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Research Article

EFFECTS OF RIFAXIMIN VAGINAL TABLETS ON VAGINAL MICROBIOTA IN BACTERIAL VAGINOSIS: INSIGHTS FROM A RANDOMIZED CONTROLLED TRIAL FOR POTENTIAL PREGNANCY OUTCOMES

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ABSTRACT

Bacterial vaginosis (BV) is a common vaginal infection associated with sexually transmitted infections and adverse pregnancy outcomes. In this randomized, double-blind, placebo-controlled study, 102 patients with BV were enrolled to investigate the effects of rifaximin vaginal tablets on the vaginal microbiota. The study aimed to assess the impact of different doses of rifaximin (100 mg, 25 mg, and 100 mg) taken daily for two days on the vaginal microbiota composition. The study utilized molecular techniques, including polymerase chain reaction-denaturing gradient gel electrophoresis (PCR-DGGE) and qualitative polymerase chain reactions (qPCR), to analyze the microbial changes induced by rifaximin treatment. Results showed that rifaximin administration led to alterations in the vaginal microbiota, characterized by an increase in the abundance of Lactobacillus genus and a reduction in bacteria associated with BV. PCR-DGGE analysis demonstrated modulation and reduction of vaginal fluid microbial communities following rifaximin treatment. Notably, rifaximin 25 mg administered four times a day showed promising results in modulating the vaginal microbiota in patients with BV. These findings suggest that rifaximin vaginal tablets have the potential to effectively modulate the vaginal microbiota composition in patients with BV. The observed increase in Lactobacillus abundance and decrease in BV-associated bacteria indicate a beneficial effect of rifaximin on restoring vaginal microbiota balance. Further pivotal studies are warranted to validate these results and assess the clinical efficacy and safety of rifaximin in the treatment of BV. Rifaximin, particularly at a dose of 25 mg four times a day, may represent a promising therapeutic option for patients with BV, offering potential benefits for the management of this prevalent vaginal infection.

Key words:-Bacterial vaginosis, Rifaximin, Vaginal microbiota, Polymerase chain reaction-denaturing gradient gel electrophoresis (PCR-DGGE), Lactobacillus, Microbial modulation.

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INTRODUCTION

The vaginal mucosa's microbial colonization plays a crucial role in maintaining ecosystem homeostasis [1]. Lactobacilli dominance is characteristic of a healthy vaginal ecosystem, offering benefits beyond microbial protection. Recent studies utilizing 16S rRNA gene sequencing have unveiled previously unidentified taxa in the vaginal microbiota. Pregnant women afflicted with bacterial vaginosis (BV) tend to harbor a more diverse microbiota compared to nonpregnant counterparts [2-5]. BV is often attributed to various pathogens including Mycoplasma hominis, Gardnerella vaginalis,

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and Gram-negative rods. Reduction of lactobacilli levels in the presence of hydrogen peroxide is observed, potentially leading to BV. Anaerobic overgrowth, facilitated by elevated proteolytic carboxylase enzyme production, contributes to BV pathogenesis, causing vaginal epithelial exfoliation and discharge of peptides. Clinical implications of BV include increased susceptibility to spontaneous preterm labor, preterm births, and colonization by Chlamydia trachomatis, Neisseria gonorrhoeae, and herpes simplex virus type 2 [6]. Diagnostic criteria for BV include the Amsel and Nugent scores, with recurrence rates reaching 58% post-treatment with metronidazole or clindamycin. Recurrent exposure to antibiotics may lead to the emergence of drug-resistant strains and polymicrobial biofilm formation [7]. Rifaximin, characterized by a wide antimicrobial spectrum and negligible absorption rate, shows promise as a local treatment for BV and urogenital infections [8]. Studies investigating the efficacy of rifaximin vaginal tablets have utilized culture-based methods and molecular techniques like quantitative PCR (qPCR) and PCR-denaturing gradient gel electrophoresis (PCR-DGGE) to assess changes in vaginal microbiome composition. These techniques allow for the tracking of bacterial population shifts, aiding in the monitoring of antibiotic treatment effectiveness and providing insights into BV etiology and treatment strategies.

