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Effect of *Lactobacillus plantarum* IS-10506 supplementation with oral metronidazole for the treatment of bacterial vaginosis: A randomized placebo-controlled clinical trial

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Abstract

Background Replacement of *Lactobacillus* spp. by anaerobic and facultative bacteria is central in pathogenesis of bacterial vaginosis (BV). Oral metronidazole is currently recommended treatment. However, cure rate is variable. Probiotic supplementation was explored as alternative therapy. This study aimed to find out the effect of oral microencapsulated *Lactobacillus plantarum* IS-10506 supplementation on oral metronidazole 500 mg twice daily for the treatment of BV.

Methods Twenty nine females with BV were treated with oral metronidazole and randomized into probiotic (Pro) (n=14) and placebo (Pla) (n=15) groups. Pro group received microencapsulated *L. plantarum* IS-10506 supplementation at 0.9×10^9 CFU, twice daily. Pla group received placebo twice daily. Cure is defined from Amsel criteria and Nugent score 0-3. Metronidazole was stopped if subjects were cured. Probiotic and placebo were continued for 4 weeks. Cure rate and mean Nugent score were assessed at baseline, end of week 1, 2 and 4.

Results Mean Nugent score for Pro against Pla group were 8.07 vs. 8.07, 5.36 vs. 6.20, 4.07 vs. 4.93, and 3.57 vs. 4.33 respectively at baseline, end of week 1, 2 and 4. Cure rate for Pro against Pla group were 28.6% vs 20.0%, 50.0% vs 33.3%, 64.3% vs 40.0% respectively at end of week 1, 2 and 4. Mean Nugent score significantly decreased in both groups at end of week 1, 2 and 4 ($p \leq 0.05$). Although not statistically significant, mean Nugent score was lower and cure rate was higher in Pro than Pla group at end of week 1, 2 and 4 ($p > 0.05$). No adverse effect was recorded.

Conclusion Oral probiotic *L. plantarum* IS-10506 supplementation in addition to oral metronidazole was safe and potentially better than oral metronidazole alone for the treatment of BV. Studies with longer probiotic supplementation and more subjects may be required to demonstrate significant effect of this combination treatment on BV.

Key words

Bacterial vaginosis, probiotic, *Lactobacillus plantarum*, Nugent score, human health.

Introduction

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Bacterial vaginosis (BV) is a vaginal disorder presenting with abnormal malodorous vaginal discharge associated with increased vaginal pH.^{1,2} BV most often affects females of reproductive age with prevalence ranging from

11.1-60.8% worldwide.¹ Although some patients may be asymptomatic, symptoms of BV may cause fear and embarrassment which lower patients' quality of life. BV may also lead to other serious complications including increased risk for acquisition of sexually transmitted infections such as *Neisseria gonorrhoea*,

Chlamydia and human immunodeficiency virus (HIV), also prematurity and low birth weight in infants born to pregnant women suffering from BV.^{2,3}

Douching of vagina, other vaginal infections, smoking, promiscuity and use of intrauterine devices were among the known risk factors for BV. However, the exact aetiology of BV is still uncertain. Dysbiosis of vaginal micro biome is thought to be central in the pathogenesis of BV. It is characterized by replacement of *Lactobacillus* spp. by anaerobic and facultative bacteria such as *Gardnerella vaginalis*, *Mobiluncus* spp., *Mycoplasma hominis*, *Bacteroides* spp., *Prevotella* spp. and *Atopobium vaginae*.^{1,2} The earliest event in the pathogenesis of BV is adhesion of *G. vaginalis* to the host cell. Subsequently, *G. vaginalis* produces sialidase and prolidase which attack vaginal mucosa resulting in increased release of proinflammatory cytokines and vaginolysin which initiates cellular death mechanisms. It also forms biofilms which act as defence against hydrogen peroxide and lactic acid produced by *Lactobacillus*, and act as environment for growth of other pathogens and exchange of genes encoding antimicrobial resistance. Other bacteria within the biofilms also act synergistically with *G. vaginalis*. *Prevotella* spp. producing fibrinolysin and collagenase to aid in the adhesion to vaginal mucosa and counter the mucosal defence system. Together with *Peptostreptococcus anaerobius*, *Prevotella* spp. also provides amino acids and nutrition for other

pathogens.^{3,4} Overgrowth of pathogens reduces nutritional support for lactobacilli. The enzymes released by these pathogens also impair vaginal barrier. The end results are reduced *Lactobacillus* spp., depleted lactic acid and hydrogen peroxide, increased vaginal pH and persistent infection.^{2,3}

