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A clinical trial of curcumin effect in comparison to metronidazole on the treatment of bacterial vaginosis

Sakine Mohamadi[1,3], Zahra Behboudi Moghadam[2,3], Saied Godarzi[1,3] & Elham Rezaei[1,3,4]✉

Bacterial vaginosis (BV) is the prevailing infection. With the growing resistance of vaginal infections to routinely prescribed antibiotics, herbal medicine can be helpful. Researchers have conducted to compare the efficacy of curcumin and metronidazole in the treatment of BV as natural product. This study was a double-blind randomized clinical trial that involving 100 married women aged 18–49 who were not pregnant that sought treatment at two private outpatient clinics from January to September 2021 recruited in study. Individuals who met Amsel's clinical and paraclinical criteria for BV were randomly allocated to the intervention or control groups. Both groups were instructed to take their respective medications every 12 h for seven days. Subsequently, two weeks following the treatment, the efficacy of the treatment was assessed utilizing Amsel's clinical and paraclinical criteria. The data was analyzed using SPSS 26. The data was analyzed using the intention-to-treat (ITT) approach. The clinical (discharge (RD: 0.21; $CI^{95\%}$: 0.17–0.90; $P = 0.01$), whiff test (RD: 0.31; $CI^{95\%}$: 0.19–0.98; $P = 0.03$), and pH (RD: 0.18; $CI^{95\%}$: 0.19–1.04; $P = 0.03$)) and paraclinical variables of Amsel criteria (clue cells (RD: 0.19; $CI^{95\%}$: 0.13–1.03; $P = 0.02$) showed significant differences between groups. The curcumin consumer group exhibited a complete improvement rate of 82%, in contrast to the metronidazole group which had a rate of 42% two weeks after intervention. This study found curcumin have comparable efficacy to metronidazole in treating BV while demonstrating superior effectiveness and fewer adverse effects in alleviating symptoms.

Keywords Bacterial vaginosis, Curcumin, Metronidazole

Ensuring women's and girls' well-being is crucial for economic and social progress. Genital tract infections (GTIs) are significant concerns that frequently pose a threat to individual well-being and, in the context of marriage, the sexual health of both partners. GTI can occasionally result in fatalities among women[1]. About 30 distinct variations of GTIs exist. Furthermore, these infections can be passed from mother to fetus during pregnancy and childbirth. Sexually transmitted diseases (STDs) pose a significant public health concern in numerous countries worldwide, particularly in developing nations[2].

Approximately 28% of women visiting STD clinics are diagnosed with vaginal infections[3]. Bacterial vaginosis (BV), which is a shift in the bacterial flora of the vagina, is the most frequent cause of vaginitis and abnormal vaginal discharge in women of reproductive age[4,5]. This infection is a clinical illness induced by a shift in the vaginal natural flora rather than by a specific microorganism. Under normal conditions, every gram of vaginal discharge typically contains 105 bacteria, with the majority being aerobic lactobacilli. In BV, the bacterial count increases to a range of 10^9 to 10^{11}, but the presence of aerobic lactobacilli decreases. Instead, there is a rise in obligate anaerobic lactobacilli such as Gardnerella vaginalis, Mycoplasma, and other anaerobic organisms like Bacteroidetes, Peptostreptococcus, and Mobiluncus. To diagnose BV, at least three of the four Amsel criteria must be met: the presence of homogeneous vaginal discharge, pH > 4.7, the presence of clue cells in vaginal secretions, and a positive whiff test[6,7]. The most dependable observation is the identification of clue cells, which are vaginal epithelial cells exhibiting a pointed morphology as a result of bacterial coating. Although 33–47% of cases of this infection occur during pregnancy and 23–28% occur after menopause, the condition remains asymptomatic in 50% of instances. The incidence of vaginal infection varies across different societies, with the

[1]Tehran University of Medical Sciences, Tehran, Iran. [2]Faculty of Nursing and Midwifery, Tehran University of Medical Sciences, Tehran, Iran. [3]Faculty of Pharmacy, Tabriz University of Medical Sciences, Tehran, Iran. [4]School of Nursing and Midwifery, Tabriz University of Medical Sciences, Tabriz, Iran. ✉email: rezai520@yahoo.com

highest prevalence of vaginitis observed in the United States of America. The global prevalence of this condition stands around 10–15%, but in America it is 29%[6,8].

