



Research Article

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Comparison of Metronidazole versus a Combination of Metronidazole plus Probiotics in the Treatment of Bacterial Vaginosis

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Abstract

Background: Due to the high prevalence of bacterial vaginosis, its complications and resistance to chemical drugs, the current research attempted to compare the effect of metronidazole with the combination of metronidazole plus probiotic capsules in the treatment of bacterial vaginosis.

Materials and Methods: In 2010, 80 women were included in the randomized clinical trial. Questionnaire, observation checklist, microscope, and pH paper were used for data collection. Bacterial vaginosis was diagnosed with Amsel criteria. Patients into two groups, receiving oral metronidazole and the combination of metronidazole plus probiotics. The criteria of Amsel and patient's complaints were recorded before treatment and then 3-7 days after completion of treatment. Results: Metronidazole and the combination of metronidazole plus probiotics produced identical and similar effectiveness in reducing the complaints related to vaginal discharge, smelly vaginal discharge, itching and dysuria (urine irritation). The Amsel criteria had identical effects on the two groups before and after treatment, but there was a significant difference in the response between the two groups. Results showed the combination of metronidazole plus probiotics had a higher degree of efficiency ($P < 0.05$).

Conclusion: Complementary treatment by probiotic lactobacillus species increased the efficiency of bacterial vaginosis treatment, but further studies are needed.

Keywords

Bacterial vaginosis; Metronidazole; Probiotic

Introduction

Bacterial vaginosis (BV) is the most common form of vaginitis among women of fertile (reproductive) age, and a type of change in bacterial flora of the vagina that leads to lose the hydrogen peroxide generator bacteria and overgrowth of bacteria by overcoming the anaerobic bacteria. The incidence of vaginitis has been reported 40- 50% in women of reproductive age [1,2]. In Iran, in 2000, the prevalence of BV was 23.3 % in Tehran, and 28.6 % in Shahrkord in 2004 [3,4]. In 50-70% of the cases vaginitis had occurred without

symptoms, while in other cases had reported inflammatory symptoms and redness of vaginal walls, along with a vaginal discharge that has a characteristic foul fish odor, especially after intercourse or during menstruation bleeding. It seems that repeated alkalization of the vagina due to intercourse or use of vaginal bath, as well as IUD are causes for vaginitis [3,5-7]. Various studies have shown that BV has undesirable consequences. Women affected by this disease are exposed to the risk of pelvic inflammatory disease following abortion, increased risk of pelvic inflammatory disease as well as postoperative infections, and post-hysterectomy vaginal cuff infection [1,3,7,8].

Although metronidazole has been suggested as the most effective drug for treating this disease, none of the antibiotics has completely been effective in the treatment and prevention of this disease [9].

Moreover, the complications associated with oral and vaginal use of this drug include vaginal candidiasis, abdominal or uterine cramps, vomiting, metal taste in the mouth or an unsavory mouth, vulvar itching, perinatal irritation, and with less prevalence: urinary darkness, headache and in rare cases complications such as hysteria, environmental neuropathy and Ataxia [10]. In addition to complications mentioned above, the drug resistance of microorganisms causing this disease, as well as frequent relapses in 30- 50% of the cases after treatment confirm the need to develop new treatment regimen(s) for BV in order to improve the low efficiency of existing treatment [11].

Substitution of *lactobacillus* (probiotics) by yoghurt or capsule is one of the suggested and alternative treatments which has been demonstrated to be less harmful and its efficiency has been proved in laboratory environment [12]. Probiotics are live microorganisms that can remain alive after passing through the human digestive system and leave beneficial effects for the host [13]. Some of the beneficial effects of probiotics include: reduction of urinary tract infections, stimulation of the immune system, decrease in *Helicobacter pylori* colonization, reduction of cholesterol and constipation, decrease in symptoms of inflammatory disease involving large intestine, syndrome of lactose intolerance, respiratory infections, treatment and prevention of allergy [14-22]. According to previous studies, *Lactobacillus* can be replaced by microorganisms causing bacterial vaginosis in an in vitro model [23]. Also, the daily use of probiotics improves the vaginal flora in menopausal women and decreases the rate of BV [11,24].

Due to limited studies and various complications of chemical drugs, resistance of microorganisms and the need to develop new treatment regimens to improve the efficiency of existing treatments, the current study has attempted to compare the effect of metronidazole with the combination of metronidazole and probiotic capsules in the treatment of BV.