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Centre for Disease Control and Prevention currently recommends oral metronidazole 500mg twice a day for one week, intravaginal metronidazole gel once to twice a day for five days or intravaginal clindamycin cream once at night for one week for treatment of BV in non-pregnant females.³ However, these treatments showed variable efficacy with cure rate of 58-92%.⁵ Anukam *et al.* even reported a cure rate of 40% among BV patients treated with oral metronidazole alone.⁶ More than 50% of BV patients also experienced recurrence and reinfection within 6-12 months after treatment, probably due to antibiotic resistance. Oral antibiotics may also negatively influence normal gut microbiome, while intravaginal antibiotics may predispose patients to vulvovaginal candidiasis.^{5,7} Therefore, alternative therapies to restore normal predominantly-*Lactobacillus* spp. vaginal micro biome were being explored, including probiotics.³

Probiotics are oral or topical supplements containing live bacteria and/or yeasts which are beneficial for health.³ Probiotics containing *Lactobacillus* spp. have been studied for treatment of vaginal dysbiosis since they are the predominant commensal bacteria of vagina. They act to prevent pathogen adhesion by production of anti-biofilm biosurfactant and competition for binding site, and produce hydrogen peroxide against BV pathogens.³ Anukam *et al.* reported that probiotics containing *L. rhamnosus* GR-1 and *L. reuteri* RC-14 together with oral metronidazole increased cure rate of BV by 48% compared to

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oral metronidazole alone.⁶ Cianci *et al.* reported that probiotic containing *L. plantarum*, which is another member of commensal vaginal bacteria, reduced risk of recurrent vaginal infections, although it wasn't statistically significant.⁸ Lin *et al.* also reported that probiotics containing *L. rhamnosus* and *L. plantarum* significantly decreased malodorous discharge, pruritus and Nugent scores in 19 BV patients.⁹

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Lactobacillus plantarum IS-10506 is an indigenous Indonesian probiotic isolated from dadih, fermented buffalo milk.¹⁰⁻¹² As this species has interacted with other pathogenic and contaminant microbes in Indonesia, *L. plantarum* IS-10506 are expected to be beneficial and appropriate for use as probiotic in local settings.¹³⁻¹⁶ Microencapsulated formulation also enhanced the survival of *L. plantarum* during storage and transit in the upper gastrointestinal tract.¹⁴ This study aimed to evaluate the effect of probiotic containing microencapsulated *L. plantarum* IS-10506 as supplementation on oral metronidazole in the treatment of BV in Indonesian female patients.

Methods

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Ethics Study protocol was approved by Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya (No. 1626/KEPK/XI/2019).

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Study design and setting This was a randomized, double-blind, placebo-controlled trial to evaluate the effect of oral probiotic microencapsulated *L. plantarum* IS-10506 supplementation on oral metronidazole for BV treatment at the Dermatology and Venereology outpatient clinic of a Dr. Soetomo General Academic Hospital, Surabaya, Indonesia from November 2019 to January 2020.

Participants Eligible participants were females, aged 18-55 years, diagnosed with BV with apparently good health and willingness to

participate in the study and sign informed consent. Diagnosis of BV was established according to Amsel criteria and Nugent scoring system. Amsel criteria requires 3 out of 4 findings to diagnose BV, namely thin, whitish-grey, homogeneous vaginal discharge, fishy odor upon addition of 10% KOH solution to the discharge (Whiff test), vaginal pH>4.5, and presence of >20% clue cells in wet mount microscopy with NaCl 0.9% (100x magnification).^{2,3} Nugent scoring system evaluated three types of bacteria in Gram-stained vaginal discharge (1000x magnification, oil-immersion field): large Gram-positive rods or *Lactobacillus* morphotypes (score 0-4), small Gram-variable rods or *Gardnerella vaginalis* morphotypes (score 0-4), and curved Gram-variable rods or *Mobiluncus spp.* morphotypes (score 0-2). Total Nugent score was graded as: normal microflora (0-3), indeterminate microflora (4-6) and bacterial vaginosis (7-10).¹⁷ The exclusion criteria were pregnancy, history of antibiotics and/ or probiotics intake within previous 4 weeks and history of allergies to antibiotics and/or probiotics used in the study. The cure rate for subjects with BV treated with metronidazole alone was assumed to be 40% according to Anukam *et al.* and the expected difference in cure rates was 50%.⁶ Using 95% level of confidence and 80% power, the calculated sample size was 26.