Several characteristics, including less education, early pregnancy, multiple sexual partners, smoking, excessive stress, and an outstanding socio-economic position, have been linked to an elevated risk of contracting this infection[9,10]. Half of women who are susceptible to BV do not experience any symptoms, while in the remaining cases, the primary symptom is the presence of malodorous vaginal discharge. After sexual activity and during menstruation, the foul fish odor associated with BV typically becomes more noticeable and intense[11].

Complications linked to BV in women encompass endometritis following childbirth or abortion, heightened susceptibility to infection after hysterectomy, vaginal cuff cellulitis, wound infection after cesarean section, pelvic inflammatory disease, premature rupture of fetal membranes, premature labor, chorioamnionitis, miscarriage, recurrent urinary infections, increased risk of cervical intraepithelial neoplasia, and transmission of human immunodeficiency virus (HIV)[4,5,12].

Oral metronidazole is commonly prescribed as the primary therapy for BV, achieving a cure rate of 75% to 84%[5]. Metronidazole is the recommended initial treatment, according to the Centers for Disease Control and Prevention guidelines. Nevertheless, it induces specific adverse effects such as the development of dysgeusia (a metallic taste in the mouth), gastrointestinal disturbances (such as pain, abdominal cramps, nausea, and vomiting)[13], drowsiness, dizziness, the interaction between disulfiram and alcohol[14], hallucinations and delusions, heightened symptoms of schizophrenia, incidents of mania[15], and decreased levels of gonadotropin, testosterone, and spermatogenesis hormones. There have been new findings indicating that metronidazole may cause cancer[16]. Additionally, there have been observations of metronidazole resistance and repeated relapses caused by the growth of Gardnerella vaginalis biofilm in the vagina[17]. According to the literature, resistance rates for *Gardnerella vaginalis*, a key bacterium associated with bacterial vaginosis, range from 27 to 76%[17,18]. Furthermore, relapses after metronidazole treatment are reported in approximately 38% of cases within 3 to 12 months[17,18].

Medicinal plants exhibit reduced adverse effects due to their compatibility with the environment and the body's natural flora. Herbal remedies are becoming more popular as an alternative to chemical medications due to concerns about their adverse effects, the rising expense of treatment, the lack of new pharmaceuticals, and the heightened sensitivity of bacteria and fungi to older ones. In industrialized nations, almost 80% of the population relies on alternative healthcare methods, including herbal remedies[5]. According to studies traditional medicine refers to turmeric and other plants as potential antibacterial herbal remedies[19–21]. Several studies have already demonstrated the antimicrobial effects of curcumin against various bacteria, including those associated with bacterial vaginosis[18,22]. As a result, this study aimed to compare the efficacy of curcumin pills and metronidazole in treating BV in women referred to outpatient clinics.

Materials and methods

Study design

The current investigation was a double-blind, parallel randomized clinical trial, participants were enrolled for study from January to September 2021 using a convenient sampling approach that followed the CONSORT standards[23] (Fig. 1).

Sample size calculation

The sample size considered that the effect of curcumin in the treatment of vaginitis is approximately 20% and metronidazole is 50%. With 95% confidence interval, the power of the test was 80% and loss to follow up was 20% according to the following formula, 50 people in each group were calculated.

Inclusion and exclusion criteria

The eligibility requirements for participating in the research study were as follows: being married, not experiencing menopause, not being pregnant or having breastfeeding, having no current menstruation, providing proof of the absence of BV (participants were confirmed to be BV-negative through clinical assessment and laboratory diagnostics (e.g., Nugent score < 7 or Amsel criteria)), abstaining from sexual intercourse within the past 24 h, having no history of curettage and providing a color scan, not having undergone surgery within the past two weeks, having no known allergies or sensitivities to curcumin (turmeric) or other medicinal plants, having no history of chronic diseases, not using herbal or chemical drugs for treating genital infections within the past two weeks, having no digestive problems, and having no history of kidney stones. The exclusion criteria encompassed the following: pregnancy during treatment, presence of concurrent vaginal infections, occurrence of complications or hypersensitivity to curcumin during treatment, participant's unwillingness to continue the study, and use of systemic antibiotics for non-vaginal bacterial systemic infection during treatment.

$$n - \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \left[P_1\left(1-P_1\right) + P_2\left(1-P_2\right)\right]}{\left(P_1 - P_2\right)^2}$$