Materials and Methods

This randomized clinical trial study consisted of women with complaints of vaginal discharges referred to women's clinics affiliated with Shahid Beheshti University of Medical Sciences.

Having registered in the Iranian Registry of Clinical Trials with the serial number IRCT201106156807N1, women were asked to complete the questionnaires. To qualify for the study, patients had to meet the following criteria:

18-45 years old and married, have sex with only their own

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legitimate partner, absence of pregnancy, breastfeeding and menopausal symptoms, lack of menstruation at the time of referral, no use of any vaginal drugs, antibiotics and immune-suppressive drugs 14 days before the start of research, no intercourse or vaginal bath during last 24 hours, no use of alcohol, anticoagulant drugs such as Coumadin and Disulfiram, no evidence of other infections such as Trichomoniasis and Candidiasis during the study, no evidence of medical disease such as diabetes, blood dyscrasia, thyroid disease, and hepatic disease, and diagnosis of BV on the basis of Amsel's criteria.

Patients who had one of the following criteria were excluded from the study:

Drug intolerance, pregnancy during treatment and obligation to use antibiotics.

Data were collected in various ways: questionnaire on demographic characteristics, observation checklist the consisting of questions on patient's complaints used to record each of the referrals and asses the Amsel's criteria, American microscope (Leica Model) and pH paper supplied by Merck.

Content validity was used in order to determine the validity of questionnaire and observation checklist. Microscope and pH paper applied in this study were supplied from Merck Co.

Reliability was determined through coefficient of agreement degree using kappa statistics and questionnaire related to the demographic characteristics along with retest. In this study, 10 women with BV referred to the clinic, were questioned and examined by two researchers simultaneously. Finally, the kappa coefficient was determined for the check lists; a minimum level of agreement of 80% was desirable.

In order to measure reliability of pH paper, five samples were prepared, and then pH was measured and confirmed by the equality of reliability results. Reliability of microscope was confirmed through device calibrating (to set up and calibrate device and review a sample by a desired microscope and the other standard microscopes), and equality of the results obtained from examining two slides taken from one sample and then having them read by the same person. The samples were placed in lithotomy position, as the vagina and cervix were evaluated with respect to inflammation after putting the sterilized speculum without lubricants.

Unnatural findings and discharges were also evaluated with respect to color, consistency and odor.

The sample of discharges was placed on two slides by a cotton swab from upper part of the lateral vaginal wall. 1-2 drops of normal saline were added to the sample of the first slide, and then was evaluated with respect to observation of key cells and existence of *Trichomonas vaginalis*. The sample was removed from the study in the presence of trichomonas (a flagellated parasite).

One drop of KOH 10% was added to the sample of the second slide and was then analyzed in respect of observation of Candidal hyphae and smell of amine. The sample was removed from the study in the presence of Candida infection. Also, pH of vaginal discharges was determined by pH paper measurement. Moreover, patient's complaints were recorded in the check list of the client's first referral.

After certain diagnosis of samples regarding BV and coding of individuals, patients were randomly assigned to treatment groups, receiving metronidazole or the combination of metronidazole plus probiotics. Metronidazole was prescribed (250 mg) orally, four times per day for 7 days.

In this research, the probiotics are balance capsules of Protexin Co. which contain probiotics such as *Lactobacillus casei*, *Lactobacillus*

rhamnosus, *Streptococcus thermophilus*, *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, vitamin A, vitamin C, vitamin E and peribiotics. Two capsules were daily prescribed orally.

Patients taking the drug were prevented from intercourse without condom, vaginal baths, spermicides or other vaginal drugs and use of antibiotics during the use of drug. The individuals referred back to the center after 3-7 days of complementary the treatment and Amsel clinical criteria. Patient's complaints were reevaluated and the results were recorded in the observation record forms.

The absence of four Amsel criteria or the existence of only one criterion of Amsel was demonstrator of the treatment's success or failure.

Results

Results showed that there were no significant differences in average of age, age of marriage, marriage duration and age of first pregnancy, delivery, caesarean section, natural child birth, abortion, and curettage using T-Test between the two treatment groups (Table 1).

47.5% of cases in the metronidazole treatment group and 52.5% in the metronidazole plus probiotic group had at least high school education or higher. Furthermore, the majority of cases in the two treatment groups (92.5%) were housewives. There was no significant difference between the two treatment groups with regard to education and job (Tested with the Mann-Whitney test).

