

Full Length Research Paper

Comparison of the effectiveness of vitamin C vaginal tablet with metronidazole vaginal gel in the treatment of bacterial vaginosis

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Bacterial vaginosis is a change of vaginal flora in which the normal lactobacilli flora is replaced by an overgrowth of *Gardnerella vaginalis* and anaerobic bacteria. Bacterial vaginosis is the most common cause of vaginal infection in women during their reproductive age. The relationship between bacterial vaginosis and increase of vaginal pH is suggested by the use of intravaginal acidification substances as a way for normalization of vaginal flora and treatment of bacterial vaginosis. The purpose of this study was to compare the effect of vitamin C vaginal tablet and metronidazole vaginal gel in treatment of bacterial vaginosis in patient referring to Ahwaz Amir Al Momenin hospital in Ahwaz city, Iran. In this randomized clinical trial 60 non-pregnant women aged between 15 - 45 years with confirmed diagnosis of bacterial vaginosis by Amsel criteria were randomly assigned to receive either 250 mg vitamin C tablet via vaginal route once daily for 6 days (n = 30) or 5 gm of 0.75% vaginal gel metronidazole once daily for 5 days (n = 30). The results of both groups compared for demographic characteristic, contraceptive and education level. The cure rate evaluated in both groups after two (1st and 2nd weeks) follow up visits. For statistical analysis, descriptive statistics, χ^2 and Fisher's exact test performed. The study shows that cure rate after 1 week in vitamin C vaginal tablet group was 76.7% and in metronidazole vaginal gel group was 80% and after 2 weeks, cure rate was 9.5 and 5% respectively. Vitamin C vaginal tablet 250 mg is as effective as metronidazole vaginal gel for treatment of bacterial vaginosis.

Key words: Bacterial vaginosis, vitamin C, metronidazole

INTRODUCTION

Bacterial vaginosis (BV) is defined as a clinical syndrome in which the normal lactobacilli-predominant vaginal flora be replaced by an overgrowth of *Gardnerella vaginalis* and anaerobic microorganisms (Ryan et al., 1999). Although perceived as a mild medical problem, BV has been associated with several gynaecological and obstetrical complications (Simos et al., 2006). Patient with BV have a six fold increased rate of postpartum endometritis after caesarean section, a threefold increased rate of pelvic inflammatory disease after therapeutic abortion

and a three - fourfold increased rate of vaginal cuff cellulites after abdominal hysterectomy. Pregnant patients with BV have a 50 - 100% increased rate of preterm low birth weight delivery, amniotic fluid infection and chorioamnionitis and an increased risk of HIV acquisition and transmission. Various studies have shown an association between urinary tract infection and vaginal infection. Bacterial vaginosis has link with abnormal pap smear results (Berek, 2002; Halman, 2001; Jacobsson, 2002; Harmanli, 2000; CU-Uvin, 2001).

Oral metronidazole is currently the choice treatment for bacterial vaginosis with a reported cure rate of 80 - 90% (CU-Uvin et al., 2001). After treatment with metronidazole, 50 - 70% women will develop recurrence in 4-6 weeks, nearly 70% will have BV again within 90 days

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days and up to 80% will experience at least another episode within a year (Berek et al., 2002). A concern with the use of systemic metronidazole is the potential for adverse effects during therapy, including nausea, vomiting, anorexia, heartburn, headache and a metallic taste in the mouth, convulsion, neuropathy, diarrhea and leucopenia. Therefore, intravaginal administration of topical metronidazole /clindamycin has been preferred because it has the advantage of fewer adverse effects because of lower dosage and low systemic absorption, even if pre-sent in a certain degree.

The potential adverse effects with metronidazole and the less-than-optimal cure rates coupled with high recurrence rates of BV after treatment has prompted a search for alternative therapies. The association of BV with elevated vaginal pH makes logical the use of intravaginal acidic preparations in an attempt to recreate an environment unfavourable to the growth of pathogens (Robert et al., 2004). Vaginal acidification leads to growth of non-pathogenic bacteria such as lactobacilli and inhibit the growth of pathogenic bacteria (Ryan et al., 1999). Therefore, this study designed on topical vaginal acidification with comparison effect of vitamin C vaginal tablet with metronidazole vaginal gel 0.75% in treatment and relapse of bacterial vaginosis among Iranian patients.

