

Conference Paper

Giving Probiotic for a Better Therapy of Bacterial Vaginosis

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Abstract

Bacterial vaginosis (BV) is a common problem in women that is characterized by a decreased colonization of *Lactobacillus* in the vagina. Such condition may lead to various complications including endometritis, pelvic inflammatory disease, miscarriage, preterm birth, chorioamnionitis, premature rupture of the membrane, postpartum endometritis and increasing failure of *in vitro* fertilization. Treating BV using antimicrobials is somehow effective but often causes recurrences and antibiotic resistance. This paper examines the use of probiotic consisting of *Lactobacillus spp.* for the treatment of BV by conducting a systematic review of research articles published in online databases. After the review process, there are 18 articles with a total of 2,442 women as participants selected in this present report. There are six mechanisms involved in BV treatment using probiotic; i.e., (1) competition mechanism with pathogens, (2) stabilization of mucin layer, (3) production of antibacterial substances for killing and preventing the colonization of pathogenic bacteria, (4) reduction of the vaginal pH, (5) stimulation of the immune system, and (6) restoration of vaginal homeostasis. Previous studies were evaluated and the findings suggest that probiotics are better than antimicrobials in treating BV due to the absence of reported side effects. In addition, giving probiotics especially *Lactobacillus sp.* can be a better therapy of BV.

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Received: 23 February 2019

Accepted: 6 March 2019

Published: 25 March 2019

Publishing services provided by
Knowledge E

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Selection and Peer-review under the responsibility of the ICO-HELICS Conference Committee.

1. Introduction

Urogenital infections can degrade the quality of women's life [1]. Bacterial vaginosis (BV) is a urogenital infection affecting an estimate of 20%–42% of women in reproductive age [2, 3]. A more specific study states that in women aged 14-49 years, the prevalence of BV reaches 29.2% [4]. A study conducted on 492 Indonesian women has reported that the minimum prevalence of BV is 30.7% with risk factors including age over 40 years and couples who do not perform circumcision or circumcision processes [5]. Bacterial vaginosis is a condition characterized by a decreasing number of microbiota *Lactobacillus spp.* and followed by an increasing number of other bacteria

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such as *Gardnerella vaginalis*, *Atopobium vaginae*, *Prevotella spp.*, *Mobilucus spp.* and *Mycoplasma hominis*. Bacterial vaginosis is also defined as a polymicrobial syndrome characterized by abnormal vaginal discharge in women. In this condition, *Lactobacillus* especially produces hydrogen peroxide (H₂O₂) [6].

Complications of BV include endometritis, an increase in the incidence of sexually transmitted infections such as human immunodeficiency virus (HIV) infection, miscarriage, preterm birth, chorioamnionitis, premature rupture of membranes, and postpartal endometritis. In women who undergo *in-vitro* fertilization, BV decreases the chance of embryo implantation thereby increasing the failure in the development of the pregnancy [2, 7].

Metronidazole is the most common antibiotics used for BV therapy. However, recent studies showed that when metronidazole is used for short term therapy (up to 30 days), the cure rate is low [8] and can lead to >50% until 69% of recurrence rates in 6-12 months after the cessation of therapy [9]. The side effects of metronidazole include gastrointestinal disorders (e.g., nausea, vomiting, leukopenia, and metallic taste in the mouth when administered orally). We conducted a systematic review to examine the use of probiotics for BV therapy in comparison with conventional therapy.

2. Methods

2.1. Search strategy and study selection

Study articles were searched in PubMed, Science Direct, Web of Science, Springer Link and the Cochrane Database. The key words included probiotic AND bacterial vaginosis, probiotic AND randomized controlled trial, probiotic AND placebo, probiotic AND metronidazole.

2.2. Assessment of study quality

The inclusion criteria were randomized controlled trials (RCTs), probiotic therapy given is *Lactobacillus spp.* or metronidazole and placebo regimens, or both. The subjects included women of reproductive age who were treated for ≥ 5 days. The studies were reviewed if the cases of lost to follow-up were <20%. Bacterial vaginosis was diagnosed based on Nugent score of $\geq 7 - 10$ which represent the number of airy morphotype organisms per microscopic field; the organisms included *Lactobacillus*, *Mobiluncus*, and *Gardnerella vaginalis* (given score 4 if there are >30 organisms per microscopic field) [10].