MATERIALS AND METHODS

Several multicenter, double-blind studies with randomized placebo controls compared rifaximin vaginal tablets to placebos. The molecular study included 102 Caucasian, postmenopausal women. We diagnosed BV using Amsel's and Nugent's criteria on the screening visit (V1). In order to meet the Amsel criteria, a patient must receive a Nugent score >3. The second post-randomization visit (V2) involved giving each group of patients vaginal tablets every day for five days. Patients in group B were given rifaximin vaginal tablets for 25 days during their five-day treatment. The first two days of the trial were spent giving placebo vaginal tablets to group D, while the first five days were spent applying rifaximin vaginal tablets to group A. Intravaginal medication was administered before bedtime. Following the end of treatment, results were obtained in the first follow-up visit 7 days later. Following completion of therapy for 28 days, patients who met Amsel's remission criteria had a positive Nugent score of 2 and a positive Gram stain Nugent score of 3. The upper vaginal vaults were flushed and breathed in to collect molecular samples as described elsewhere. When the fluids had been rinsing, they were stored at -80°C until use. Through biochemical analysis, DNA can be extracted from vaginal rinse fluid. A centrifuge at 9,500 g at 40°C for 15 minutes was used to remove stains from vaginal rinse serum fluids. The pellets were lysed with Tris-HCl [pH 8] with 2 mM EDTA, 1.2% Triton X-100, and 20 mg/ml lysozyme for 30 minutes after addition of the liquid lysis solution. One minute of vortexing was used to mix glass beads (200 mg) with sample. An initial pretreatment to remove Gram-positive bacteria was performed before extracting the whole genome with the DN easy blood and tissue kit. After incubating glass beads with proteinase K, the amount of DNA was measured using Thermo Scientific's NanoDrop 1000. It was possible to correlate the amount of PCR product with the fluorescence signal by using a Light Cycler apparatus (Roche, Mannheim, Germany). Using primers designed specifically for each genus or species, we amplified the 16SRNA gene or the 16S-23S rRNA spacer region. Bact-0011f/Lab-0677r was used for screening Lactobacillus and Gloeobacterium vaginalis; c-Atopo-f/c-Atopo-r for Atopobium, 226 R for Prevotella, VeilloF/VeilloR for VeilloF/VeilloR for MycF/MycR for Mycobacterium. In Mobiluncus, one species is called Homo sapiens, while the other is called Mob-s/Mob-as. With 40-l of primers and no template control (no template), Light Cycler-FastStart DNA Master SYBR green I (Roche) was used for amplification. Cells of Lactobacillus, Atopobium, Gardnerella vaginalis, Veillonella, and Mobiluncus were denaturated for 10 minutes at 95°C, and then cooled for 30 minutes. Following denaturation at 95°C for 15 seconds, Topobium, Prevotella, Gonorrhoea vaginalis, or Lactobacillus, Mobiluncus) are annealed to 63°C, whereas Veillonella, M. hominis are annealed to 62°C.

These isolates were extracted for 45 minutes with Atopobium, Prevotella, Lactobacillus, and Geobacillus vaginalis. Atopobium, Gardnerella vaginalis, Veillonella, Mobiluncus, Mobilillus, and Atopobium were measured during a five-second window of time, while Prevotella and Mobilillus were measured at 87°C and 88°C, respectively. The ATCC 29,303 spot strain of Mobilillus fluorescent bacteria at 88 degrees Celsius was also acquired along with Veillonella parvula ATCC 10790, Gardnerella vaginalis ATCC 14018, and Veillonella parvula ATCC 10790. DNA from the vaginal canal is amplified using a set of three primers. As a result of the total number of DNA molecules in each species or genera, DNA concentrations differ.

A 16S rRNA gene V2-V3 region has been amplified using the universal eubacterial primers GCclamp-HDA1 and HDA2. An Amplification device by Biometra (Göttingen, Germany) was used for the amplification. The GoTaq Flexi enzyme from Promega is thermostable as well as high temperature stable. To a reaction mixture of 25 liters, 500 mM magnesium chloride, 200 mM primers, and 1.25 u GoTaq Flexi DNA polymerase were added. At a concentration of 30ng, DNA was extracted from bacteria. Using a thermocycler, 95 degrees C were maintained for five minutes, 56 degrees C for 30 seconds, 72 degrees C for 60 seconds, and 95 degrees C for eight minutes. In order to elucidate the design of the experiments, samples of amplified

products (200 bp) (5L) were electrophoresed on 1.5% agarose gels.

