ORIGINAL ARTICLE

The Effect of Prangos Ferulacea Vaginal Cream on Accelerating the Recovery of Bacterial Vaginosis: A Randomized Controlled Clinical Trial

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Abstract

Background: The present study was conducted on the effect of prangos ferulacea vaginal cream on accelerating the recovery of bacterial vaginosis.

Methods: This randomized controlled clinical trial was conducted on 100 non-pregnant women referring to health centers affiliated to Lorestan University of Medical Sciences in 2016 with the diagnosis of bacterial vaginosis based on the patient's complaints, Amsel's clinical criteria, and the Nugent microscopic criteria. The women were randomly divided into two groups of 50. One group was treated with oral metronidazole plus Prangos ferulacea vaginal cream and the other with oral metronidazole plus a placebo vaginal cream for seven days. The patient's complaints, Amsel's clinical criteria and the Nugent microscopic criteria were assessed seven days after treatment. The data were analyzed using SPSS, version 20, with a significance level of 0.05.

Results: The response to oral metronidazole plus Prangos ferulacea vaginal cream treatment was 94% according to Amsel's clinical criteria and 88% according to the Nugent microscopic criteria. The response to oral metronidazole plus placebo vaginal cream treatment was 94% according to Amsel's criteria and 86% according to the Nugent criteria. The analysis of the patients' complaints, Amsel's clinical criteria and the Nugent microscopic criteria showed significant differences in each group before and after the treatment.

Conclusion: This trial showed that Prangos ferulacea vaginal cream accelerated the recovery of

bacterial vaginosis of patients with bacterial vaginosis. It can be used effectively as a complementary treatment with oral metronidazole in cases of medication resistance and also in people wishing to use herbal remedies

Trial Registration Number: IRCT2016042327534N1

Keywords: Bacterial vaginosis, Complementary alternative medicine, Metronidazole, Therapeutics, Vaginal cream

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Introduction

Bacterial Vaginosis (BV) is the most common type of vaginitis in women of reproductive age. BV is a change in the normal vaginal flora that leads to the loss of hydrogen peroxide-producing lactobacilli and the overgrowth of predominantly anaerobic bacteria. The normal vaginal flora contains a variety of lactobacillus species that help maintain the acidic pH of the vagina (below 4.5), which is suitable for the production of lactic acid.[1] The classic signs of BV include abnormal discharge and pungent amine odors. The exact cause of disruption in the normal vaginal flora is still unknown, but the frequent alkalinity of the vagina due to frequent intercourse or the use of vaginal douche is identified and accepted contributors.[2] The known risk factors of this form of vaginitis include socioeconomic status, poor hygiene, early sexual activity, several sexual partners, psychological stress, and biogenetic factors.[3]

Although BV is the most common cause of vaginal discharge with a prevalence of 33% to 47% during pregnancy,[4] it is asymptomatic in 50% of the cases.[5] There is little statistical information on the prevalence of BV in Iran, but it was reported to be 15.6% in Yazd,[6] 16.2% in Zanjan,[7] and 70.34% in infertile women in Qom.[8]

The complications of BV include Pelvic Inflammatory Disease (PID), infertility, endometritis, vaginal cuff cellulitis, urinary tract syndrome and increased susceptibility to sexually transmitted infections (STI) such as HIV.[9]

The recommended treatment for bacterial vaginosis is administration of metronidazole for one week.[10] Oral metronidazole is associated with gastrointestinal and cutaneous rashes as its side-effects and may cause dizziness, seizure, peripheral neuropathy, metallic taste and dry mouth and insomnia or sleepiness after passing through the blood-brain barrier.[11, 12]