A chi-square test showed that there was no significant difference between the two treatment groups regarding dysuria (urine irritation), itching and smelly discharge before treatment (Table 2).

Amine test was reported positive in 100% of patients assigned to two groups before treatment. There was no significant difference between the two groups regarding Asmel's criteria before treatment.

The comparison of two groups according to Amsel's criteria showed that both treatment methods produced identical and similar effectiveness in removing the Asmel's criteria ($P < 0.001$), (Table 3).

McNemar statistical test showed that there was significant difference among patients who experienced vaginal symptoms including vaginal discharges, smelly discharge and itching in the metronidazole group before and after treatment ($P < 0.001$).

22.5% of women reported complaints of dysuria (urine irritation),

Table 1: The comparison of average and standard deviation of variables in patients, in the two treatment groups of metronidazole and combination of metronidazole and probiotic in women with bacterial vaginosis.

Groups	Metronidazole	Metronidazole Probiotic	Result of test	
Indicator variable	Mean and standard deviation	Mean and standard deviation	Statistic	p-value
Age of marriage (year)	19/3 ± 3/43	4/46 ± 19/35	-0/25	0/801
Marriage duration (year)	6/78 ± 14/35	6/95 ± 10/05	2/79	0/06
Age of first pregnancy	3/89 ± 21/74	3/61 ± 20/42	1/52	0/131
Number of pregnancy	1/10 ± 2/05	1/21 ± 1/75	1/15	0/252
Number of delivery	0/84 ± 1/83	0/71 ± 1/50	1/85	0/067
Cesarean delivery	0/71 ± 0/45	0/74 ± 0/58	0/76	0/447
normal vaginal delivery	1/15 ± 1/28	0/87 ± 0/90	1/64	0/105
Number of abortion	0/37 ± 0/10	0/40 ± 0/12	-0/28	0/776
Number of curettage	0/33 ± 0/13	0/42 ± 0/15	-0/29	0/771

Table 2: The distribution of absolute and relative frequency of patients in terms of complaints before treatment, in two treatment groups of metronidazole and combination of metronidazole and probiotic.

Groups	Metronidazole		Metronidazole Probiotic		Total	
	Number	Percentage	number	Percentage	Number	Percentage
Vaginal discharge	35	87/5	38	95	73	25/91
Stinky discharge	31	5/77	26	65	57	71/25
Itching	20	50	21	52/5	41	51/25
Dysuria	9	22/5	15	37/5	24	30

Table 3: The distribution of absolute and relative frequency of patients in terms of comparison of Amsel criteria before and after treatment, in two treatment groups of Metronidazole and combination of Metronidazole and Probiotic in women with bacterial vaginosis.

Groups	Metronidazole				Intra group comparison	Metronidazole Probiotic				Intra group Comparison
Indicator	Before treatment		After treatment			Before treatment		After treatment		
	number	Percentage	Number	Percentage		number	percentage	Number	percentage	
Amstel's criteria										
Discharge of gray hemogenia	34	85	10	25	P<0/001	35	87/5	5	12/5	P<0/001
Positive amine test	40	100	19	47/5	P<0/001	40	100	15	37/5	P<0/001
Clue cell	29	72/5	9	22/5	P<0/001	32	80	9	22/5	P<0/001
5/4 <PH	26	65	7	17/5	P<0/001	20	50	4	10	P<0/001
Comparison of groups	N.S									

whereas 15% of whom complained after treatment.

McNemar statistical test didn't show significant difference in the reduction of this complaint.

The McNemar test showed that there was a significant difference among patients who experienced vaginal symptoms including vaginal discharges, smelly discharge, itching and dysuria in the group receiving the combination of metronidazole plus probiotics before and after treatment.

A chi-Square statistical test did not show significant difference between the two groups regarding vaginal discharge, smelly discharge, dysuria and itching after treatment (Table 4).

In this research, the improvement of Amsel's criteria was considered as therapeutic response.

The findings of the research demonstrated that 67.5% of patients in the metronidazole group and 87.5% in the group receiving the combination of metronidazole plus probiotics were successfully treated for BV.

According to the chi-square test, there was significant difference between the two treatment groups receiving metronidazole and the combination of metronidazole plus probiotics with respect to success of treatment ($X^2 = 4.588$, $P = 0.032$), and the latter one had better treatment efficiency (Table 5).

Table 4: The distribution of absolute and relative frequency of patients in terms of patient's complaints before and after treatment in two treatment groups of metronidazole and combination of metronidazole and probiotic in women with bacterial vaginosis.