We processed DGGE gels 20 cm x 20 cm x 0.75mm using Bio-Rad's D-Code universal mutation system (Hercules, CA). Prepare TAE buffer by mixing 20mM Tris with 80% acrylamide-N and bisacrylamide-N. In a mixing bowl, combine the first two ingredients and add 10 mM EDTA and 20 mM glacial acetic acid. The electrophoresis direction was increased to produce urea and formamide gradients on denaturing gels. There were 7 million urea atoms and 40 percent formamide in a denaturing solution. A weight/volume ratio between 5 and 8 is required to stack polyacrylamide denaturing gels with an 8% weight/volume ratio. PCR samples were electrophoresed using an 8-liter stacking gel. Ward clustering is used in Gel Docs. Pearson correlation coefficients were used to calculate similarity indices (SIs). In this study, the DGGE profiles of two women were compared in order to determine whether they had similar profiles. FPQuest densitometric curves were used to calculate a richness index (RI). An analysis of the number of bands in a profile can reveal a profile's microbial complexity [9]. In order to stimulate or perturb an ecological niche, SI or RI can be modified. Analyses were conducted by SigmaStat statistical software. Numerous bacteria and genera have been identified using the qPCR method [10]

A Kruskal-Wallis analysis of variance (ANOVA) was used to compare all women and women in remission at V3. In order to test for pairwise differences, Dunn's test was applied to all pairwise comparisons. Different doses and durations of treatment were compared using a two-way ANOVA. By comparing Wilcoxon's Signed Rank Test results for women in remission at V3 with V3 and V3-V4 we can determine the degree of remission. A Friedman repeated-measures ANOVA and Tukey's tests were used to compare women in remission at V3 and those with RIs related to V1, V3, and V4. The significance threshold for all statistical tests was 0.05 or less.

RESULTS

During the evaluation of remission at the first follow-up (V3), Amsel's criteria (clinical cure) were applied as well as Gram stain Nugent scoring systems. In each group, remission rates were calculated using three doses daily for two days: 100 mg, 25 mg, and 100 mg. A 48% remission rate was recorded in group B, followed by 22% in group A; and 36% in group C. A low remission rate (16%) was recorded with placid vaginal tablets. According to the clinical outcomes do not seem to be different from what can be found in a separate study. There are two populations of bacteria related to BV and lactobacillus. The following species also experience major changes with BV progressions: Atopobium, Prevotella, Veillonella, Mesospora hominis, Mobiluncus, and Lacrobacillus vaginalis. Genomic DNA standards had correlation coefficients exceeding 0.99, and qPCR efficiencies ranged from 90% to 110%.

The results were 94%, 85%, 99%, 98%, 30%, 78%, and 20% for Lactobacillus, Gonococcus vaginalis, Atopobium, Prevotella, Veillonella, and Methanospermophilus hominis, respectively. The vaginal ecosystem of women with BV was dominated by Atopobium, Mobiluncus hominis, and Gastropoda vaginalis. A quantitative comparison between lactobacilli and bacteria associated with BV. In each horizontal bar, the log medians of each genus or species are reported for each microgram of total bacterial DNA extracted from vaginal samples. (A, B, C, and D) were the four treatment groups randomized among the 102 participants. Lactobacillus levels increased following rifaximin treatment, but atopobium levels decreased,

Compared to Lactobacilli, it had a similar log median value at V3. The treatment did not affect the composition or concentration of other BV-related groups. Atopobium, Pre-votella, and Lactobacillus were all significantly increased by Rifaximin 25 mg/day for 5 days. A log median of 2.55 was recorded by Lactobacillus (V3). Following a five-day regimen of 25 mg of rifaximin per day, Amsel's combined criteria and Nugent's scoring system revealed a reduction in BV-related bacteria and a restoration of lactobacilli. At 100 mg/day for two days, Rifaximin reduced Gonorrhoea vaginalis infection by 1.65 log ng/g for V1, 11.6 log ng/g for V3 ($P<0.001$). In addition, Micrococcus hominis at 1.5 logng/g and Atopobium at 1.11 logng/g had very low levels ($P<0.003$). Atopobium and Gastricoccus vaginalis had higher log median values after treatment with Rifaximin for 2 days. In this case, 10 mg once a day for 5 days is equivalent to 25 mg twice a day for 5 days. Statistically significant reductions in bacteria were observed in all groups except the placebo group (group D).