Sampling

In addition, the usage and reporting of study interventions followed the TIDieR guidelines[24]. After receiving the relevant approvals, data were collected from two women's outpatient clinics in Alborz province, Iran. The study sample comprised 100 married women aged 18–49 who were not pregnant and sought medical attention at the clinic due to vaginal discharge and were diagnosed explicitly with BV, excluding other vaginal infections. The rationale for selecting these two clinics was their substantial daily patient volume for treating gynecological conditions, encompassing diverse forms of genital infections. Additionally, the clinics were conveniently

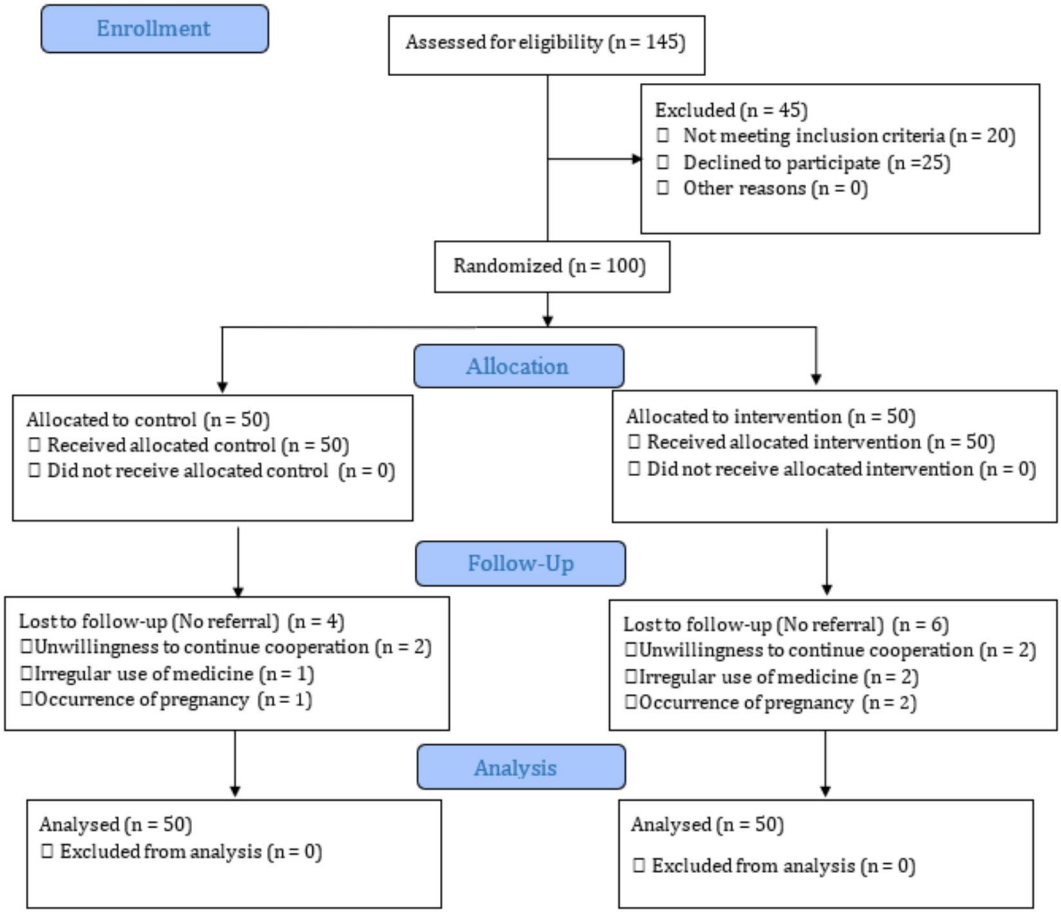

Fig. 1. CONSORT flow diagram.

accessible to non-pregnant married women, making them acceptable research subjects, and they provided adequate representation of various demographic groups.

Following self-introduction, researchers provided eligible women with a clear explanation of the research objectives and methodology. Then they got written and oral informed consent from the women, assuring them of the confidentiality of the information. Subsequently, the women were invited to participate in the study.