Another criteria used for diagnosing BV is Amsel criteria. According to Amsel criteria, someone is considered suffer from bacterial vaginosis when three of these symptoms are present: (i) the acidity or pH > 4.7; (ii) vaginal discharge color is gray or white; (iii) the release of fish odor when the whiff test is done; (iv) there are clue cells on microscopic examination with saline solution [11, 12]. This review reported articles published in English from 1994 until 2017.

3. Results

The review process and the number of articles found is shown in Figure 1.

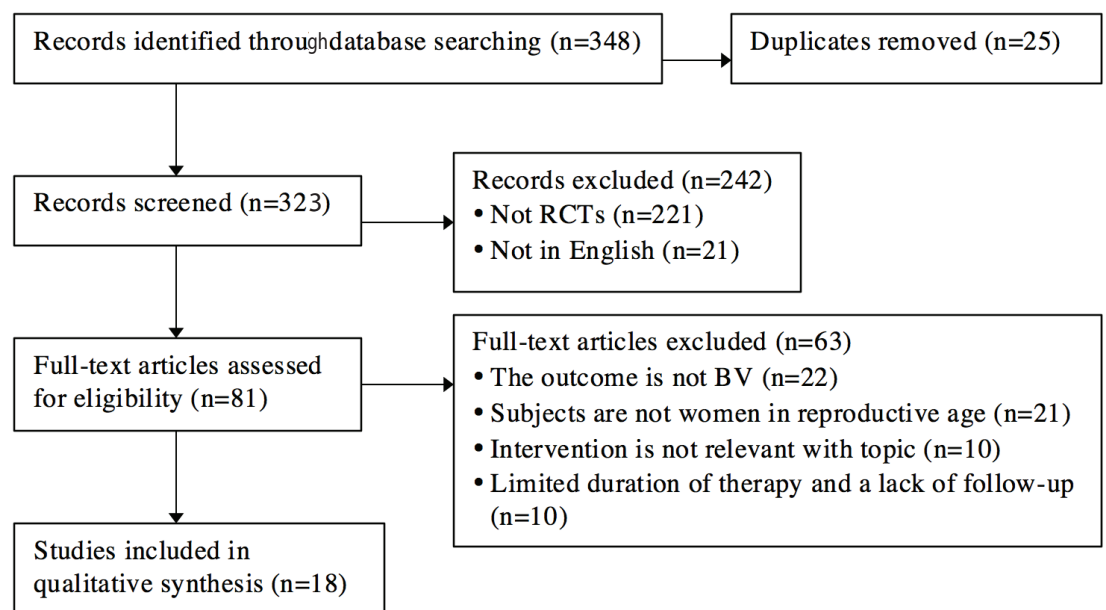


Figure 1: Flow diagram of the study.

4. Discussion

Antimicrobial therapy for BV can cause various side effects especially for long-term use but will cause recurrences when the duration of therapy is too short. This phenomenon promotes researchers to look back to the natural vaginal defense process relying on the *Lactobacillus spp.* which control and kill pathogens causing bacterial vaginosis such as *Gardnerella vaginalis*. Three studies show that oral probiotic gave better therapeutic effect rather than metronidazole [12]. However, another study shows that the therapeutic effect of 500 mg of metronidazole is better than probiotic [13]. This contradicting results might be due to the number of BV cases is unequal for each group. Previously, the authors of this present paper have conducted a meta-analysis and found that the administration

of probiotics is as effective as metronidazole therapy with the combination of probiotics and metronidazole is a better choice rather than antimicrobial and for preventing BV recurrences [14, 15].

4.1. *Lactobacillus* sp mechanism to combat BV

Probiotics against BV through various mechanisms, including competition with pathogens in the process of erythrocytes adherence [16], stabilization of mucin layer and prevention of the growth of pathogenic bacteria [17], and producing antibacterial substances such as bacteriocin, reuterin, reutericyclin, and hydrogen peroxide. Bacteriocin is antibiotics synthesized from probiotic bacteria that are active against pathogenic bacteria [18]. *Lactobacillus reuteri* produces heavy antibiotics components but tends to have a wide spectrum of resistance to reuterin and reutericyclin. Both of them have a benefit in decreasing the levels of urease in the feces so as to suppress the growth of bacteria and inhibit the growth of pathogens [19]. *Lactobacillus* can produce hydrogen peroxide as a result of its high affinity with oxygen compared to other species. The effects of H₂O₂ on pathogenic bacteria depend on the oxidizing ability of the bacterial cell wall. Hydrogen peroxide works alongside with other organic acids to overcome pathogenic bacteria such as *Listeria monocytogenes*, *Bacillus cereus*, *Bacillus subtilis*, *Yersinia enterocolitica*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Gardnerella vaginalis* and *Klebsiella pneumoniae* [20].