Various studies have been conducted on non-pharmaceutical substances that can be replaced with metronidazole. Particular attention is currently being paid to herbal medicines as alternatives to chemical medicines in the treatment of infectious diseases.[13] A herb with antibacterial properties is Prangos ferulacea (Jashir in Persian), which is a traditional Iranian medicinal plant. Prangos ferulacea has a highly fragrant, yellowish, saffron-colored resin that is extracted from the plant's roots and stems. In traditional medicine, Prangos ferulacea is used for the treatment of joint inflammation[14] vascular occlusion, hemorrhage, vaginal itching and infection, neutralization of toxins, uterine infections, and removal of dead fetus.[15, 16]

In Eastern Anatolia, Prangos ferulacea was used as a food item.[17] The essence of Prangos ferulacea is a secondary plant metabolite that is used in food, pharmaceutical and hygiene industries as an antimicrobial compound.[14] Due to the lack of clinical trials so far, prangos ferulacea is contraindicated in pregnancy.

Given the complications caused by bacterial vaginosis, the microbial resistance developed against chemical medications in recent years, the acceptability of herbal and traditional medicines, the present study was

conducted to determine the effect of Prangos ferulacea vaginal cream on accelerating the recovery of bacterial vaginosis.

Materials and Methods

The present triple-blind, randomized, controlled, clinical trial was conducted from late November 2015 to late November 2016 in health centers affiliated to Lorestan University of Medical Sciences. The study subjects included non-pregnant, non-lactating, non-menopausal, married women aged 15 to 49 with complaints of vaginal discharge, with regular menstrual cycles, no other forms of vaginitis, not having used vaginal or antibiotic medications over the last two weeks, not having participated in other studies over the last four weeks, and having no cervical problems/abnormalities or chronic medical diseases; those who were also willing to participate in the study were enrolled after submitting their informed written consents, Also, those who were unwilling to continue cooperation at any stage of the study or forgot to take one of their medication doses, had intercourse, became pregnant, had menstrual bleeding, and did not visit on time were excluded from the study.

The study population consisted of women visiting the aforementioned clinics. 214 people entered the study. 104 people were excluded because of not meeting the inclusion criteria (n=83), lack of willingness to participate (n=15), and other reasons (n=6). Finally, 110 women remained in the study. In each group, 5 women were excluded. (Consort flowchart 1: Figure 1).

A total of 100 women with bacterial vaginosis were selected through convenience purposive sampling and based on Amsel's criteria, their gram-staining results, and the Nugent microscopic score. Based on random allocation software, the women were then divided into an intervention group (50 women) and a control group (50 women). The presence of three out of the following four Amsel's criteria confirmed the diagnosis of bacterial vaginosis: (1) Thin, gray, homogeneous discharge; (2) pH>4.5; (3) positive whiff (amine) test; and (4) more than 20% clue cells in the wet mount.[18] Gram-staining was then used based on the Nugent