Interventions and randomizations Participants were recruited by consecutive sampling and were randomly assigned into one of the two treatment arms, probiotic (Pro) and placebo (Pla) groups. Both groups were treated with oral metronidazole 500mg twice daily. Pro group was also given oral probiotic, consisting of 950 mg (0.9×10^9 CFU) microencapsulated *L. plantarum* IS-10506, twice daily. Pla group was also given oral placebo, consisting of cellulose (Avicel) and skim milk mixture which has identical color, taste, odor, shape and packaging

to the oral probiotic, twice daily. The probiotic or placebo was given 1 hour after metronidazole intake. The probiotic was packaged by the Pharmacy Department of our institution. Randomizations were carried out by the Pharmacy Department of our institution using a computer-generated scheme and participants were given numbers. Metronidazole and identical-looking probiotic or placebo capsules were supplied in numbered containers. Randomization data were kept in the pharmacy and were not disclosed until the study ended. Both researchers and participants were blinded to the treatment given. Amsel criteria, Nugent score and side effects were assessed at the end of week 1, 2 and 4. Oral metronidazole was stopped if participant was cured of BV, but oral probiotic or oral placebo was continued for 4 weeks. Cure was determined from Amsel criteria (presence of less than 3 out of 4 findings) and Nugent score of 0-3. The primary outcome of this study was the cure rate at the end of week 1,

2 and 4. The secondary outcome of this study was Nugent score and reported side effects at the end of week 1, 2 and 4. The research flow is illustrated in **Figure 1**.

Results

Twenty nine subjects met the inclusion criteria and were randomized into 14 subjects in the Pro group and 15 subjects in the Pla group. Fisher's exact test was used to compare baseline demographic and clinical characteristics between groups showing no statistically significant difference (**Table 1**). All subjects completed the study for 4 weeks. There was significant reduction of mean Nugent score from baseline at the end of week 1, 2 and 4 in both groups ($p \leq 0.05$) (**Table 2**). The mean Nugent score of Pro group was similar to Pla group at baseline, but consistently lower than Pla group at the end of week 1, 2 and 4.

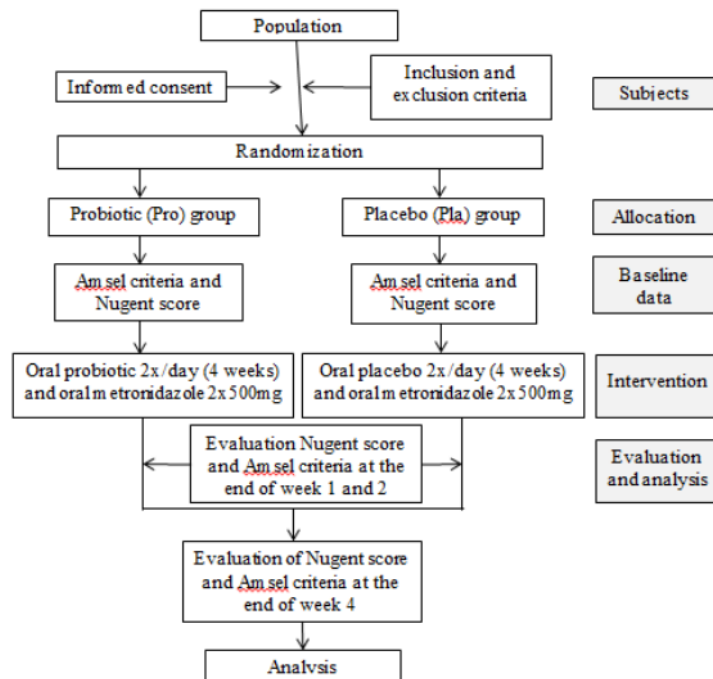


Figure 1 Research flow.

Table 1 Baseline demographic and clinical characteristics.