MATERIALS AND METHODS

The study was designed as randomized, double blind, controlled, two-group comparative study on 60 women aged 15 - 45 years old with clinically and microbiologically proven BV in Ahwaz Amir Al Momenin Hospital, Iran.

The diagnosis was made by identifying three of following four findings:

- (1) Thin, dark or dull gray, homogenous discharge;
- (2) Vaginal pH (≥ 4.5);
- (3) Positive whiff test; and
- (4) Presence of clue cells on wet smear microscopic evaluation (Amsel et al., 1983).

Non-pregnant women diagnosed suffering from BV considered eligible for the study. Exclusion criteria were treatment with immunosuppressive drugs, treatment with antibiotics in the past 14 days, any other clinically relevant concurrent disease, additional treatment with other topical antiseptic drugs, vaginal infection due to *Candida* spp. history of hypersensitivity to Vitamin C and history of drug abuse. Consenting subjects underwent a pelvic examination. At baseline, the vaginal secretion collected from the lateral vaginal walls cultured and subjected to whiff test, gram stain and pH measurement. Patients who met the selection criteria enrolled in the study by researcher and randomly assigned to one of the two groups by a midwife based on admission code number. Based on studies (Ryan et al., 1999; Peterson et al., 2004), the first group received 250 mg of vitamin C vaginal tablet at bedtime for 6 days ($n = 30$). The second group received 5 gm of metronidazole vaginal gel 0.75% once a day at bedtime for 5 days ($n = 30$).

Culture of the vaginal discharge, whiff test and pH measurement were repeated on the 1st week (visit 2) for 30 patients in two group and 2nd week (visit 3) for 21 patients in vitamin C group and 20 patients in metronidazole group after baseline. Symptom of vaginosis, adverse events and treatment compliance recorded. Table 1

presents the basic characteristics of recruited patients. Previous abortion or preterm labour, previous vaginitis, relation with intercourse and relation with menstruation cycle were comparable across the treatment groups ($p > 0.05$ Table 1). Written informed consent obtained from each patient before starting the study. The Ethical Committee of the Ahwaz Joundishapoor University of Medical Sciences approved the protocol.

Microbiological laboratory tests

Amine/whiff test

One smear was made from the lateral vaginal walls and a small amount of 10% potassium hydroxide (KOH) was dripped on it. A rotten fishy odor was recorded as positive. The smear then microscopically examined for *Candida Albicans* especially as Hiff form.

PH measurement

Vaginal discharge collected was scraped off to a pH paper (Merck .5, Germany) and read in comparison to the standard reading provided by the manufacturer.

Wet smear

Vaginal discharge collected from the lateral vaginal walls and mixed with 2 drops of normal saline for microscopic examination. Clue cells and mobile *Trichomonas vaginalis* were searched for in the vaginal smear.

Gram stain

Two smears made from vaginal discharge and gram stain. One smear was read by the research assistant at the study site. The second smear was sent to the microbiology laboratory for validation by the microbiologist, then by a pathologist for the presence of clue cells and permanent *T. vaginalis*.

Statistical methods

The statistical analysis was done by χ^2 test and Fisher exact test, using SPSS version 13. A probability (p value) of < 0.05 was considered statistically significant.

RESULTS

Before treatment, two groups compared for following factors that were not significantly different ($p > 0.05$): Age ($P = 0.8$), Marriage age ($p = 0.7$), women education ($p = 0.8$), Spouse education ($p = 0.6$), Deliveries numbers ($p = 0.7$), previous abortion or preterm labour ($p = 0.7$), contraceptive method ($p = 0.8$), previous vaginitis ($p = 0.4$), relation with intercourse ($p = 0.5$) and relation with menstruation cycle ($p = 0.9$); (Table 1).

Homogenous vaginal discharge

Foul-smelling vaginal discharge was the most common complaint of patients in treatment groups. The incidence

Table 1. Frequency and percent of demographic and clinical characteristics at baseline by treatment groups.

