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Study of the Effect of High Dose Vitamin D on the Improvement of Bacterial Vaginosis in Vitamin D Deficient Women

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Abstract

Background: The current evaluation was planned to study the effect of vitamin D on improving bacterial vaginosis in premenopausal women with vitamin D deficiency.

Methods: This study was an open-label clinical trial. Forty premenopausal vitamin D deficient women with bacterial vaginosis enrolled in this study. Patients received metronidazole tablet 500 *mg* twice daily for seven days in both groups. In the vitamin D group, patients also received 50000 *IU* per day for five days.

Results: Fourteen days after completion of the study, the number of patients complaining of malodor vaginal discharge, vaginal itching, and discharge discoloration was significantly lower than that in the control group. Regarding the laboratory results, in the vitamin D group, the numbers of *Gardnerella vaginalis*, gram-negative bacilli, and clue cells in the smear of vaginal secretions were significantly less than in the control group ($p<0.05$). Furthermore, none of the patients had a positive whiff test after treatment in the vitamin D group ($p<0.05$). Fourteen days after the completion of the study, the plasma level of 25-OH vitamin D in the vitamin D group was significantly higher than that in the control group. However, the short course of high-dose vitamin D therapy did not increase the plasma concentration of 25-OH vitamin D to the average level.

Conclusion: Vitamin D supplementation can improve the therapeutic response to metronidazole in vitamin D deficient women with BV. However, large-scale double-blind, randomized clinical trials must confirm this finding.

Keywords: Bacterial vaginosis, Metronidazole, Premenopausal women, Vitamin D deficiency, Whiff test

Introduction

Bacterial Vaginosis (BV) is the most common vaginal infection in women. The alteration of normal vaginal flora, absence of lactobacilli, and overgrowth of anaerobic bacteria such as *Gardnerella vaginalis*, lead to infection. Anaerobic bacteria consist of less than 1% of the vaginal flora in normal women, but their concentration is 100-1000 times higher in women with bacterial vaginosis (1). There is no need for treatment of BV in asymptomatic patients, but symptomatic women need to receive antibiotics (2).

Although all vaginal infections are not entirely preventable, proper hygienic behaviors can substantially prevent many vaginal infections. Some of these behaviors include avoiding hot and public baths and irritants such as perfume tampons, pads, and scented soaps, keeping the genital area dry, especially after urination, and wearing cotton underwear (2-4).

Metronidazole is the choice treatment administered as 500 *mg* orally every 12 *hr* for seven days (5-7). Metronidazole has a low molecular weight across the cell membrane, and its activity is against anaerobic (8). Acquired resistance to metronidazole is rare, and 95% of anaerobic are susceptible to metronidazole (9-11).

Vitamin D is a fat-soluble vitamin and has a vital role in Calcium-phosphate homeostasis. Its deficiency leads to osteomalacia in adults and rickets in children (12,13). There are many reports about the role of vitamin D deficiency as a predisposing factor to infections such as tonsillitis, sepsis, influenza, urinary tract, and vaginal infections (14-16). Vitamin D has an essential role in chemokine production and immune regulation. B & T lymphocytes and dendritic cells, which regulate immune reactions, have Vitamin D Receptors (VDRs). Macrophages also have VDRs, and vitamin D enhances their oxidative power (17).

Studies have shown that cathelicidin activity, which has an antibacterial role in the body (18), is low in patients with serum vitamin D concentrations less than 20 *ng/ml* (19). In a study, Yang *et al* demonstrated that vitamin D supplementation decreased the likelihood of Urinary Tract Infection (UTI) in vitamin D deficient infants (20). Nseir *et al* studied the frequency of vitamin D deficiency in menopausal women with UTIs. Vitamin D deficiency was more frequent in women with recurrent UTIs than in healthy subjects (21). Turner *et al* examined the relationship between vitamin D levels and the prevalence of bacterial vaginosis in Zimbabwean pregnant and non-pregnant women separately (22). Vitamin D levels less or equal to 30 *ng/mL* were not associated with a prevalence of bacterial vaginosis in non-pregnant or pregnant women.