Initially, BV was validated using clinical criteria (homogeneous vaginal discharge, the whiff, and the pH test (Amsel's criterion)) and paraclinical criteria (the presence of clue cells in the microscopic inspection of vaginal secretions (Amsel's criterion)). In this manner, the women were positioned in the lithotomy position in the gynecological clinic's examination room, and a disposable sterile speculum was inserted into the vagina without being smeared with anything. The cervix and vagina were assessed for inflammatory symptoms, the form of secretions (color, smell, consistency, and amount), and any abnormal findings. In individuals with a high risk of getting BV, the secretions in the side walls of the vagina and posterior fornix were sampled using two sterile swabs, which were put in an autoclave for 15 min at 120 degrees before the inspection. Furthermore, for the exact sampling among subjects, all samples were taken from the lateral walls of the vagina and the posterior fornix. The secretions from the first swab were placed in a sterile tube containing 0.2 ml of physiological serum and sent to the laboratory to be tested for clue cells, candidiasis, and trichomoniasis. The researcher applied a 10% potassium hydroxide drop to the secretions from the second swab before placing them on a clean glass slide and conducting a rapid smell test for an amine odor. Also, the acidity of the vagina was measured using pH meter paper according to the manufacturer's instructions, which was included on the box containing the pH meter paper. In this way, the paper strip was contacted with a tweezer and kept in place for one minute. After the paper was completely soaked with vaginal secretions and the color of the paper changed, the number related to the acidity of the vagina was read and interpreted according to the table on the box of the PH meter paper. pH of secretions above 4.5 is the most sensitive and specific diagnostic criteria for BV. All slides were examined by a laboratory specialist without knowing the results of clinical evaluations on the same day of sampling. The same night, the women whose diagnosis of BV was confirmed were asked to visit the clinic the next morning. Written informed consent was obtained again before delivering the medicine to female volunteers who were eligible to participate in the research. Women who had trichomoniasis and candidiasis according to clinical and paraclinical criteria were excluded from the study.

BV is diagnosed when three of the four clinical criteria of Amsel are met: vaginal secretions that are thin, homogeneous, grayish-white, or yellowish-white in color; secretions with a pH greater than 4.5; a positive whiff

test result; and the presence of clue cells in the vaginal moist smear sample. Regarding the diagnosis of BV, the sensitivity and specificity of this method are satisfactory.

Randomization and intervention

Subsequently, the women were allocated randomly in block of six by an impartial individual who was not part of the research process. The allocation ratio was 1:1, with half of the women assigned to the intervention group (taking oral curcumin capsules) and the other half assigned to the control group (taking oral metronidazole tablets). The researcher conducted interviews to administer the questionnaire and scales.

The researcher provided the participants with the drugs (metronidazole and curcumin) and instructions on how to use them. The drugs were coded in the same unknown covered envelope by the person in charge of random allocation. The Curcumin nano micelle pill contained 40 mg of curcumin and was formulated by the pharmacology doctor at Exir Nano Sina Company[22,25,26]. The investigation also utilized a 500 mg tablet of metronidazole manufactured by the Aburaihan company as the second medication. Both drugs were administered at 12-h intervals for one week.

Data collection tools and follow up

Given that the individuals in the intervention group did not get the typical treatment using metronidazole, only cases of vaginitis characterized by mild symptoms (excluding excessive discharge) were included in the study after obtaining their informed consent. The data-gathering instrument utilized was a comprehensive questionnaire that included personal attributes, patient complaints, and documentation of observations, examinations, and laboratory findings. The patients were instructed to document their symptoms, complaints, and complications, along with the time of medication intake, on the provided report sheet. They were also advised to reach out to the researcher in case of any issues. Indeed, throughout the trial, the researcher communicated with the patients via telephone. Participants were given the freedom to discontinue treatment at any point. Furthermore, the research participants were instructed to promptly notify the researcher or seek medical attention at a clinic if they experienced any symptoms of medication allergy, such as skin issues, nausea, vomiting, diarrhea, allergic reactions, irritation, itching, or burning. The participants were instructed to fill out the drug consumption checklist and record any potential adverse effects on a daily basis, ensuring they bring it along for their next session. The research participants were provided with a comprehensive explanation regarding the methodology and dosage of the drugs. The participants were supplied with a set of health advice, both in written and oral form, that was developed under the supervision of the supervisor. Participants were advised to adhere to several genital health recommendations, which included daily underwear changes, sun-drying or ironing of underwear after washing, drying the genital area from front to back after each bowel movement, wearing cotton and loose shorts, and abstaining from sexual intercourse or using a condom until the time of re-examination. In addition, the study patients were provided with essential instructions regarding the avoidance of antibiotic usage during the treatment time, proper storage of medication, and refraining from using vaginal douche, creams, tablets, or other specialized health items. Patients were monitored based on the scheduled date of their next appointment, during which both clinical and non-clinical examinations were conducted again, specifically 14 days following the completion of the treatment. The impact of medications on the disease's clinical and non-clinical factors was examined and documented in the observation checklist to assess their therapeutic effect.