Groups	Previous abortion or preterm labour				Previous vaginitis				Relation with intercourse				Relation with menstruation cycle			
	Test		Control		Test		Control		Test		Control		Test		Control	
	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%
Yes	10	33.3	11	36.7	17	56.7	20	66.7	23	76.7	21	70	3	10	2	6.7
No	20	66.7	19	63.3	13	43.3	10	33.3	7	23.3	9	30	27	90	28	93.3
Total	30	100	30	100	30	100	30	100	21	100	21	100	30	100	30	100
p value	0.7				0.4				0.5				0.9			

Test- Vitamin C, Control- Metronidazole. This table shows that by using χ^2 test there is not any significant differences between two groups in demographic and clinical characteristics

of homogenous vaginal discharge was not significantly different across treatment groups ($p = 0.3$, $p = 0.6$ respectively; Table 2) but with a trend of lower incidence in homogenous vaginal discharge in follow-up visits.

Whiff test

There was a significant decrease in the proportion of patients with positive whiff tests across clinic visits ($p < 0.5$) but there was not a significant difference in whiff test at follow-up visits between treatment groups ($p = 0.7$, $p = 0.9$ respectively; Table 3).

Change in pH level

Table 4 presents descending pH levels through time but such changes were not significantly different across treatment groups ($p > 0.5$).

Clue cells

The improvement of patients was associated with the percent of cells less than 20% in the gram

stain. One week after treatment, only 13% in the vitamin C group but 40% in the metronidazole group were positive of clue cells. This difference was statistically significant ($p = 0.02$). While after 2 weeks of treatment, only 19% in vitamin C group and 20% in metronidazole group were positive of clue cells but, there was no significant difference across treatment groups ($p = 0.9$; Table 5).

Cure rate

Table 6 presents the observed cure rate at each visit in two treatment groups. One week after treatment cure rate in vitamin C group was 77% and in patients who received metronidazole it was 20%. This difference was not significant ($p = 0.7$) and 2 weeks after treatment cure rate was 9.5% in vitamin C group and 5% in metronidazole group, but there was no significant difference between treatment groups ($p = 0.9$).

Tolerability and safety

Adverse events were fewer in vitamin C group (10%) versus 13.3% in metronidazole group. The

incidence of adverse events was not significantly different across treatment groups ($p > 0.5$).

DISCUSSION

The premise that normal vaginal flora protects the host against pathogen colonization has intensified the interest of researchers in the various factors that may control the vaginal ecosystem. The predominant organism in the vagina is the Doderlein bacillus, member of the genus lactobacillus. However, recent studies have found that the flora is made up of a diversity of anaerobic and aerobic organisms. The low vaginal pH appears as the primary mechanism in controlling the composition of the micro flora (Boskey et al., 1999). Typically, the normal vaginal pH among women of reproductive age ranges 3.8 - 4.2 (Faro, 1994). Studies have shown that acidification by the lactobacilli group can inhibit the growth of pathogenic organisms such as *Candida albicans*, *Escherichia coli*, *Gardenerella vaginalis*, and other bacteria cultured from women diagnosed with BV.

Anaerobic vaginitis or anaerobic vaginosis is characterized by malodorous vaginal discharge and increased discharge that is homogenous, low

Table 2. Frequency and percent of homogenous discharge at each clinic visit by treatment groups.

Group	Baseline				1 week after treatment				2 weeks after treatment			
	Test		Control		Test		Control		Test		Control	
Homogenous discharge	Freq	%	Freq	%	Freq	%	qFre	%	Freq	%	Freq	%
Present	30	100	30	100	10	33	7	23	6	29	7	35
Absent	0	0	0	0	20	67	23	77	15	71	13	65
Total	30	100	30	100	30	100	30	100	21	100	20	100
p value	.9				.3				.6			

This table shows that by using χ^2 test there is not any significant differences between two groups in homogenous discharge before treatment, 1st and 2nd week after treatment.

Table 3. Frequency and percent of whiff test results at each clinic visit by treatment groups.