Since there is evidence of the relation between vitamin D deficiency and risk of BV, and due to a high frequency of vitamin D deficiency in Iranian women, we conducted a study to evaluate the effect of high dose vitamin D supplementation on the improvement of bacterial vaginosis in vitamin D deficient women.

Materials and Methods

This study was an open-label clinical trial (IRCT20150609022637N7) conducted in the women's diseases clinic of Motahary Hospital, affiliated with Urmia University of Medical Sciences. Eligible patients, who signed the informed consent forms, were randomly assigned to the intervention or control group. The study was conducted from 16/5/2020 to 20/8/2020.

Sample size calculation

Considering α=0.05, p=0.88 for vitamin D and p=0.45 for Metronidazole with power of 80%, d=0.2, the calculated sample size was 40 patients.

Inclusion criteria

Premenopausal married women aged >16 years with vitamin D deficiency and bacterial vaginosis were included.

Exclusion criteria

Women with any of the following conditions were excluded: pregnancy, lactation, menstruation, history of allergy to metronidazole, presence of candida or trichomonas in the vaginal smear, and systemic or vaginal use of antibiotics in the last two weeks.

Intervention

Patients were randomly assigned to the intervention or control group using block randomization with randomly selected blocks of sizes 4, 6, and 8. Patients in the intervention group received oral tablets of metronidazole 500 *mg* (made by Jalinous

Pharmaceutical Company, Iran) twice/day for one week and an oral 50000-unit pearl of vitamin D (made by Daana Pharma Company, Iran) daily for five days (23). Patients in the control group received only oral tablets of metronidazole 500 *mg* twice/day for one week. After the initial intervention, all vitamin D deficient patients were referred to an endocrinologist to complete their treatment.

Outcome measures

Outcomes, including serum level of vitamin D and improvement of BV, were evaluated 14 days after the completion of metronidazole treatment. Clinical improvement of BV was defined as normalization of odor and color of vaginal discharge, negative whiff test, and reduction in the pH of vaginal secretion to less than 4.5. The absence of clue cells in the smear of vaginal discharge is considered a laboratory improvement. It should be noted that the demographic characteristics of the patients were recorded in predesigned forms.

Diagnosis of vitamin D deficiency

The serum level of 25-hydroxyvitamin D (25(OH) D) less than 20 *ng/ml* is considered a vitamin D deficiency (24). The serum concentration of 25(OH) D was measured by standard laboratory methods (Vitamin D diagnostic kit).

Diagnosis of BV

Amsel criteria (25) was used for the diagnosis of BV. According to the results of different studies, the Amsel criteria have 91-99% specificity and 38-77% sensitivity for BV diagnosis (21,26,27). The presence of at least three Amsel criteria are diagnostic for BV. Amsel criteria are:

- Homogenous gray vaginal discharge
- Positive whiff test
- Presence of clue cell
- pH >4.5
- Whiff test

For preparing vaginal smears, a sterile speculum was inserted into the vagina, and secretions were gathered with a cotton swab. The sample was spread on a slide, and finally, fixation and staining were done. A KOH 10% solution was added to the sample. Fishy odor means a positive whiff test, a diagnostic criterion for bacterial vaginosis. The whiff test is negative in the absence of a fishy odor (28).

Clue cell

Clue cells are epithelial cells of the vagina covered by adherent gram-negative rods, observed in vaginal smears from women with bacterial vaginosis. If clue cells are present, women may have bacterial vaginosis (29). The presence of clue cells in the samples of vaginal secretion was investigated by microscopic examination.

Statistical analysis

Statistical analyses were performed using SPSS version 23. Baseline characteristics of the patients were compared with an independent t-test or Chi-square test. The Chi-square test (and Fisher exact test if necessary) was used to compare some patients who reported resolution of abnormal vaginal discharges between the two groups. An independent t-test was utilized for normal data of vaginal pH and the number of clue cells between the two groups at the end of the study. The normality of data was tested using the Kolmogorov-Smirnov test. The level of significance was considered <0.05.

Ethical issues

The ethics committee approved the study protocol of the Kerman University of Medical Sciences (IR.KMU.REC.1399.102). Participants received informed consent. They did not pay for their medical visits and laboratory exams. All patients' information remained confidential. This clinical trial was submitted for IRCT, and the code number is IRCT20150609022637N7.