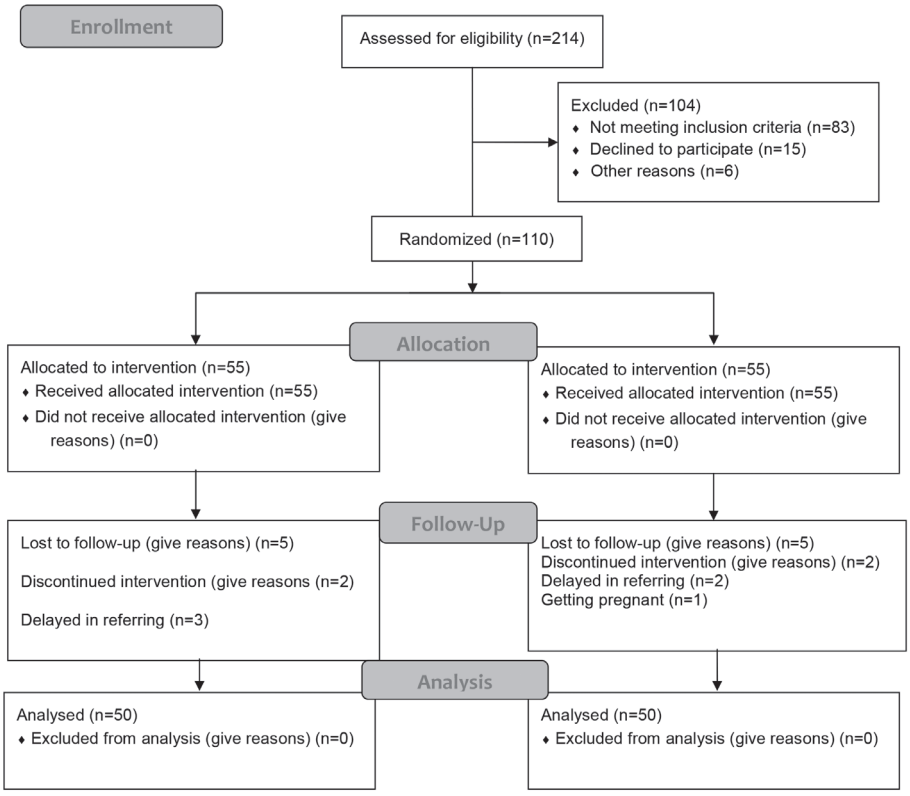

Figure 1: Consort flow chart

scoring system to make the final confirmation (scores 0-3=normal; 4-6 =intermediate; and 7 and higher =definite bacterial vaginosis). Recovery from BV was assumed with only 0 or 1 criterion out of the four Amsel's criteria and a Nugent score of 0-3.

The data collection tools used in the study included a demographic questionnaire, an observation checklist for pre-post-medication differences considering the patient's complaints, Amsel's clinical criteria, the Nugent microscopic criteria and the medication side-effects.

The study was conducted after obtaining the approval of the ethics committee of Shahid Beheshti University of Medical Sciences (ID: IR.SBMU.RETECH.REC.1395.25). For data collection, the researcher visited the study settings, introduced herself, obtained the permission of the directors of the centers, and conducted preliminary interviews with the patients (briefed them on the study objectives and the confidentiality of the data). Eligible candidates were then selected for participation in the study. One of the checklists used in the study inquired about the patients' demographic and obstetrical history and complaints and the other checklist was about direct observation during the examination; in addition, a vaginal pH measurement, the whiff test and a microscopic observation of the clue cells in the wet mount and the stained slides based on the Nugent scoring system were completed. The patient was placed in a lithotomy position; using a disposable speculum (without lubricant), we assessed her discharge and symptoms through direct observation. If the discharge was uniform, thin and gray and no cervicitis was observed, a specimen was taken from the vaginal sidewalls using a sterile cotton swab. The vaginal discharge was smeared onto a pH indicator strip from one side of the slide to the other. The pH was determined by comparing the color change in the pH indicator strip with the instructions on the box. If pH>4.5, the second swab was prepared and a drop of potassium hydroxide 10% was poured onto it, and the whiff test result was confirmed as positive if the swab took the pungent smell of rotten fish (due to the release of aromatic amines). For the microscopic observation of the wet vaginal discharge at ×40 magnifications, a drop of normal saline was poured onto the slide and an 18×18 slide was placed onto it. Immediately after that, the absence of polymorphonuclear cells, red blood cells (RBC), sperm, trichomoniasis and yeast with the scientific name Pseudomycelia or candidiasis, and the observation of clue cells[19] were assessed. If three of the four Amsel's clinical criteria were positive, the diagnosis of bacterial vaginosis was confirmed[18] and the fourth swab was prepared for the microscopic diagnosis of bacterial vaginosis, smeared onto a slide in the same way, dried at room temperature, and then fixed with an alcohol burner. The slide was then immediately stained in four stages using the gram-staining method. For better clarity, a drop of immersion oil was poured onto the slide and then observed under a photomicroscope at thousand magnifications (×100). Gram-negative diplococci, gram-negative coccobacilli and an abundance of gram-variable bacteria, mobiluncus or clue cells indicated BV based on the Nugent score, and the final diagnosis of BV was confirmed by gram-staining according to the Nugent scoring system. The medication administration self-reporting form was distributed among the patients. The patients had to record their symptoms, full recovery, recurrence of symptoms and medication side-effects on a daily basis over the seven days of the medication administration and the following seven days. Both vaginal creams were prepared by the physicochemical control laboratory of the School of Pharmacy of Shahid Beheshti University of Medical Sciences in aseptic conditions. The Prangos freulecea gum is a 30gr vaginal cream. Each tube has 20 grams of active ingredient. Herbarium number was HSP-102. The Prangos ferulacea was extracted from the Apiaceae species and the genus Prangos genus. The placebo consists of Seto astyaril alcohol, Petroleum