Group	Baseline				1 week after treatment				2 weeks after treatment			
	Test		Control		Test		Control		Test		Control	
Whiff test	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%
Yes	29	97	28	93	9	30	8	27	5	24	3	15
No	1	33	2	67	21	70	22	73	16	76	17	85
Total	30	100	30	100	30	100	30	100	21	100	21	100
p value	0.9				0.7				0.9			

This table shows that by using χ^2 test there is not any significant differences between two groups in whiff test before treatment and 1st week and by using fisher exact test in 2nd week after treatment.

Table 4. Frequency and percent of vaginal acidity rate at each clinic visit by treatment groups.

Group	Baseline				1 week after treatment				2 weeks after treatment			
	Test		Control		Test		Control		Test		Control	
pH	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%
≥ 4.5	30	100	30	100	18	60	22	73	17	81	18	90
< 4.5	0	0	0	0	12	40	8	27	4	19	2	10
Total	30	100	30	100	30	100	30	100	21	100	20	100
Mean	4.8		4.9		4.3		4.4		4.4		4.6	
SD	0.4		0.7		0.3		0.3		0.2		0.7	
p value	0.6				0.2				0.4			

This table shows that by using fisher exact test there is not any significant differences between two groups in pH before treatment and by using χ^2 test in 1st week and by using fisher exact test in 2nd week after treatment.

in viscosity, and smoothly coats the vaginal mucosa. The pungent odor is the usual complaint. The amines produced by the anaerobes action contribute to the signs and symptoms of BV by elevating the vaginal pH and producing the characteristic fishy odor (Thomason, 2000; Chen, 1982; Brand, 1986).

In this study, vaginal tablet of vitamin C and metronidazole vaginal gel 0.75% (as usual treatment) for BV were utilized. Treatment of BV with any of the two regimens resulted in the increased number of patients with normal vaginal pH (pH < 4.5). The mean pH level significantly decreased across time (p < 0.05) but was not significantly different across treatment groups (p > 0.05).

In (Ditas et al., 2006) study 39% of cases 8 days after treatment by lactic acid had a pH < 4.5 that is comparable to this study results. Our findings suggest that vaginal tablet vitamin C is as effective as metronidazole vaginal gel on vaginal pH one week after treatment.

Furthermore, in a study performed by Aroutcheve et al. (2001) the number of bacteria in the vagina environment was found to be responsible for pH changes and a relationship found to exist between the production of lactic acid and vaginal pH. According to Boris and Barbers (2000) lactic acid and other fatty acids produced by lactobacillus metabolism may contribute to vaginal acidity, although this is not necessarily the primary source

Table 5. Frequency and percent of Clue cell at each clinic visit by treatment groups.

Group	Baseline				1 week after treatment				2 weeks after treatment			
	Test		Control		Test		Control		Test		Control	
Clue cell > 20%	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%
Yes	29	97	28	93	4	13	12	40	4	19	4	20
No	1	3	2	67	26	87	18	60	17	81	16	80
Total	30	100	30	100	30	100	30	100	21	100	20	100
p value	0.3				0.2				0.9			

This table shows that by using fisher exact test there is not any significant differences between two groups in Clue cell > 20% before treatment and by using χ^2 test in 1st week and by using fisher exact test in 2nd week after treatment.

Table 6. Frequency and percent of cure rate at each clinic visit by treatment groups.

Group	Cure after 1 week				Cure after 2 weeks			
	Test		Control		Test		Control	
	Freq	%	Freq	%	Freq	%	Freq	%
Yes	23	76.7	6	20	2	9.5	1	5
No	7	23.3	30	30	19	90.5	19	95
Total	30	100	30	100	21	100	20	100
p value	0.7				0.9			

This table shows that by using χ^2 test there is not any significant differences between two groups in cure rate and by using fisher exact test in relapse rate.