Results

Of 424 patients with bacterial vaginosis screened for vitamin D deficiency, 108 patients fulfilled the entrance criteria and participated in the study. 68 patients left the study (42 patients in the vitamin D group and 26 patients in the control group); therefore, 40 patients (20 patients in each group) completed the study (Figure 1), and their data were analyzed. The study was conducted from 16/5/2020 to 20/8/2020.

At baseline, there were no significant differences in the demographic characteristics of the participants

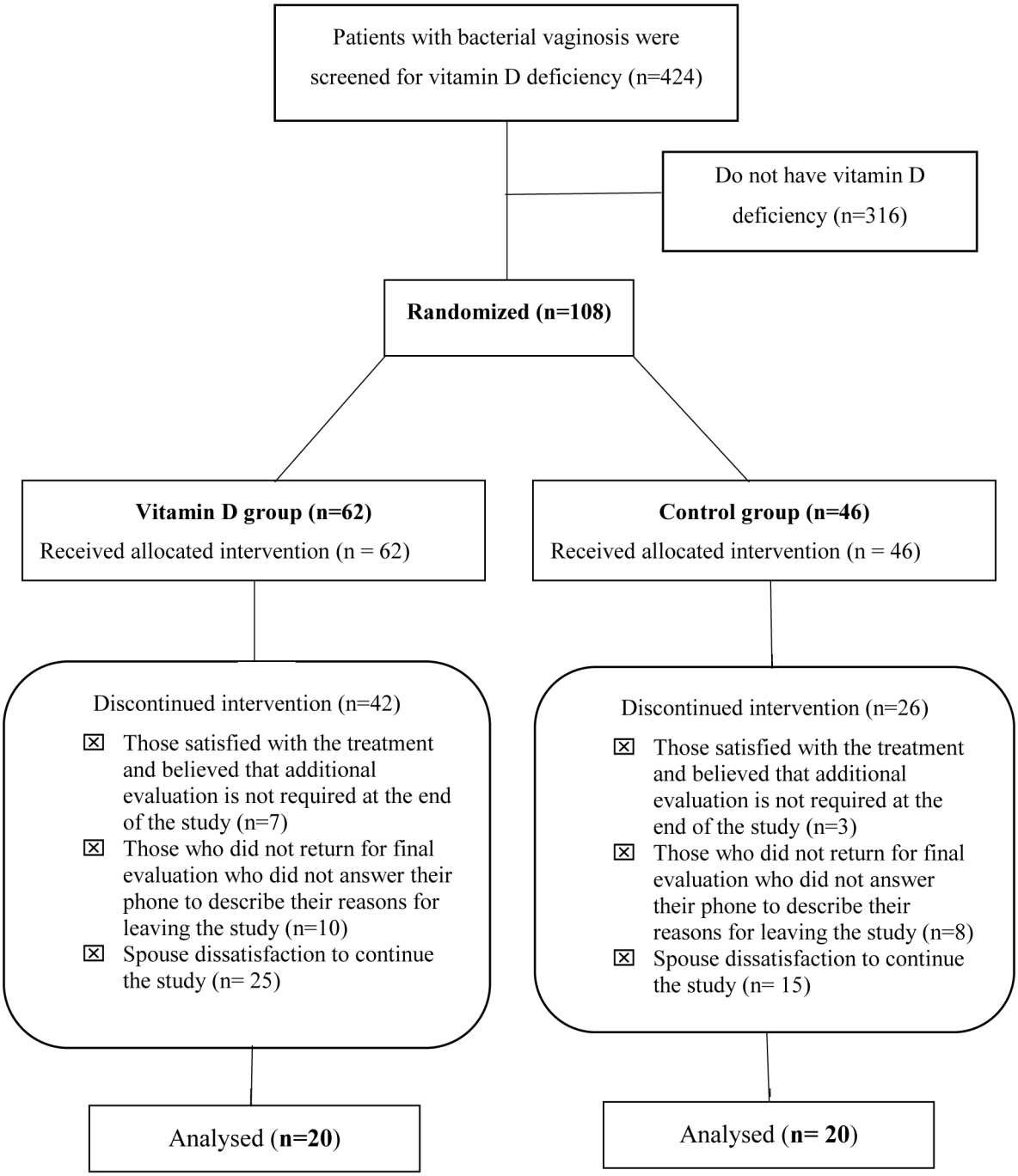

Figure 1. Flow diagram of participants in the study.