Groups	Metronidazole				Intra group comparison	Metronidazole Probiotic				Intra group comparison
Complaints	Before treatment		After treatment			Before treatment		After treatment		
	number	Percentage	Number	Percentage		Number	percentage	Number	percentage	
Vaginal discharge	35	87/5	14	35	P<0/001	38	95	7	5/17	P<0/001
Stinky discharge	31	77/5	9	22/5	P<0/001	26	65	6	15	P<0/001
itching	20	50	7	17/5	P<0/001	21	52/5	7	5/17	P<0/001
dysuria	9	22/5	6	15	P=0/493	15	37/5	4	10	P<0/001
Comparison of groups	N.S									

Table 5: The distribution of absolute and relative frequency in terms of therapeutic response of under research units in two treatment groups of metronidazole and combination of metronidazole and probiotic in women with bacterial vaginosis.

Groups	Metronidazole		Metronidazole probiotic		total	
	Number	Percentage	Number	Percentage	Number	Percentage
Indicator						
Treatment response						
Treatment success	27	5/67	35	87/5	62	77/5
Treatment failure	13	32/5	5	12/5	18	22/5
Total	40	100	40	100	80	100

Discussion

The study revealed that there was a significant difference between the two study groups, receiving metronidazole and the combination of metronidazole plus probiotics with respect to the success of treatment. It also showed that patients receiving the combination of metronidazole plus probiotics had better efficiency. The study performed on 125 premenopausal women with BV, showed that, 96% of women in the probiotic group and 53% of women in the placebo group had full recovery [24]. In this study, all symptoms were not examined and analyzed after treatment and the rate of disease recovery was not mentioned before and after the treatment. In Iran, no study has been done to investigate the clinical effects of probiotics compared to metronidazole alone. The results of the study carried out to compare the effect of metronidazole gel and metronidazole vaginal suppository showed that 95% of patients in the gel group complained of vaginal discharge and 60% of patients complained of smelly discharge, while only 33% of patients complained of these two symptoms after treatment [25].

As it was shown in this study, vaginal discharge is the most common complaint of women with BV. Most of the patients with vaginal discharges are expected to be treated after drug use; therefore, they may consider normal vaginal discharges as infectious discharges.

In addition, according to other studies, the complaints will not be totally removed. According to the present results, the second most complaint has been related to smelly vaginal discharge.

This complaint may more or less exist after treatment due to a lack of health standards, and it may not be resolved completely.

There was no significant difference between the symptoms of

vaginitis including vaginal discharge, smelly vaginal discharge, dysuria and itching between the two study groups after treatment-value and χ^2 for dysuria were 0.06 and 3.7, respectively-value is given at threshold value and it shows that the effect of metronidazole plus probiotics on dysuria is 2.2 times greater than metronidazole alone.

Also, treatment by metronidazole plus probiotics, as well as metronidazole alone have been effective in the improvement of criteria including white-gray homogenous discharge, positive amine test (whiff), clue cell in wet mount grayish and vaginal acidity level ($\text{pH}>4.5$). So, two treatment methods produced identical and similar effectiveness in removing the Asmel's criteria. Balogu, et al. demonstrated that 80% of women with BV had clue cell in wet mount before treatment, while it was decreased by 20% after treatment. Positive amine test was reported 80% and 4% before and after treatment, respectively [26]. Musavi, et al. showed that grayish homogenous discharge was 100% before treatment and 20% after treatment, clue cell 87.5% before treatment and 10% after treatment, positive Amine test 100% before treatment and 6.6% after treatment and $\text{pH}>4.5$ was 100% before treatment and 13.3% after treatment [9].

In a study, the effect of each treatment on symptoms of BV was expressed as follows:

In the treatment group receiving oral clindamycin, clinical discharge was reduced from 100% to 20%, clue cell from 87.5% to 6.6%, amine odor from 100% to 3.3% and $\text{pH}>4.5$ from 100% to 20%.

In the oral metronidazole group, vaginal discharge was reduced from 100% to 20%, clue cell from 87.5% to 10%, amine odor from 100% to 6.6% and $\text{pH}>4.5$ from 100% to 13.3% [8].

In this study, the improvement of Amsel criteria was considered as therapeutic response. According to the findings, there was a significant difference between the two treatment groups receiving metronidazole and the combination of metronidazole plus probiotics. Based on the work of Kovachev, et al. when treating the vaginal disbacteriosis with dominant anaerobic species, local monotherapy with probiotics is less effective than the combined therapeutic schemes [27].