of low vaginal pH. Acids produced by the vaginal epithelial cells and released into the secretions are probably a more important source. One of the factors controlling the growth of organisms in the vagina is lactobacilli. However, our knowledge of the various elements that control the vaginal micro flora is still incomplete. More studies with a larger sample size are required to clarify some of the inconsistent results presented. On the other hand, the fishy odor produced by the alkalization of vaginal fluid in BV is due to the presence of amines. The discharge contains an increased concentration of several amines which are produced by anaerobic bacterial decarboxylation (Faro, 1994; Andersch, 1986). Based on Peterson (2004), 77% of patients in vitamin C group 1 week after treatment and 70% of patients 2 weeks after treatment had normal discharge that is comparable to this study result. In addition, Chaudhric (1996) showed that metronidazole was effective in all of patients in BV. However, in 26% patients, the discharge was permanent. According to Livengood (1999), two treatment methods were statistically effective on reducing vaginal discharge. Whiff test is one of the diagnostic tests in BV with sensitivity of 34 and specificity 15%. The study showed a significant decrease in the number of patients with positive whiff tests for two groups ($p < 0.5$) but there was not a significant difference in whiff test at follow-up visits between treatment groups ($p = 0.7$, $p = 0.9$ respectively; Table 3). According to Ditas (2006), 8 days after treatment by lactic acid, 60% of patients and 14 days after treatment 55% of patients had a negative whiff test that is comparable to this study

results. According to Peterson (2004), 1 week after treatment 91% of patients and 2 weeks later 85% of patients in vitamin C group had a negative whiff test. This difference between two studies may be is due to difference in the population under study. In Peterson study (2004), the patients took drug for only one day.

The criteria developed by Amsel et al. (1983) are the current standard method for diagnosing BV. The diagnosis is made by identifying three of following four findings:

- (1) Thin, dark or dull gray, homogenous discharge
- (2) Vaginal pH (≥ 4.5);
- (3) Positive whiff test
- (4) Presence of clue cells on wet smear microscopic evaluation.

These criteria have a sensitivity of 90% and a positive predictive value of 90%. The presence of clue cells on wet smear is highly specific and virtually pathognomonic of the syndrome. Clue cells are vaginal epithelial cells that have a stippled appearance due to adherent *Coco* bacilli. To be significant for BV, more than 20% of the epithelial cells on the wet smear should be clue cells. In our study, there was a consistent decline in the number of clue cell positive patients in two treatment groups but Vitamin C vaginal tablet was more effective in 1 week after treatment ($p = 0.02$). While 2 weeks after treatment there was not significantly different across treatment groups ($p = 0.9$; Table 5). According to Peterson (2004) 79% of patients 1 week after treatment and 77% patients

after 2 weeks, had lower than 20% clue cells in vaginal discharge, that is comparable to this study result. In Simos study (2006) in 77% of patients 1 week after treatment by metronidazole gel had clue cells in vaginal discharge. These differences between two studies may be due to using different indices for diagnosis of clue cells. According to Simos (2006), the presence of clue cells in discharge was an index for clue cell positive.

Based on our study, vitamin C vaginal tablet was as effective as metronidazole vaginal gel on cure rate of BV symptoms at each visit (Table 6). In Peterson and Magnany (2004), the cure rate in vitamin C group was 86% that is comparable to our results. Also, Livengood et al. (1999) showed that the cure rate in metronidazole group that used metronidazole gel once a week, was 77% that is comparable to this result. According to Dias (2006), the cure rate of BV 15 days after treatment by lactic acid was 67% that is comparable to our results.

Three patients in the vitamin C group were noted to have heartburn and increased vaginal discharge. Four patients who received metronidazole had minimal side effects like vaginal and vulva itching and increased vaginal discharge. According to Peterson (2004) four patients in vitamin C group complained of vaginal itching and burning that is comparable to our results. In addition, Bro F. (1990) showed that 3% of patients after using topical metronidazole had vaginal itching and burning or an increased vaginal discharge.

Conclusion

We therefore conclude that: (1) vitamin C vaginal tablet is as effective as metronidazole vaginal gel on cure of BV symptoms. (2) Vitamin C vaginal tablet could be suggested for treatment of BV in situations such as pregnancy, diabetes mellitus, high-risk sexual behavior, long-term steroid treatment and after menstrual cycles for restoration of normal vaginal flora without any local and systemic side effect. (3) Vitamin C vaginal tablet is safe and be well tolerated.

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