Characteristics	Frequency (%)		p-value
	Pro group (n=14)	Pla group (n=15)	
Age (years)			
18-25	2 (14.2)	3 (20.0)	0.785
26-35	4 (28.6)	6 (40.0)	
36-45	4 (28.6)	2 (13.3)	
46-55	4 (28.6)	4 (26.7)	
Education			
Elementary school	0	2 (13.3)	0.104
Junior high school	2 (14.2)	0	
Senior high school	6 (42.9)	10 (66.7)	
College	6 (42.9)	3 (20.0)	
Marital status			
Married	12 (85.8)	14 (93.3)	0.598
Unmarried	2 (14.2)	1 (6.6)	
Duration of illness (days)			
1-14	8 (57.1)	12 (80.0)	0.249
15-30	6 (42.9)	2 (13.3)	
> 30	0 (0.0)	1 (6.6)	
Episode of BV			
Primary	13 (92.9)	14 (93.3)	1.000
Recurrent	1 (7.1)	1 (6.6)	
Risk factors			
Sexually active	13 (92.9)	12 (80.0)	0.598
Multiple sexual partner	0 (0.0)	1 (6.7)	
Vaginal douching	9 (64.3)	5 (33.3)	0.143
Contraceptive use*	7 (50.0)	4 (26.7)	0.264
Concomitant STI**	4 (28.6)	2 (13.3)	0.390

BV=Bacterial vaginosis, Pla=placebo, Pro=probiotic, STI=sexually transmitted infections, * intrauterine device and hormonal, ** condyloma acuminata.

However, there was no statistically significant difference ($p>0.05$) (Table 3 and Figure 2). The cure rate of Pro group was also consistently greater than Pla group at the end of week 1 (28.6% vs. 20.0%), week 2 (50.0% vs. 33.3%) and week 4 (64.3% vs. 40.0%). However, there

was no statistically significant difference ($p>0.05$) (Table 4). In both the groups all subjects who were cured of BV at the end of week 1 and 2 showed no recurrence at the end of week 4. No participant reported any side effect throughout the study.

Table 2 Difference of Nugent score in both groups at baseline and on follow ups.

Difference of Nugent score	Pro group (n=14)		Pla group (n=15)	
	Mean±SD	p-value*	Mean±SD	p-value*
Baseline and end of week 1	2.72±2.867	0.005	1.87±2.475	0.011
Baseline and end of week 2	4.00±2.680	0.003	3.13±2.973	0.003
Baseline and end of week 4	4.50±2.133	0.002	3.73±2.374	0.001

Pla=placebo, Pro=probiotic, *Wilcoxon signed rank test.

Table 3 Mean Nugent score in both groups at baseline and on follow ups.

Nugent score	Mean±SD		p-value*
	Pro group (n=14)	Pla group (n=15)	
Baseline	8.07±0.475	8.07±0.883	0.865
End of week 1	5.36±3.003	6.20±2.484	0.582
End of week 2	4.07±2.759	4.93±2.658	0.407
End of week 4	3.57±2.344	4.33±1.951	0.317

Pla=placebo, Pro=probiotic, *Mann-Whitney U test.

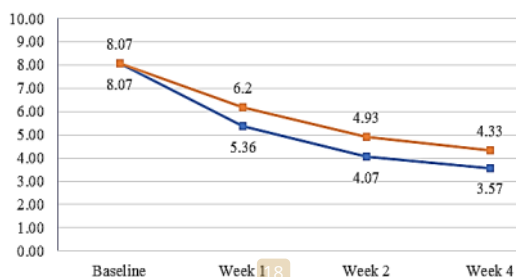


Figure 2 Mean Nugent score at baseline, week 1, week 2 and week 4 in both groups

Discussion

In this study, the mean Nugent score decreased significantly at each follow up compared to baseline in both Pro and Pla group. This study also showed increasing cure rate of BV at each follow up in both groups. The cure rate of BV patients treated with antibiotic only in this study (40.0% in Pla group) is similar to report by Anukam *et al.* (40%), but lower than reports by Li *et al.* (66.31%) and Munoz-Barreno *et al.* (74.6%). The cure rate of BV patients treated with antibiotic and probiotic combination in this study (64.3% in Pro group) is lower than reports by Anukam *et al.* (88%), Li *et al.* (78.38%) and Munoz-Barreno *et al.* (74.1%). These differences may be attributed to different route of administration (oral or intravaginal), types of antibiotics (such as metronidazole, tinidazole, clindamycin) and probiotics (such as *L. crispatus*, *L. rhamnosus*, *L. reuteri*, *L. acidophilus*, *L. brevis*, *L. salivarius*, and *L. plantarum*), and also to dose and duration of treatment in these studies.^{6,18,19} The low cure rate may also be caused by persistence of risk factors

for BV among the participants with treatment failure. Formation of biofilm and development of antibiotic resistance by BV pathogens may also contribute to treatment failure in this study.^{4,5}