M1 levels were 2.55 log ng/g in the sample ($P <0.04$), and M1 and M3 levels were 1.83 and 1.49 logng/g, respectively ($P = 0.005$). The log median values of Atopobium and Geobacillus vaginalis were higher at V3 than those of lactobacilli. Women with small proportions of Veillonella and Mobiluncus had the same concentrations of these bacteria. Veillonella and Mobiluncus rates decreased as a result of a reduction in infection rates (Veillonella 11.1% vs 7.4%; B, V1, 24.0% vs 8.0%; C, V1, 28.0% vs 12.0%; D, V1, 28.0% vs 24.0%); Mobiluncus (A, V1, 4% vs V3, 0%; B, V1, 8.0%; C, V1, 20.0% vs 4.0%; D, 16.0% compared 12.0%). Compared to V3, -3.4 log ng/g, and V4, log ng/g showed a significant difference. In Atopobium, NG/g differed significantly from V1, 2.02 log ng/g, V3, 0.4 log ng/g, and V4, 0.56 log ng/g, while in Man, NG/g differed significantly from V1 -2.32 log ng/g, V3, -2.81 log ng/g, and V4, -3.34 log ng/g. Prevotella levels at V1 and V3 differed significantly only at V3 ($P <0.0001$).

When lactobacillus concentrations increased at V3 but significantly decreased at V4 following two days of 100 mg/day rifaximin therapy (group C), a relapse occurred [V3, 1.80 log ng/g; V4, 0.33 log ng/g (P<0.03)]. V3 and V4 saw a decrease in BV-related bacteria and a significant increase in G. A total of 1.91 log nanograms were found in the V1, 3.40 log nanograms in the V3, 1.96 log nanograms in the V4 sample (P <0.005, V3 versus V1) and 2.17 log nanograms in the V4 sample (P < 0.003, V3 versus V1) (P < 0.005, V4 versus V3), respectively. There were 1.18 log nanograms per kilogram, 1.06 log nanograms per kilogram and 1.79 log nanograms per kilogram in the Prevotella sample (P < 0.008 compared to V3 versus V1) (P < 0.03) (P < 0.03). At V3 and V4, Prevotella decreased but Lactobacillus increased, despite no notable differences between groups D and E. In comparison with Gonorrhea vaginalis and Atopobium, Lactobacillus log median concentrations were higher after treatment. Because Veillonella and Mobiluncus occur at low concentrations and are rare, the total number of women was not affected.

The PCR-DGGE method is used for profiling bacterial populations. A PCR-DGGE assay was performed using a universal primer pair (HDA1-GC/HDA2) to determine if rifaximin affected the BV microbiota composition at V1, V3, and V4. DGGE profiles were grouped by treatment for cluster analyses. For Group A (100 mg/day for five days), Group C (100 mg/day for two days), and Group D (placebo) participants, detailed cluster analyses are shown in the supplementary material. On Figure 3, you can see a cluster of patients treating themselves with 25 mg/day for five days. According to the treatment groups A, B, C, and D, 37%, 24%, 28%, and 56% of women with V1 and V3 profiles clustered. Taking 25 mg/day for 5 days produced the most significant effect of rifaximin. According to the DGGE profiles, remission women cluster together at V3 and V4, but rifaximin affected the vaginal community more than treatment groups A and B. As shown in Table 2, V1-V3 profile similarity indexes (SIs) in all analyzed women and V1-V3 and V3-V4 profile similarity indexes (SIs) in remission women are different. According to the total number of women, group D received the highest mean SI (75.4% of the women), which had the highest placebo rate. Sixteen percent of patients in treatment group A had the highest mean SI value, followed by 54.0% of patients in treatment group C, and 48.4% of patients in treatment group B. The mean SI value for remission patients at V3 shows a similar pattern. Complying with the placebo group was very high