(Table 1). The mean age of patients was 31.1±3.56 years in the vitamin D group and 33.4±5.16 years in the control group (p=0.759).

Obstetric history

There were no significant differences in the number of gravidities and children and the type of last delivery between the two groups (Table 2).

Methods of contraception

Using a condom was the most common contraceptive method in the two groups, while any couple did not use vasectomy. There were no significant differences between the two groups regarding contraception methods (p>0.05).

Table 1. Patients' demographic characteristics

Participants' characteristics		Vitamin D group (n=20)	Control group (n=20)	p
Age (Mean ± SD) (year)		31.10 ± 3.56	33.40 ± 5.16	0.759
Body weight (Mean ± SD) (*kg*)		77.14 ± 4.83	72.03 ± 6.31	0.941
Job	Housewife	15 (75%)	14 (70%)	0.088
	Working women	5 (25%)	6 (30%)	
Education	Elementary	4 (20%)	7 (35%)	0.285
	Middle school	8 (40%)	7 (35%)	
	High school	5 (25%)	3 (15%)	
	University	3 (15%)	3 (15%)	
Husbands' job	Unemployed	3 (15%)	1 (%5)	0.411
	Free	13 (65%)	17 (85%)	
	Government employee	4 (20%)	2 (10%)	
Husbands' education	Elementary	5 (25%)	6 (30%)	0.214
	Middle school	5 (25%)	7 (35%)	
	High school	4 (20%)	3 (15%)	
	University	6 (30%)	4 (20%)	

Mean ± Standard Deviation. According to the chi-square test and t-test, there were no significant differences in the demographic characteristics of the participants (p>0.05).

Table 2. Obstetric history of participants in the study

Obstetrical history		Vitamin D group (n=20)	Control group (n=20)	p
Gravidity	None	1 (5%)	2 (10%)	0.244
	One	9 (45%)	4 (20%)	
	Two	6 (30%)	8 (40%)	
	More than two	4 (20%)	6 (30%)	
Number of children	None	3 (15%)	4 (20%)	0.312
	One	8 (40%)	9 (45%)	
	Two	5 (25%)	2 (10%)	
	More than two	4 (20%)	5 (25%)	
Type of the last delivery	Vaginal delivery	12 (60%)	15 (75%)	0.115
	Cesarean section	8 (40%)	5 (25%)	

According to the chi-square test and fisher exact test, there were no significant differences in the number of gravidities, children and the type of last delivery of the participants (p>0.05).

Participants' chief complaint

At baseline, the most common clinical complaint was fishy odor vaginal discharge, followed by the discoloration of the vaginal discharge in both groups. Furthermore, the number of patients complaining about each clinical symptom did not differ in both groups. However, fourteen days after completing the study, the number of patients complaining of each clinical symptom except for suprapubic pain and dyspareunia was significantly lower in the vitamin D group than in the control group (Table 3).

Participants' laboratory results

At baseline, there were no significant differences in patients' laboratory results between the two groups. However, fourteen days after completion of the study, all laboratory results significantly improved in the vitamin D group compared to the control group (Table 4).

Side effects

The treatment side effects prevalence in the two groups were not statistically significant (p>0.05), one patient had vaginal burning, and two patients had abdominal pain in the vitamin D group. Four patients had vaginal burning in the control group, and three patients had abdominal pain. Side effects resolved spontaneously.

Subjective satisfaction with treatment

Comparing participants' general satisfaction with treatment in two groups is statistically significant (p=0.044). The number of patients subjectively satisfied with the vitamin D treatment was significantly more than those in the control group. Eighty percent of patients in the vitamin D group were completely satisfied, 15% were relatively satisfied with the treatment, and 5% were relatively unsatisfied; however, in the control group, 65 and 25% of patients entirely and relatively satisfied, respectively. Also, 10% of the patients were relatively unsatisfied in the control group.