In this study, Pro group showed lower mean Nugent score (3.57 vs. 4.33) and higher cure rate (64.3% vs. 40%) compared to Pla group at the end of week 1, 2 and 4. However, there were no statistically significant differences. All subjects in this study also reported no side effects. Munoz-Barreno *et al.* also reported no significant difference between pooled clinical cure rate of BV patients treated with antibiotic and probiotic combination or antibiotic alone.¹⁸ However, Anukam *et al.* reported significantly higher cure rate at day 30 in BV patients treated with oral metronidazole supplemented with probiotics containing *L. rhamnosus* GR1 and *L. reuteri* RC-14 compared to oral metronidazole alone.⁶ Li *et al.* also reported significantly higher cure rate in BV patients treated with antibiotics and probiotics compared to antibiotics alone.¹⁹ Wu *et al.* proposed that conflicting results on effects of probiotics in BV may be due to variation in probiotic species and route of administration.⁷ The importance of probiotic species is related to normal vaginal microbiome which varies according to ethnicity. *Lactobacillus crispatus* is reported to be higher in Asian and Caucasian females compared to African females.^{5,7} This species is also reported to confer protection against vaginal dysbiosis and improve stability of vaginal microbiome.²

Table 4 The cure rate of bacterial vaginosis in both groups at baseline and on follow ups.

Time	Group	Cured*	Not cured	p-value**
Baseline	Pro	0 (0.0%)	14 (100.0%)	1.000
	Pla	0 (0.0%)	15 (100.0%)	
End of week 1	Pro	4 (28.6%)	10 (71.4%)	0.682
	Pla	3 (20.0%)	12 (80.0%)	
End of week 2	Pro	7 (50.0%)	7 (50.0%)	0.462
	Pla	5 (33.3%)	10 (66.7%)	
End of week 4	Pro	9 (64.3%)	5 (35.7%)	0.272
	Pla	6 (40.0%)	9 (60.0%)	

Pla=placebo, Pro=probiotic, *Cured if negative Amsel's criteria and Nugent score of 0-3, **Fisher's exact test

Despite of 100% short term cure rate, 70-79.5% long term cure rate, and higher remission rate than placebo, studies on *L. crispatus* as probiotics in BV are relatively lacking compared to other species. Unsuitable probiotic species may explain the wide variation of BV cure rates between studies.⁷ Route of probiotic administration may also affect the cure rate of BV. Probiotics containing *L. reuteri* RC-14 and *L. rhamnosus* GR-1 showed better BV cure rate by intravaginal compared to oral route. This may be due to immediate replacement of BV pathogens by the probiotic species.⁷ On the other hand, oral probiotics require migration of lactobacilli through gut, perineum and vulva to vagina.²⁰ However, oral probiotics are developing more rapidly than intravaginal probiotics, because they are not regulated as drug but as food supplements.⁷

This study has some limitations including lack of assessment of biofilm formation and antimicrobial resistance and unavailability of intravaginal formulation of the probiotic used. Another limitation of this study is the short follow up period for subjects who were cured of BV. The follow up period completed at the end of week 4, which ranged from 14 to 21 days for subjects who were cured of BV at the end of week 1 or 2. Although all cured subjects showed no recurrence until the end of week 4, the follow up period is much shorter than average time to BV recurrence. Heczko *et al.* reported average time to BV recurrence of 47.3 days in subjects receiving placebo and 71.4 days in subjects receiving oral supplementation of *L. gasseri* 57C, *L. fermentum* 57A and *L. plantarum* 57B after stopping oral metronidazole.²¹ This short follow up period precludes accurate assessment of recurrence rate in this study.

Conclusion

Oral probiotic microencapsulated *L. plantarum*

IS-10506 supplementation in addition to oral metronidazole were safe and potentially better than oral metronidazole alone for treatment of BV. Studies with more subjects, also longer probiotic supplementation and follow up period may be required to demonstrate significant effect of this combination treatment on BV.

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