Kruskal-Wallis test was conducted to compare SIs. When compared to all treatment groups, the SIs for V1-V3 were significantly different from the total number of women (P <0.001). It was found that A and D had a significant difference (P<0.05), and B and D had a significant difference (P <0.05). Dunn's comparison showed that B and C were significantly different from each other (P 0.05) in women in remission (P <0.05). SIs for 100 mg and 25 mg DGGE profiles were compared using ANOVA. Antibiotic doses were significantly different (P 0.05), but antibiotic treatment periods were not significantly different (P > 0.05). According to this study, dosage has the greatest impact on vaginal microbiota composition. Overall, RI decreased at V3, which indicates that the antibiotic simplified the vaginal microbiota. Groups A (10.2) and B (9.0) seem to have maintained antibiotic effects at V4. A decrease in RIs at V3 followed by an approximate return to baseline values at V4 for group C (14.6), a sign that BV microbial diversity has been restored

Wilcoxon signed rank tests demonstrated statistically significant differences between groups A and B and C and between V1 and V3 when women in remission were taken into consideration. As shown by Friedman repeated measures ANOVA, the RIs of V1, V3, and V4 were significantly different in groups B and C, and a pairwise Tukey's test indicated that V1 compared to V3 and V1 compared to V4 were significantly different. Treatment efficacy was also confirmed after two days of using 100 mg/day rifaximin and five days of using 25 mg/day rifaximin. A great deal of agreement is seen between the DGGE results and the qPCR results. After molecular analysis, it was found that 25 mg of rifaximin per day for five days was the most effective treatment for BV.

Table: 1 Remission rates and geographic origins.

Treatment	No. of women	No. (%) in re-emission at V3
Group		
A	27	6 (22)
B	25	12 (48)
C	25	9 (36)
D	25	4 (16)

Table 2 DGGE profiles' average SIs

A	61.6	53.3	66.8
B	48.4	45.3	62.1
C	54.0	40.4	42.8
D	75.4	83.9	58.7

Table 3 Profiling DGGE by mean RIs

Treatment group	V1	V3	V1	V3	V4
A	13.5	10.9	12.5	9.8	10.2
B	14.0	10.7	13.6	8.2	9.0
C	15.4	12.2	16.2	10.4	14.6
D	13.3	13.9	11.3	10.8	9.5

DISCUSSION

In order to maintain reproductive tract health, the vaginal microbiota must work in harmony with the human host. In addition to its severe gynecological and obstetric complications, BV creates an environment conducive to the acquisition of sexually transmitted infections conventional treatments for BV are limited [11], primarily metronidazole and clindamycin. Recurrence rates are high when bacteria associated with BV are not completely eradicated after antibiotic treatment, though a new infection might also occur [12]. As a result of these treatments, Genitalium vaginalis and Prevotella species have started to develop drug resistance. The fifth and nineteenth. Alternative therapeutic tools are needed since conventional antibiotics failed to cure or eradicate BV. Despite being nonabsorbable, rifaximin is not a major source of bacterial resistance. The therapeutic effects of rifaximin on digestive disorders have been reported (33, 35), however there has never been any study on its effects on genital tract infections. 102 patients with BV were examined to determine whether 100 mg rifaximin vaginal tablets were effective in curing and maintaining remission of their disease in this study. PCR-DGGE and qPCR were combined to determine whether bacterial composition of the vaginal environment was associated with antibiotic effect.

Microbiota associated with BV contained anaerobic bacteria, which was inconsistent with previous reports. Anaerobic bacteria do not exist or are low in concentration in a healthy vagina, but they are significantly increased in women with BV [13]. Screening results from the present study (V1) found that Atopobium and G. vaginalis were more abundant in the vaginal area than lactobacilli. Prevotella and Veillonella and Mobiluncus infections have been associated with a small number of women and a low baseline concentration [14, 15]. The Mobiluncus virus infected 78% of BV-affected women, whereas only 20% were infected by it. In 26% of cases, Gram stains indicated Mobiluncus based on Nugent scores of 9 or 10. In this case, both Mobiluncus [16] and BVAB1 might be present, which might mean that there are differences at the microscopic and molecular levels. BVAB1 and Mobiluncus share many similarities. A previously published study [17], showed that the concentration of *A. vaginae* was highly related to Nugent scores, with patients with Nugent scores of 9 and 10 having the highest levels of the organism. Patients with TB may experience microbial disturbances caused by atopobium. Due to the fact that the usefulness of A. motiluncus in diagnosing BV may be excessively overrated at 9, it is important to reevaluate its usefulness. A mobility uncus score of 4 to 6 was assigned while a vaginal fluid score of 6 to 8 was assigned.