jelly, Glycerine, Mineral Oil, Antioxidant, and protective materials.

The creams were labeled A and B (the researcher was blinded to their content). Oral metronidazole tablets (250 mg, made by Dr. Abidi Pharmaceutical Company, drug registration NO: 128067198) were purchased and delivered to the researcher. The patients received their Prangos ferulacea or placebo vaginal cream by drawing a card containing the letter A or B from a box (each letter corresponded to one of the treatments and the box contained an equal number of cards labeled A and B). The two groups received similar metronidazole tablets (500-mg, to be administered 12-hourly) while one group received Prangos ferulacea vaginal cream and the other placebo vaginal cream (to use 5 grams every night with an applicator). The patients were asked to return for reassessment a week after completing the course of their treatment, and the same diagnostic method as in their first visit was repeated for them (based on the patient's complaints, Amsel's clinical criteria and the Nugent microscopic criteria). The patients were informed of their recovery status immediately after the examination, and those with a negative response underwent another course of treatment.

The data obtained were analyzed in SPSS-20 using descriptive and deductive (independent t-test, the Chi-square test, Fisher's exact test, Mann-Whitney's test and McNemar's test) statistics at a significance level of $P<0.05$.

Results

This study examined 110 married women who were randomly divided into two groups of 55 each. Four women were later excluded from the study for late attendance, one for getting pregnant and five others for lack of attendance for follow-up. A total of 100 women (50 per group) with a Mean±SD of 31.96±8.93 years remained in the study. The results showed no significant differences between the two groups in terms of their demographic characteristics (Table 1).

The Chi-square test and Fisher's exact test performed before the treatment showed no itching, burning or vaginal and vulvar irritation in any of the women in the Prangos ferulacea and metronidazole groups. A total of 97% of the patients in both groups complained about profuse discharge and 94% about bad odor; Table 2 presents these complaints and their changes after the treatment.

According to the examiner, the clinical observation showed no redness or inflammation of the vagina, vulva or cervix in any of the participants in the two groups. Before the treatments, Amsel's clinical criteria showed that 92% of the participants in both

Table 1: Comparison of demographic characteristics of participants in the control and intervention groups

Variable			Intervention group N (%)	Control Group N (%)	P value*
Education	Patient	A primary school& school	24 (48)	23 (46)	0.918
		High school	4 (8)	5 (10)	
		Collegiate	22 (44)	22 (44)	
	Husband	A primary school& school	18 (36)	13 (26)	0.232
		High school	29 (58)	32 (64)	
		Collegiate	3 (6)	5 (10)	
Profession	Patient	Housekeeper	43 (86)	40 (80)	0.221
		Worker	4 (8)	9 (18)	
		Employee	3(6)	1 (2)	
	Husband	Unemployed	2 (4)	1 (2)	0.118
		Worker	19 (38)	9 (18)	
		Employee	10 (20)	16 (32)	
		non-government	19 (38)	24 (48)	

*Chi square test

Table 2: Comparison of clinical improvement in patients' complaints in the control and intervention groups (N=50)

