.468	4.07±0.44 [#]	3.46±0.42 ^{**}	<0.001 [*]
Candida albicans	5.82±0.68	5.79±0.65	0.420	5.04±0.51 [#]	4.28±0.44 ^{**}	<0.001 [*]
Mycoplasma	4.62±0.61	4.56±0.57	0.326	3.94±0.41 [#]	3.25±0.35 ^{**}	<0.001 [*]

*P < 0.05 vs. before treatment, **p < 0.05 vs. before treatment, [#]p < 0.05 vs. before treatment

Table 4: Recurrence rate (n, %)

Group	Sample Size	1-Month recurrence	3-Month recurrence	χ ²	P-value
Control	48	4(8.33)	6(12.50)	2.250	0.134
Study	52	2(3.85)	4(7.69)	1.289	0.257

Adverse events

The treatment regimens were generally well-tolerated. There were no adverse events documented in the control group during treatment indicating a favorable tolerance to metronidazole monotherapy. In the study group, only one case (2.33 %) of mild adverse reactions was reported, characterized by dizziness and headache. These adverse effects resolved spontaneously without requiring specific intervention and did not impact the overall continuity of treatment, thus highlighting the safety of combination therapy.

DISCUSSION

The human vagina, under normal physiological conditions, is predominantly colonized by Lactobacillus species, which actively produce hydrogen peroxide to inhibit the adherence and proliferation of pathogenic microbes on the vaginal epithelial cells. This mechanism helps maintain a mildly acidic microenvironment within the vagina [13,14]. Bacterial vaginosis (BV) is closely associated with vaginal microbiota imbalance, as numerous studies have confirmed that patients with BV often exhibit a reduction in Lactobacilli species [15,16]. The higher overall treatment effectiveness observed in the study group suggests that the exogenous addition of Lactobacillus enhances the short-term therapeutic effect in patients with bacterial vaginosis.

Vaginal microbiota distribution directly impacts female reproductive health, and alterations in pH as well as a decline in estrogen levels may lead to the disruption of vaginal ecological balance [17]. This imbalance creates a favorable environment for opportunistic pathogens to overgrow, ultimately leading to the development of bacterial vaginosis. Lactobacillus is the

dominant flora under normal physiological conditions, with enterobacteria and *E. coli* also colonizing the vagina [18]. The dominance of Lactobacilli inhibits excessive proliferation of other bacteria, stimulates the host to produce antibodies, and strengthens immune response. Furthermore, metabolic products of Lactobacillus form a biological barrier in the vagina, preventing intrusion of foreign bacteria. *Candida albicans* and Mycoplasma are among the most common pathogenic bacteria in the vagina. A reduction in the number of Lactobacilli weakens the immune system, and leads to the colonization of pathogenic bacteria, disrupting vaginal health and potentially causing inflammatory diseases [19]. This study demonstrated a significant improvement in short-term therapeutic efficacy when bacterial vaginosis was treated with a combination of metronidazole and Lactobacillus live capsules, compared to treatment with metronidazole alone. This finding is consistent with previous study highlighting the role of Lactobacilli in restoring vaginal microbiota. Probiotics, such as Lactobacillus, are known to restore normal vaginal microbiota, thereby contributing to increased therapeutic effectiveness. [20].

The distribution of vaginal flora did not show any significant difference between control and study groups ($p > 0.05$), ensuring their comparability at baseline. However, after treatment, there was a significant difference in the distribution of vaginal flora in the study group compared to control group ($p < 0.05$). These findings suggest that addition of Lactobacillus live capsules to metronidazole therapy significantly altered vaginal microbiota, promoted a healthier balance of bacteria, including Lactobacilli, *E. coli*, *Candida albicans*, and Mycoplasma.

The efficacy was investigated by comparing recurrence rates one and three months after treatment. While the addition of Lactobacillus live

capsules was found to enhance immediate treatment response, it did not significantly affect the rates of bacterial vaginosis recurrence one and three months after treatment. This finding suggests that the impact of probiotic supplementation may primarily be on the immediate treatment response rather than preventing bacterial vaginosis recurrence. However, larger, long-term follow-up studies are needed to conclusively determine the effect of probiotics on the recurrence of bacterial vaginosis.

Also, both treatment regimens were well-tolerated by the patients. No major adverse effect was reported in the control group, suggesting a good tolerance to metronidazole alone. In the study group, there was a single report of mild adverse reactions (2.33 %) presenting as dizziness and headache. This adverse event resolved without specific intervention, indicating the safety of the combination therapy. Although the overall adverse event rate was low, ongoing patient monitoring is essential to assess any potential long-term side effects related to the combined treatment regimen. Additionally, a more detailed documentation of patient experiences, including minor and non-severe side effects, may offer more comprehensive insights into the tolerability profiles of the treatments.

Limitations of this study

This study is limited by the small sample size used, a relatively short (three-month) follow-up period, and focused solely on symptomatic bacterial vaginosis. Additionally, the absence of a double-blind design may have potentially introduced bias during the investigation.

CONCLUSION

The combination of metronidazole and Lactobacillus live capsules enhances short-term efficacy, and provides more favorable equilibrium of vaginal microbiota. This combination therapy provides a promising adjunctive treatment option for bacterial vaginosis. The lack of attention to non-bacterial constituents of the vaginal flora and potential long-term adverse effects of Lactobacillus live capsules represents an area for future study.

DECLARATIONS

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Ethical approval

This study was approved by the Ethics Committee of Zhejiang University School of Medicine (approval no. 20201326-15).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We certify that the work in question was performed by the author(s) identified in this article. All claims referring to claims related to the material in this paper will have to be borne by the writers.

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