According to previous studies, lactobacillus can be replaced by microorganisms causing BV in vitro model [23].

In a study conducted by Anukam et al., 100% of patients in the probiotic /antibiotic group and 70% in the group of probiotic /placebo recovered after treatment [17]. In another study, recovery occurred in 60% of patients in the group of lactobacillus intervention versus 16% of patients included the control group [24]. Larsson's, et al. research on patients with BV revealed that 77% of patients in the lactobacillus-antibiotic treatment group and 78% in the placebo- antibiotic group improved after treatment [11].

Thus, our study is consistent with the majority of the previous studies, but its differences lay in various reasons, including the use of lactobacillus alone in some studies, the difference in the Lactobacillus colony count, the vaginal use of lactobacillus, and the use of clindamycin instead of metronidazole.

Limited studies investigating the effect of probiotics in the treatment of BV showed to some extent the effect of these live microorganisms on the reconstruction of the normal vaginal flora by lactobacillus, which is not away from the conception considering several suggested mechanisms of actions for probiotics. The results of the study conducted by Ehrstrom, et al. on 399 vaginal samples regarding lactobacillus showed that short-term (5 days) probiotic supplementation can lead to vaginal colonization of exogenous lactobacillus for more than 6 months. The women in the intervention

group had less complaints of discharge after using lactobacillus bacteria, and after their second menstruation ($P = 0.04$) compared to the placebo group [28].

The results of Martinez's et al. study indicated that most of the cases treated with fluconazole and probiotics, had no vaginal discharge, itching, vaginal irritation, dyspareunia or dysuria-value was decreased in positive culture of candida in comparison with the cases who had been treated with fluconazole and placebo ($P<0.05$) [29]. Pirota, et al. on their randomized controlled trial showed that neither oral nor vaginal forms of lactobacillus used during antibiotic treatment and 4 days after treatment completion were effective in preventing vulvovaginitis after antibiotic treatment [30].

After a follow-up period of 90 days, Marcone, et al. concluded that combinational treatment with probiotics decreases the rate of the relapse of BV. ($P=0.05$) [31]. Senok, et al. also indicated that the combination of metronidazole plus probiotics is more effective in the treatment of BV compared to other regimens [32]. Kovachev et al. showed that using the combination of 5-nitroimidazoles and vaginal probiotic therapies can lower the risk for recurrence of BV. They also showed that this combination can restore normal vaginal flora [33]. After a follow-up period of 3 months, Tsetkov et al. found that the rate of relapse of BV was less common in the probiotic-treated group [34]. Based on the work of Kovachev et al. the risk of BV recurrence is not minimized when first line treatment is a combination of oral metronidazole and vaginal clindamycin or oral metronidazole with long-term consumption of a vaginal L-acidophilus probiotic [27]. After a follow-up period of 6 months, Larsson et al. showed the positive effect of probiotics in the relapse of disease [11]. Parma et al. concluded that supplementing probiotic with vaginal lactobacilli can be advised to prevent the BV recurrence, as it delays the bacterial growth after antibiotic therapy [35]. Nouraei et al. on their randomized controlled trial showed the efficacy probiotic on candida vaginitis [36]. Huang et al. analyzed the results of 12 trials in which 1,304 patients were studied. Based on their analyses treating adult BV patients is more effective when probiotics is supplemented. Their statistical analysis showed that probiotics can be significantly effective when considering Europe population. They also concluded that Probiotics can have positive impact on the short-term follow up days [37]. In order to improve the health condition among women, Homayouni et al. recommended consuming probiotic products daily as most studies showed the positive effects of probiotics in preventing or treating BV, with no adverse effects reported [38].

Conclusion

The findings of our research showed that the combination of metronidazole and probiotics produced identical and similar effectiveness in reducing the complaints of vaginal discharges, itching and dysuria.

Also all of the Amsel criteria, including homogenous grayish discharge, positive amine test, presence of clue cell in wet mount and $\text{pH}>4.5$, had equal effect before and after treatment. The results of the research showed that there was a significant difference in the therapeutic response between two groups receiving metronidazole alone and the combination of metronidazole plus probiotics. In other words, the combination of metronidazole plus probiotics increases the treatment efficiency compared with metronidazole alone.

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Conflicts of Interest

This study was supported by Shahid Beheshti University of Medical Sciences & Zardband private company. The authors declare no conflict of interests.

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