Confounding variable

We included most of major confounding variable in inclusion criteria like history of vaginal doosh, not using other antibiotics (during and two weeks after intervention), and married women who living with partner and not having history of multi partner. So other minor or unpredictable variables were controlled by random allocation and allocation concealment.

Ethical considerations

All stages of this study followed the guidelines and regulations conducting based on the Helsinki Declaration[27]. The study objectives and Methods were clearly explained to the participants, and they were assured that all their information would remain confidential and their unwillingness to participate in the study would not affect their care. All participants signed an informed consent form before participating in the study. The study protocol was proved by the Ethics Committee of Tehran University of Medical Sciences (Ethical code: IR.TUMS.FNM.REC.1399.093, 06/09/2020). Then registered at the Iranian Registry of Clinical Trials (www.IRCT.IR) with registration code (IRCT20120414009463N61, 02/12/2020).

Statistical analysis

The study included 100 female participants, all of whom completed the researcher-administered interview and observation questionnaire. Figure 1 shows that 10 women were removed from the study due to their inability to meet the necessary prerequisites for further participation in the research. The final analysis was conducted on a cohort of 90 female participants using intention-to-treat (ITT) analyses. The analysis included the worst-case scenario, accounting for protocol deviations in the handling of missing data, given that there was a 10% attrition rate in this trial.

The medications' therapeutic efficacy on the disease's signs and symptoms was examined and documented in the observation checklist following the intervention. Additionally, to definitively establish the existence of clue cells in the vaginal secretions following the treatment, slides were once again produced and sent to the laboratory. Following the intervention, the lack of Amsel's criterion and clue cells in the vaginal secretions were seen as indicators of therapy efficacy or complete recovery. If the patient did not show improvement and the medication did not work, they were instructed to return the next day and begin regular treatment, which included 500 mg

of metronidazole every 12 h for seven days. All services offered to the participants in this research were supplied free of charge. SPSS version 27 (SPSS Inc., Chicago, IL, USA) was used to analyze the data, and $P<0.05$ was deemed significant. Quantitative data were given as means (standard deviations), while qualitative variables were provided as frequencies (percentages). Following the assessment of the data's normal distribution using the Smirnov-Kolmogorov test, we employed the independent t-test, chi-square test, and Mann–Whitney statistical test to evaluate the data.

Results

A total of 100 women were included in this investigation, with 10 participants voluntarily discontinuing their involvement during the study (Fig. 1). The ultimate data analysis was conducted utilizing the ITT approach.

Participant characteristics

The mean (standard deviation) age and Body Mass Index of women in the control group was 30.91 (8.29) and 26.33(6.15), while in the intervention group, it was 30.82(8.42) and 26.45(4.86). Most of women 26(57.8%) in both groups had education less than a diploma. Also, Most of women's husband in the intervention (22 (48.9)) and control (24 (53.3)) groups were Less than a diploma. Majority of women in both groups were in the luteal phase of their menstrual cycle. Table 1 provide a summary of the characteristics of the other participants. Before the intervention, the normality of the distribution of sociodemographic and midwifery quantitative variables was evaluated using the Kolmogorov–Smirnov test. The two groups were homogenous, and there was no significant differences between the two groups before the intervention (Table 1).

Table 2 shows that all clinical and paraclinical variables of Amsel's criterion exhibited complete significance following the intervention in both groups.

Table 3 indicates that in the intervention group (curcumin), 82% of women obtained full recovery, whereas the control group (metronidazole) reported a total recovery rate of 42%.

a: Independent t-test; b: Chi-square for trend; c: Mann–Whitney U; d: Chi-square.