Variable				Intervention group N (%)	P value within Intervention Group*	Control Group N (%)	P value within Control Group	P value Between*
Patient complaints	Abundant discharge	Before treatment	Yes	49 (98)	<0.001	48 (96)	<0.001	1.000
			No	1 (2)		2 (4)		
		After treatment	Yes	8 (16)		15 (30)		0.0961
			No	42 (84)		35 (70)		
	Malodor	Before treatment	Yes	44 (88)	<0.001	50 (100)	<0.001	0.0272
			No	6 (12)		0 (0%)		
		After treatment	Yes	0 (0)		2 (4)		0.495
			No	50 (100)		48 (96)		

*Chi square test

groups had homogeneous gray discharge, 100% had pH>4.5, and 100% had positive amine tests. Two-thirds of the patients in the Prangos ferulacea group and half of those in the metronidazole group at four hundred magnification (×40) had clue cells>20%. Moreover, 100% of the patients at thousand magnifications (×100) had Nugent scores≥7 before the treatment; Table 3 presents these scores and their changes after the treatment.

The analysis of the patients' complaints, Amsel's clinical criteria and the Nugent microscopic criteria using McNemar's test showed significant differences in each group before and after the treatment (Table 4).

On average, the first day when the symptoms subsided over the seven days of the medication administration period was day 3.14±1.01 in the Prangos ferulacea group and day 3.88±0.917 in the metronidazole

Table 3: Comparison of clinical improvement in Amsel clinical criteria and Microscopic Nugent criteria in the control and intervention groups

Variable				Intervention group N (%)	P value within Intervention Group*	Control Group N (%)	P value within Control Group*	Pvalue*
Amsel clinical criteria	Gray homogeneous discharge	Before treatment	Yes	46 (92)	<0.001	46 (92)	<0.001	1.000
			No	4 (8)		4 (8)		
		After treatment	Yes	3 (6)		8 (16)		0.110
			No	47 (94)		42 (84)		
	4.5≥pH	Before treatment	Yes	50 (100)	<0.001	50 (100)	<0.001	1.000
			No	0 (0)		0 (0)		
		After treatment	Yes	3 (6)		6 (12)		0.478
			No	47 (94)		44 (88)		
	Whiff test positive	Before treatment	Yes	50 (100)	<0.001	50 (100)	<0.001	1.000
			No	0 (0)		0 (0)		
		After treatment	Yes	5 (10)		12 (24)		0.062
			No	45 (90)		38 (76)		
	Clue cells more than 20%	Before treatment	Yes	35 (70)	<0.001	26 (52)	<0.001	0.065
			No	15 (30)		24 (48)		
		After treatment	Yes	2 (4)		1 (2)		1.000
			No	48 (96)		49 (98)		
Microscopic criteria Nugnt	Before treatment	Score ≥ 7	Yes	50 (100)	<0.001	50 (100)	<0.001	1.000
	After treatment	Score ≥ 7	Yes	6 (12)		7 (14)		0.766
		Score 0-3	No	44 (88)		43 (86)		

*Chi square test

Table 4: Comparison of the distribution of the participants according to patient complaints, the Amsel clinical criteria and Nugent microscopic criteria in the control and intervention groups (Before and after treatment)

Variable		Intervantion group N (%)			Control Group N (%)		
		Before treatment	After treatment	P value*	Before treatment	After treatment	P value*
Patient complaints	Abundant discharge	49 (98)	15 (30)	<0.001	48 (96)	8 (16)	<0.001
	Malodor	44 (88)	0 (0)	<0.001	50 (100)	2 (4)	<0.001
Amsel clinical criteria	Gray homogeneous discharge	46 (92)	3 (6)	<0.001	46 (92)	8 (16)	<0.001
	Clue cells more than 20%	35 (70)	2 (4)	<0.001	26 (52)	1 (2)	<0.001
	Whiff test positive	50 (100)	5 (10)	<0.001	50 (100)	12 (24)	<0.001
	pH≥4.5	50 (100)	3 (6)	<0.001	50 (100)	6 (12)	<0.001
Microscopic criteria Nugent	7≥	50 (100)	6 (12)	<0.001	50 (100)	7 (14)	<0.001
	0-3	0 (0)	44 (88)		0 (0)	43 (86)	