Discussion

Bacterial vaginosis is the most common vaginal infection in women (30). Some evidence

Table 3. Clinical complaint of the patients at baseline and fourteen days after completion of the study

Clinical complaint, n (%)		Baseline			14 days after completion of the study		
		Vitamin D group (n=20)	Control group (n=20)	p	Vitamin D group (n=20)	Control group (n=20)	p
Fishy odor vaginal discharge		19 (95%)	20 (100%)	0.584	1 (5%)	4 (20%)	0.027
Color of discharge	Gray	14 (70%)	15 (75%)	0.936	0	3 (15%)	0.041
	Yellow or white	6 (30%)	5 (25%)		3 (15%)	5 (25%)	
Dyspareunia		18 (90%)	17 (85%)	0.886	1 (5%)	5 (25%)	0.128
Suprapubic pain		10 (50%)	8 (40%)	0.752	3 (15%)	7 (35%)	0.125
Itching		17 (85%)	14 (70%)	0.245	0	2 (10%)	0.034

According to the chi-square test and fisher exact test, there were no significant differences in patients' laboratory results. However, fourteen days after completing the study, patients complaining of each clinical complaint except for suprapubic pain and dyspareunia were significantly lower in the vitamin D group than in the control group.

Table 4. Laboratory data of the patients at baseline and fourteen days after completion of the study

Laboratory data		Baseline			14 days after completion of the study		
		Vitamin D group (n=20)	Control group (n=20)	p	Vitamin D group (n=20)	Control group (n=20)	p
Positive whiff test, n (%)		20 (100%)	20 (100%)	1	0	2 (10%)	0.032
pH >4.5, n (%)		20 (100%)	20 (100%)	1	2 (10%)	5 (25%)	0.012
Vitamin D (*ng/ml*), Mean±SD		14.11±4.08	16.22±2.51	0.443	19.31±2.77	15.17±3.06	0.001
Clue cell n (%)		13 (65%)	11 (55%)	0.163	3 (15%)	6 (30%)	0.041
Number of lactobacilli n (%)	One>	12 (60%)	14 (70%)	0.738	0	2 (10%)	0.026
	4-1	7 (35%)	4 (20%)		1 (5%)	1 (5%)	
	30-5	1 (5%)	2 (10%)		5 (25%)	6 (30%)	
	>30	0	0		14 (70%)	11 (55%)	
Number of gram-negative bacilli (*CFU/ml*) n (%)	1>	0	0	0.589	16 (80%)	12 (60%)	0.049
	4-1	2 (10%)	3 (15%)		4 (20%)	7 (35%)	
	30-5	4 (20%)	5 (25%)		0	1 (5%)	
	>30	14 (70%)	12 (60%)		0	0	
Number of gardnerella (*CFU/ml*) n (%)	One>	0	1 (5%)	0.291	12 (60%)	13 (65%)	0.042
	4-1	2 (10%)	2 (10%)		7 (35%)	4 (20%)	
	30-5	8 (40%)	4 (20%)		1 (5%)	3 (15%)	
	>30	10 (50%)	13 (65%)		0	0	

Mean ± Standard Deviation. According to the fisher exact test and t-test, fourteen days after completion of the trial, all laboratory results significantly improved in the vitamin D group.

demonstrated that vitamin D deficiency has a role in the susceptibility of humans to different infections and treatment responses to antibiotics (2,3,14-16). The present study showed that high dose vitamin D supplementation significantly improved clinical and laboratory outcomes of BV treatment in premenopausal vitamin D deficient women.

Hensel KJ *et al* conducted a study in 2011. They studied the relationship between vitamin D deficiency and bacterial vaginosis in non-pregnant women. Results indicated a relation between vitamin D deficiency and bacterial vaginosis. Moreover, vitamin D supplementation can prevent bacterial vaginosis (27).