Chi-square *

Variables		Groups		*P*-value
		Intervention	Control	
Age (mean ± SD)		30.82 ± 8.42	30.91 ± 8.29	0.96[a]
Education level N (%)	Illiterate	2 (4.4)	1 (2.2)	0.56[b]
	Less than a diploma	26 (57.8)	26 (57.8)	
	Diploma	4 (8.9)	8 (17.8)	
	University	13 (28.9)	10 (22.2)	
Economic status N (%)	Good	22 (44)	25 (50)	0.909[b]
	Moderate	19 (38)	17 (34)	
	Poor	9 (18)	8 (16)	
Employment status N (%)	Employed	24 (53.3)	14 (31.1)	0.329[d]
	Housewife	21 (46.7)	31 (68.9)	
Husband Employment status N (%)	Employee	14 (31.1)	16 (35.6)	0.795[d]
	Worker	3 (6.7)	5 (11.1)	
	Free	25 (55.6)	22 (48.9)	
	Retired	3 (6.7)	2 (4.4)	
Smoking	Yes	19 (42.2)	17 (37.8)	0.415[d]
	No	26 (57.8)	28 (62.2)	
Menstrual cycle status	Follicular	20 (44.4)	18 (40)	0.699[d]
	Luteal	25 (55.6)	27 (60)	
Age of First coitus (mean ± SD)		22.51 ± 4.52	22.67 ± 4.86	0.74[c]
Contraceptive Method N (%)	Tablet	5 (11.1)	3 (6.7)	0.69[d]
	Condom	2 (4.4)	3 (6.7)	
	IUD	30 (66.7)	2 (4.4)	
	Vasectomy	0 (0)	1 (2.2)	
	Withdrawal	2 (4.5)	22 (48.9)	
	None	43 (95.5)	14 (31.1)	
History of using vaginal douche N (%)	Yes	14 (31.4)	1 (2.3)	0.53[d]
	No	31 (68.6)	44 (97.7)	
History of vaginal infection N (%)	Yes	46 (41.1)	16 (35.6)	0.65[d]
	No	4 (8.9)	29 (64.4)	
Total N (%)		50(100)	50(100)	

Table 1. Comparison of demographic characteristics of the two groups.

Criteria				Groups		Risk Difference	Confidence Interval	*P*-value *
				Intervention	Control			
Para clinical	Clue cells N (%)	Before Intervention	Yes	50 (100)	50 (100)	-	-	-
			No	0	0			
		After Intervention	Yes	7 (14)	15 (77.7)	0.19	0.13–1.03	X2: 3.73 /df:1 0.025
			No	43 (86)	35 (22.3)			
Clinical	Discharge N (%)	Before Intervention	Yes	50 (100)	50 (100)	-	-	-
			No	0	0			
		After Intervention	Yes	23(46)	34 (68.8)	0.217	0.17–0.90	X2: 4.93/df:1 0.013
			No	27 (54)	16 (31.2)			
	PH N (%)	Before Intervention	Yes	50 (100)	50 (100)	-	-	-
			No	0	0			
		After Intervention	Yes	27 (54)	36 (58)	0.183	0.19–1.04	X2: 3.45/df:1 0.031
			No	23 (46)	14 (42)			
	Whiff test N (%)	Before Intervention	Yes	50 (100)	50 (100)	-	-	-
			No	0	0			
		After Intervention	Yes	17 (34)	27 (54)	0.31	0.19–0.98	X2: 4.05/df:1 0.034
			No	33 (66)	23 (46)			
				50 (100)	50 (100)			

Table 2. Comparison of Amsel Criteria between two groups.

Criteria	Groups		Risk Difference	*P*-value
	Intervention	Control		
Complete improvement	41 (82)	24 (48)	0.355	X^2: 14.40 /df:1 < 0.001
Partial improvement	5 (10)	21 (42)		
Unimproved	4 (8)	5 (10)		
	50 (100)	50 (100)		

Table 3. Comparison of two groups according to improvement grade of vaginosis bacteria.

Complete improvement means more than or equal to three criteria of Amsel improved.
Partial improvement means one or two criteria of Amsel improved.

Discussion

This study assessed the similarity between curcumin and metronidazole regarding various factors that could affect the treatment of BV. These factors included random allocation between the two groups, personal and midwifery factors, disease and medication records, health information, and body mass index. Based on the In Vitro Test, curcumin is a safe and effective herbal drug for BV treatment that meets the Amsel requirements.