*McNemar's test

group, suggesting a statistically significant inter-group difference by independent t-test (P<0.001). In other words, according to Mann-Whitney's test, symptoms had subsided in 78% of the patients in the oral metronidazole plus Prangos ferulacea vaginal cream group and 38% of those in the oral metronidazole group by the third day, suggesting a statistically significant inter-group difference (P<0.001) (Figure 2).

The frequency distribution of the day of full recovery over the seven days of treatment showed that 78% of the patients in the oral metronidazole plus Prangos ferulacea vaginal cream group and 30% of those in the oral metronidazole group fully recovered by the end of the fourth day, suggesting a statistically significant inter-group difference (P<0.004)(Figure 3).

Examining the medication side-effects showed that none of the patients in either of the two groups experienced sensitivity to light, diarrhea, vomiting, vaginal bleeding, pelvic pain and vaginal or vulvar itching, burning, and inflammation. A total of 16% of the patients in the Prangos ferulacea group and 24% of those in the metronidazole group experienced medication side-effects (nausea, metallic taste and stomach ache), with metallic taste and nausea being the most frequent side-effects in both groups; none of the patients in the Prangos ferulacea group had stomach ache. The Chi-square test showed no significant differences between the

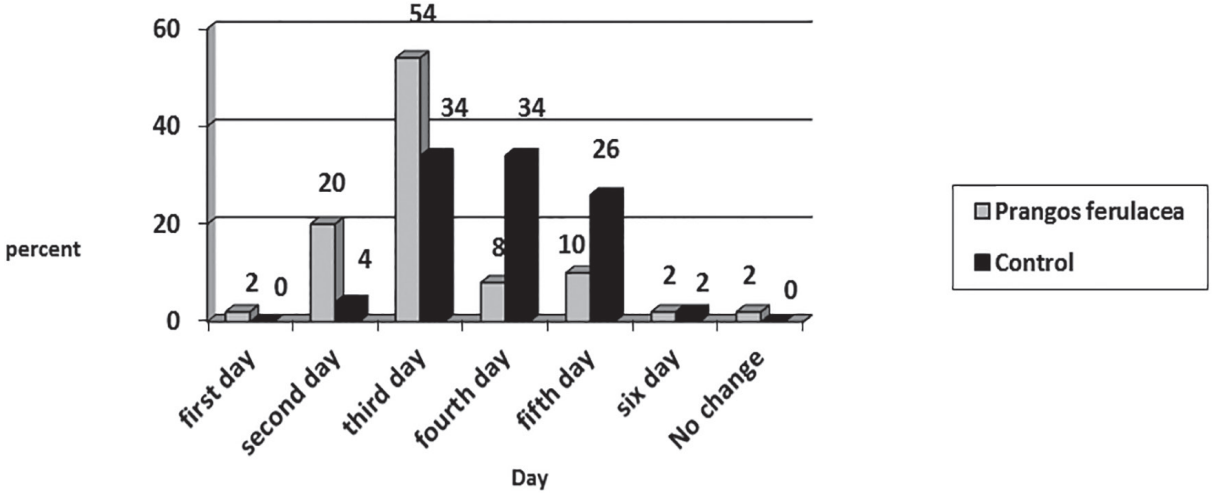

Figure 2: Distribution of the participants according to the day when the symptoms of bacterial vaginosis (patient self-report) reduced in the control and intervention groups