Tahery *et al* studied the effect of vitamin D supplementation on bacterial vaginosis in asymptomatic patients in two groups. They administered vitamin D drop at a dosage of 2000 units/day for 105 days for one group. The other group did not receive any vitamin D supplement. Improvement was 63% in the treatment group and 19% in the control group. The study demonstrated that taking vitamin D orally at

2000 units daily for 105 days could effectively relieve asymptomatic vaginosis and prevent the symptoms of bacterial vaginosis and its complications (31).

Harandi *et al* conducted a clinical trial to compare the efficiency of metronidazole alone with metronidazole and probiotics in the treatment of bacterial vaginosis. Forty-one women enrolled in their study. Their study showed that all Amsel criteria, including gray homogeneous secretions, pH>4.5, positive whiff test, and presence of clue cell, resolved completely in both groups (32).

Bondar *et al* demonstrated that the prevalence of bacterial vaginosis was higher in women with low serum levels of vitamin D. There was a significant relationship between vitamin D levels and the prevalence of bacterial vaginitis (24).

Dunlop *et al* investigated the relationship between total serum vitamin D level and bacterial vaginosis among American black women in early and late pregnancy. One hundred and thirty-seven women participated in this study. Thirty-seven (27%) women initially had adequate vitamin D, while 70 women (51%) had insufficient vitamin D and 30 women (22%) had vitamin D deficiency. Their study suggested that the probability of vaginitis in late pregnancy was significantly higher for women whose vitamin D levels were slowly elevated (33).

Turner *et al* studied the effect of high-dose vitamin D supplementation on reducing the recurrence of bacterial vaginosis. One hundred and eighteen women participated in this study, divided into two groups vitamin D and control (n=59). They all received 500 *mg* metronidazole tablets twice daily for seven days. Also, the vitamin D group received nine doses of 50,000 *IU* vitamin D for 24 weeks. Their bacterial vaginosis was assessed at weeks 4, 12, and 24. Bacterial vaginosis prevalence among the vitamin D group was very similar to those in the placebo group at the 4- and 12-week visits, but by the 24-week visit, BV prevalence was 65% in the vitamin D group and 48% in the control group (34). The results of this study were in contrast to our study results.

In our study, vaginal fishy-odor and vaginal discharge resolved completely when vitamin D was added to the metronidazole treatment. However, 15% of patients in the control group had vaginal discharge and fishy odor after treatment only with the antibiotic. This difference was statistically meaningful.

A questionnaire was prepared regarding satisfaction with the treatment of patients, and the patients' satisfaction was asked. The results demonstrated that treatment satisfaction was more significant in the vitamin D group. Eighty percent of patients in the vitamin D group improved utterly. However, in the control group, it was 65%. Also, none of the patients in the two groups were unsatisfied. Regarding the improvement of burning and itching caused by bacterial infection, our study findings showed further improvement in the vitamin D group after 14 days of intervention.

More patients in the vitamin D group had vaginal pH<4.5 compared to the control group, 14 days after treatment. No one in the vitamin D group had a positive whiff test after treatment, but it was positive in 10% of patients in the control group. The presence of clue cells was less common in the vitamin D and control groups. In our study, clue cell number declined more in the vitamin D group, which was statistically significant. The presence of clue cells in more than 20% of epithelial cells is one of the most specific diagnostic criteria for bacterial vaginitis, observed in 95% of the infected patients (35-37). More lactobacilli were in the vitamin D group than the control group after treatment.

In our study, patients in the vitamin D group had fewer clinical symptoms such as vaginal discharge, fishy odor, itching, and dyspareunia. Objective findings, including vaginal pH, whiff test, and clue cell number, decreased more in the vitamin D group.

Conclusion

Using 50000 *IU*/day of vitamin D for five days was an effective way to treat BV. Patients in the vitamin D group were recovered entirely according to clinical and laboratory findings compared to the control group. Our study demonstrated the importance and effectiveness of adding vitamin D supplementation to antibiotic therapy in women with bacterial vaginosis and vitamin D deficiency.

Limitations

Limitations of the present study include the small sample size and the short duration of the study.

Trial registration

This clinical trial was submitted for IRCT, and the code number is IRCT20150609022637N7.

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Conflict of Interest

The authors declare that there were no competing interests.

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