The results of other studies, consistent with the current investigation (women age that participated in it were 30.87(8.3) (Min–Max: 18–47) years old), demonstrated the disease frequency among individuals of reproductive age. In the survey conducted by Jafarnejad et al.[28], titled "Comparative study of the success rate of Phytovagex vaginal suppository and metronidazole oral tablet in women with vaginosis," the average age of the patients was 32.1 (9.7). Adan et al.[29] found that the occurrence of vaginosis in women aged 25 and older ranged from 47.8% to 60%.

The current study found that 28.90% of the participants in the intervention group and 22.20% of the participants in the control group had completed a university education. The research conducted by Adan et al.[29] revealed that BV among women with a university education was 35.9%, whereas 44.7% among women with a high school education or below. This finding indicates a statistically significant association with the current study. The study results' correlation with education level may be explained by the fact that persons with high awareness and knowledge are less likely to contract BV because they are more conscious of the need to follow health guidelines and are more motivated to do treatment or prevention. The current investigation revealed that the majority of participants in the curcumin group are homemakers. In the study conducted by Jafaranjad et al.[28], the intervention group consisted of 83.9% housewives, while the control group consisted entirely of housewives (100%). The conducted studies are consistent with the current study. The congruence between the study outcomes and job status can be attributed to the consistent evidence indicating that engaging in social activities and subsequently earning income contributes to an elevation in individuals' socio-economic status, as well as enhances their health awareness and disease prevention practices.

It was found that the majority of women's spouses were self-employed. Consistent with the current study, Jafaranjad et al.[28] found that 45.2% of the intervention group's spouses were self-employed, compared to 50% of the control group's husbands. This group consisted of 26 women.

Twenty percent of the intervention group and eighteen percent of the control group disclosed having had an abortion in the past. Some of the women (35%) who took part in the study by Godarzi et al.[30] had experienced premature birth or a miscarriage in the past. Women who reported a past abortion had a greater BV prevalence (53.8%) than those who did not mention a past abortion (46.8%), according to research by Adan et al.[29]. A study conducted by Haji Shafiha et al.[31] found that BV and other GTIs are associated with implantation problems and a rise in abortions. A history of infertility was present in 26.3% of the control group and 24.5% of the intervention group in the current investigation.

The current study found that the average age of first sexual intercourse was 22.67 (4.86) years old in the control group and 22.51 (4.52) years old in the intervention group. Those who began having sexual relations at a younger age had a greater prevalence of BV, according to Alsort et al. The prevalence of vaginosis was 38% in those whose sexual activity began between the ages of 14 and 19 and 24% in those whose sexual activity started after the age of 20[6].

The current study found that 66.7% of women in the control group and 48.9% in the intervention group utilized the intermittent method for contraception, which was more prevalent compared to other contraceptive methods. The study conducted by Tafzali et al.[32] found that the intermittent contraceptive method had a reported effectiveness rate of 71.1%, which aligns with the findings of the current investigation. Direct exposure of the vagina to semen is a significant contributing factor for BV and leads to inflammation in the vaginal region in individuals who engage in sexual intercourse without using protection.

Smoking was reported by 42.2% of those in the intervention group and 37.8% of those in the control group. The most significant independent non-sexual risk factor for BV is smoking. Furthermore, the number of cigars smoked is directly correlated with the risk of BV (OR = 1.9)[33].

Vaginal douching was not mentioned by 95.5% of the intervention group and 97.7% of the control group. Consistent with the current study, Tafzali et al.[32] found that 98.3% of study participants did not utilize vaginal douching. The usual vaginal flora can be disrupted by vaginal douching, leading to vaginosis.

In the present study, 31.1% of individuals in the intervention group and 35.6% of individuals in the control group reported a previous occurrence of vaginal infection. This suggests that most women with BV in the study did not have a history of vaginal infection. According to the study conducted by Adan et al.[29], the prevalence of BV was found to be 43.3% in women with a previous history of vaginosis and 50.4% in those without such a history. These findings align with the results of the current study that a previous history of vaginosis in women were almost 35%. In Mohammadzadeh et al.'s[34] study, 73.2% of the participants reported a previous occurrence of vaginal infection. The findings of this study are incongruous with the current research. This inconsistency may be attributed to variations in individuals' health views, the research setting, and the features of the study population.

The current investigation found that the rate of BV negative, as determined by Amsel's criteria, two weeks after curcumin treatment was 86% for clue cells, 54% for discharge, 46% for pH, and 66% for the whiff test, in comparison, the rate for metronidazole was 22.3%, 31.2%, 14%, and 46%, respectively (Table 2). The curcumin group had a complete recovery rate (where all Amsel criteria were negative) of 84%, while the metronidazole group had a recovery rate of 48% (Table 3).