We examined whether rifaximin treatment followed by changes in bacterial DNA concentrations after screening (V1) was associated with a cure for BV by comparing data from the screening visit (V1). To minimize BV-related bacteria levels and promote Lactobacillus growth as part of the research, we identified the most effective method. Striking for the maximum amount of bacteria in the vaginal environment. It was found that rifaximin (100 mg/day for five days, group A) was less effective at reducing atropobium levels than lactobacilli recolonizing after antibiotic treatment. A 2 day course of rifaximin was administered to group C at the first follow-up visit (V3). In the women in remission, lactobacillus levels increased significantly, reaching higher levels at V3 than in the other groups, as BV-associated bacteria (Atopobium, G. vaginalis, Prevotella, and M. hominis) levels decreased significantly. A relapse was likely caused by the short duration of antibiotic treatment, as the bacterial count was similar at V4 as it was at baseline. Rifaximin 25 mg/day treated group B showed a good response at V3, followed by a continued response at V4. BV-associated bacteria decreased significantly at both V3 and V4, while lactobacillus organisms increased at both V3 and V4. Lactobacilli are susceptible to rifaximin in vivo, which is not surprising. In spite of its ineffectiveness against harmful bacteria, rifaximin doesn't adversely affect Topobium/Collinsella bacteria and Lactobacillus bacteria. [18]. BV can be treated best by rifaximin taken twice daily for five days (group B) according to Amsel and Nugent's criteria for remission. Remission rates among group B patients were 48 %, 22 %, and 36 %, respectively, while those among group A patients were 22 %. In some cases, placebo vaginal tablets (D) have been reported to induce spontaneous remissions [19, 20].

With PCR-DGGE data and qPCR data targeted at specific bacteria, we analyzed the diversity and richness of the global microbiota. According to DGGE profiles, rifaximin modulated the vaginal microbiota composition after treatment compared with placebo treatment. Treatment groups A, B, and C had lower similarity indices for V1-V3 profiles, whereas Women with V1 profiles tended to cluster less frequently. According to the number of women and remission rate at V3, groups B and C had the lowest SIs. Based on their highest SIs for women in remission at V3 and V4,

antibiotics maintained the vaginal bacterial community effect at V3 and V4. A two-day course of 100 mg/day rifaximin treatment did not prevent relapse for group C, based on lowest SI. Rifaximin 25 mg/day for five days is recommended by qPCR as the best treatment. V3-V4 profiles for group B with DGGE showed high degrees of similarity, suggesting the effect of antibiotic consumption is maintained. A low level of similarity was observed between V1 and V2 DGGE profiles. While rifaximin can be taken at different dosages and for different durations, it is a highly effective treatment for BV, which confirms that it is also supportive of its efficacy.

CONCLUSION

As a measure of the complexity of vaginal communities, we calculated the richness indices (RI) of DGGE profiles. Rifaximin restored a microbiome structure similar to a healthy one in all treated groups after antibiotic intake. Despite being in remission for five days after 25 mg/day rifaximin, women in remission after two days of 100 mg/day rifaximin relapsed. The molecular results of our study support the use of rifaximin to treat BV. It is clear from the strong correlation between clinical outcomes and molecular techniques that molecular techniques are uniquely suited to explore the mechanisms underlying therapeutic effects. Combined 25 mg/day rifaximin with lactobacillus may be effective against BV-causing bacteria without affecting the normal gut flora. Fastidious bacteria must be specifically targeted by BV therapy for it to be effective. There has also been evidence of this effect with vaginal metronidazole, despite its inability to reduce BV-associated bacteria levels in persistent BV cases. As a result of the positive results reported in this study, a clinical study will be conducted to determine if rifaximin is a good alternative to standard BV treatments.

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