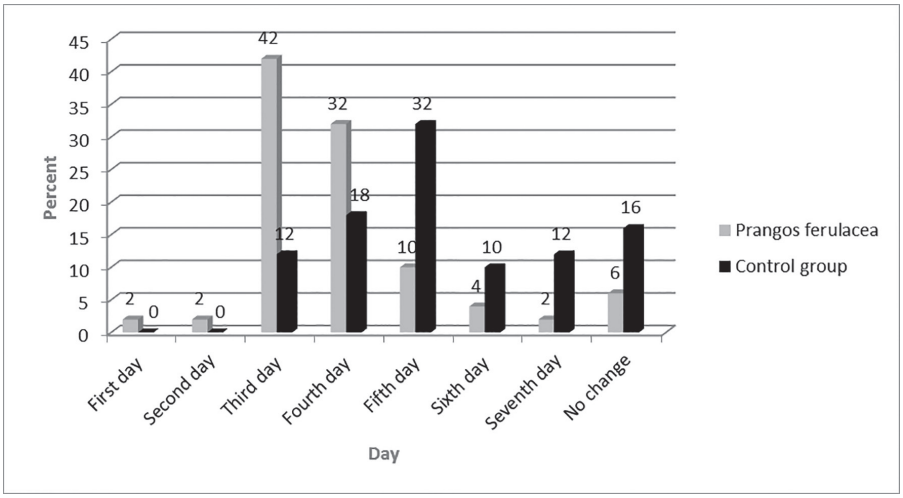

Figure 3: Distribution of the participants according to days of complete remission (patient self-report) in the control and intervention groups

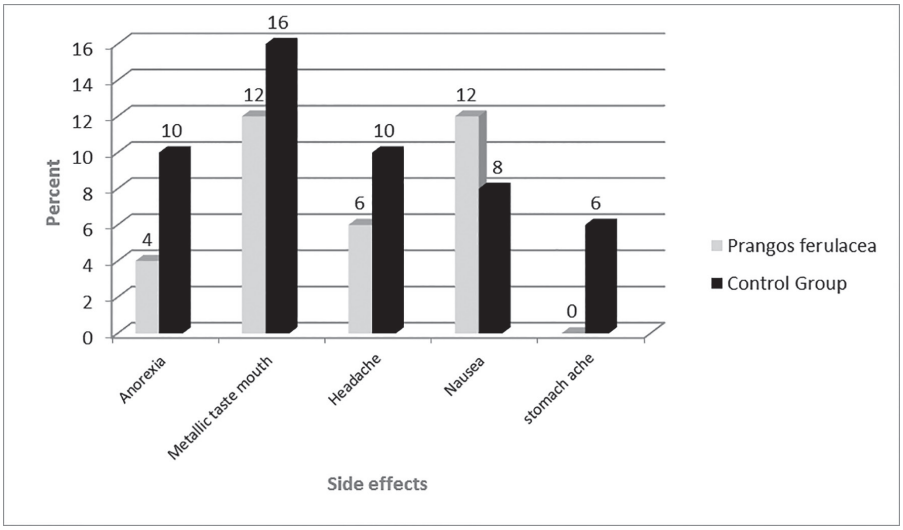

Figure 4: Distribution of the participants according to the type of drug side effects in the control and intervention groups

two groups in terms of the side-effects of the medications (Figure 4).

Discussion

The present findings showed the high efficacy of oral metronidazole plus Prangos ferulacea vaginal cream and oral metronidazole alone. After receiving the treatments, the homogeneous discharge reduced in the two groups. None of the patients in the oral metronidazole plus Prangos ferulacea vaginal cream group had a bad odor after treatment. Bad odor is one of the main features of bacterial vaginosis that is caused by polyamine metabolism in the bacteria, which is evaporated by the vaginal discharge. The response to treatment based on Amsel's clinical and Nugent microscopic criteria was similar in both groups. No serious medication side-effects were observed in any of the groups.