Jafarnejad et al.[28] discovered that aberrant vaginal discharge and odor were considerably reduced in the Fitovagex group, which is consistent with the current study. According to Hafizi et al.[35], abnormal vaginal discharges in the intervention group decreased from 38% before treatment to 7% after treatment with Mycosin vaginal gel, while in the metronidazole vaginal gel group they decreased from 38% before treatment to 13% after treatment, which is consistent with the current study. Mohammad Alizadeh et al.[20] found that the unpleasant odor of vaginal secretions dropped from 94% before to 4% after treatment, which is consistent with the current study. The compatibility of the research mentioned above is due to the frequent and indiscriminate use of antibiotics such as metronidazole, which develops drug resistance in the body. According to Hafizi et al.[35], 68% of participants in the Mycosin vaginal gel group and 70% of participants in the metronidazole vaginal gel group tested negative for the presence of clue cells in vaginal secretions after the intervention, which is consistent with the current study. Mohammad Alizadeh et al.[20] discovered that 73.2% of participants tested negative for the presence of clue cells in vaginal secretions following therapy, which is nearly identical to the current study. According to Rozafzai et al.[36], 25.8% of the metronidazole group tested negative for the presence of clue cells in the microscopic inspection of vaginal secretions compared to 82.5% of the metronidazole plus lactobacillus group. The Amsel criteria (disease symptoms) improved significantly in both groups after one and four weeks of treatment. However, Metronidazole with lactobacillus group showed more improvement than the metronidazole group ($P < 0.0001$). The study on the negativity of the Amsel criterion and clue cells in the metronidazole group did not match the current investigation, which may be attributed to the samples' resistance to metronidazole in terms of geographic region and ethnic disparities.

The present investigation demonstrated that the efficacy of curcumin oral capsules in enhancing Amsel criteria 14 days following treatment was considerably superior to metronidazole oral tablets. There were no reports of medication side effects from patients in the intervention group. In contrast, two people in the control group had dysgeusia, and one person vomited after taking metronidazole, according to the current research. This study contradicts the findings of Jafaranjad et al.[28], where the control group did not experience any issues. While most people take metronidazole orally, Jafaranjad's trial involved vaginal administration. This study's results are in agreement with those of Hafizi et al.[35], where one individual in the control group experienced dysgeusia, and six others vomited after taking oral tablets containing metronidazole.

The Centers for Disease Control and Prevention state that metronidazole should be used as the first line of bacterial vaginosis (BV) treatment. However, metronidazole has several side effects, such as dysgeusia, digestive disorders (pain, cramps in the abdomen, nausea, and vomiting), drowsiness, dizziness, and an adverse reaction to disulfiram and alcohol[14], hallucinations and delusions, mania attacks[15], and a decrease in gonadotropin, testosterone, and spermatogenesis hormones.

The reason both trials found a higher prevalence of gastrointestinal side effects after taking metronidazole tablets is that the technique of taking the tablets was the same in both. Adverse drug reactions can contribute to the persistence of some symptoms in patients. Consequently, patients decline to finish the treatment because of the adverse effects of the medication, which hinders their recovery.

Limitation

Due to time constraints, it was not possible to follow up with the participants over an extended period to determine the infection recurrence rate, which was one of the research's drawbacks. Also we did not measure plasma or tissue levels of curcumin in this study and unable to include in vitro antimicrobial tests in the study design. As well as comparing the efficacy of vaginal metronidazole to oral curcumin is an important area for further research, we recognize this as a limitation and will consider addressing this aspect in future studies.

Conclusions

In addition to having fewer side effects than metronidazole oral tablets, nano-curcumin oral capsule therapy has better results in reducing vaginosis symptoms and signs. As such, it can be used alone or with other BV-fighting medications to improve women's health.

Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

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Author contributions

S.M.: Writing proposal and investigation, Data curation, Writing – original draft; Z.B.M.: Conceptualization, Methodology, Supervision, Writing – review & editing; S.G.: Investigation, Helping to produce and ready herbal medicine, Resources, Project administration; Writing – original draft ; E.R.: Conceptualization, Investigation, Project administration, Formal analysis, Validation, Visualization, Writing – review & editing. All authors reviewed the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to E.R.

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