In addition, organic acids with antibacterial properties, including acetic acid and lactic acid, are produced as a result of hexose fermentation by probiotic bacteria. Different species of probiotic bacteria will affect the levels and types of organic acids produced. The acid diffusion through the probiotic bacteria membrane cells which are increasingly hydrophobic or directly into the cell, stimulate the release of hydrogen ions that acidify the cytoplasm of pathogenic bacteria. The acidity of acetic acid is stronger than lactic acid; thus, more potent for inhibiting pathogenic bacteria and fungi. The acidity causes the collapse of the electrochemical proton gradient resulting in bacterial death [21].

Probiotics will suppress the inflammatory reaction, normalize mucosal permeability, and improve the immunologic barrier, especially the IgA response. This can stimulate the body's immune system [22, 23]. Combination of probiotic and antimicrobial therapies after previously administered antimicrobial therapy can improve *Lactobacillus* colonization in the vagina and the addition of *Lactobacilli* can rebuild vaginal homeostasis. This can explain why women treated with probiotics have a lower and longer recurrence rate [8]. All of these mechanisms explain why the results of comparison between probiotic

and placebo from eight studies show that probiotics are more effective than placebo [2,3, 22-27] and one study shows the contrary [28].

4.2. The recommended dosage

The evidence has shown that probiotics can be an alternative therapy for bacterial vaginosis. Important information required is the optimum dosage and the composition of probiotics with the best therapeutic results. There are two studies comparing the dosage with standard administered 10^8 CFU *Lactobacillus* [29, 30]. The results showed that twice daily dosage gave better therapeutic effects than once daily dosage but the results are not statistically significant.

4.3. The risk factors of BV

An increasing number of pathogens that cause BV and a decrease in the number of vaginal normal flora that can become natural protective of the vagina can be caused by various factors including the levels of estrogen and progesterone, psychological and environmental factors, age and contraception. The menstrual cycle that women experience every month induces estrogen secretion. This hormone is very influential on BV occurrence because a decrease in estrogen level has been linked to a decrease numbers of *Lactobacillus* in the vagina [31]. Estrogen also plays a role in supporting the proliferation process of the vaginal epithelium. In addition to estrogen, during the menstrual process there is also the release of progesterone. This hormone has a role in supporting the cytolysis process of epithelial cells, where glycogen is re-used by *Lactobacillus* and other microbiota that metabolize and convert it to glucose and maltose which will further be converted to lactic acid which makes the vagina have a level of acidity ranging from 3.8 - 4.4 under normal conditions [32, 33].

Psychological and environmental factors that can increase the likelihood of BV include sexual activity and smoking habits. Health conditions of sexual partners especially circumcision can reduce the risk of BV. It is not known with certainty the magnitude of genetic influences on the incidence of BV, but genetic polymorphisms have been known to interfere with the innate immune system, even allelic polymorphisms in gene introns, especially in interleukin-1 cytokines (IL1RN2) are associated with increased vaginal acidity (pH) and followed by a decrease in the amount of *Lactobacillus spp.* in the vagina [34-36].

Women in menarche age has an unstable amount of *Lactobacillus*. However, after getting the menstrual cycle as explained above, the hormones estrogen and progesterone released during menstruation contribute to the survival of *Lactobacillus*. Women who enter menopause, post menopause or those who no longer have a normal menstrual cycle are very likely to suffer from BV [34]. The choice of contraceptive method has been shown to change the amount of microbiota in the vagina. Research conducted on 331 women who used cervical cap and diaphragm-spermicide experienced an increase in the number of colonization from *Escherichia coli* in contrast to women who use pill contraception who were found to have a decrease in the number of colonization of microbiota such as *Escherichia coli* and *Candida spp.* [37].

5. Conclusion

The results of this systematic review recommend probiotic therapy twice daily in a concentration of 8×10^8 CFU of *Lactobacillus spp.* because this therapy is more effective than metronidazole. Another advantage of probiotic is it does not have side effects for therapy and prevention of BV.

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