A study compared the administration of oral metronidazole alone and oral metronidazole plus probiotic; it was reported that the response to treatment in the metronidazole alone group was better than that in the metronidazole plus probiotic group, suggesting no significant intergroup differences. Nonetheless, the rate of the recurrence of the disease two weeks after the treatment was almost similar in both groups and the side-effects were also negligible in both.[20]

Metronidazole is an antiprotozoal

nitroimidazole with an unclear mechanism of effect, but it is the gold standard of treatment for bacterial vaginosis[11, 12] and has a strong antimicrobial activity against anaerobes.[2]

The most common systemic side-effects of oral metronidazole include gastrointestinal complications, including nausea, vomiting, loss of appetite, diarrhea, abdominal cramps, constipation and tongue and mouth inflammation.[11] The lengthy course of treatment with metronidazole can sometimes cause rapid changes in the human microbial flora due to the high level of antibiotics administered. Intermittent preventive treatment is recommended for preventing the rapid reappearance of BV after discontinuation of the treatment.[9]

In a study, the efficacy of long-term treatment was less than expected and the subjects developed significant bacterial resistance.[21] Despite these treatments, the rate of recurrence of BV was very high and the medications administered had many side-effects.[22] One study showed that the combination of routine antibiotics with natural antibiotics improved the treatment of bacterial vaginosis, especially in cases of microbial resistance.[23]

Iran has a long history of using traditional medicine and medicinal plants for the treatment of different conditions. Herbal medicines are either effective or ineffective; their side-effects should, therefore, be carefully monitored. When a drug is effective, it must have some side-effects.[13] According to the present findings and the results of the discussed studies regarding the side-effects of oral or topical metronidazole, Prangos ferulacea vaginal cream appears to have no additional side-effects over metronidazole while accelerating full recovery compared to the use of oral metronidazole in the treatment of BV.

The review of literature showed the lack of clinical trials performed in Iran or abroad on the use of Prangos ferulacea on humans although its medicinal properties have been proved in-vitro. Aluminum, iron, potassium, manganese, sodium, phosphorus, and zinc are the main minerals contained in the Prangos ferulacea plant.[24] Prangos ferulacea is a rich source of antioxidants, and its antioxidant and protective effects are reportedly higher than those of vitamin E. in traditional medicine.[25]

Moreover, the presence of phenolic compounds in Prangos ferulacea confirms its high antioxidant properties. The medicinal properties of Prangos ferulacea are due to the presence of Monoterin, Sescoueeterin, Coumarin, Flavondeid, Tannin, Salpounin, and Alkaloid.[14]

The antimicrobial properties of the essence of this plant work against gram-positive Staphylococcus epidermidis, Staphylococcus aureus, gram-negative Salmonella typhi, shigella, and E. coli. Nonetheless, this plant has moderate antimicrobial effects on Staph saprophyticus.[26] In addition to these properties, the flower of Prangos ferulacea has also been found to be effective on cereus bacillus and its leaves are effective on rod-shaped gram-negative bacteria.[17] The antibacterial properties of this plant are probably due to the enzymatic inhibition of oxidized compounds or reaction with sulfhydryl groups.[27]

One of the strengths of this study was the use of the Nugent method as a standard golden method for the diagnosis and treatment of vaginosis, and its innovation in the field of antibacterial effect of Prangos ferulacea gum in humans, according to researchers. This study is the first study done on humans. However, it also had limitations, including failure to follow up patients with recurrence of the disease and the use of oral metronidazole in both treatment groups. The results showed that the treatment group improved faster than the control group, but as to the use of Prangos ferulacea, as an alternative medicine, more studies are recommended to be conducted.

Conclusion

Prangos ferulacea or Prangos ferulacea vaginal cream accelerated the recovery of bacterial vaginosis of patients with bacterial

vaginosis based on Amsel's clinical criteria, the Nugent microscopic criteria and the patients' reduced complaints. Thus, it can be used as an effective complementary treatment with oral metronidazole in cases of medication resistance and also in people wishing to use herbal remedies. Nonetheless, further studies are required before it can be adopted as a common treatment without metronidazole.

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Conflict of Interest: None declared.

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