

Comparison of the Effects of *Myrtus Communis L*, *Berberis Vulgaris* and Metronidazole Vaginal Gel alone for the Treatment of Bacterial Vaginosis

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ABSTRACT

Introduction: There is a growing tendency towards herbal medicines for treatment of vaginitis. Antibacterial and antifungal effects of *Myrtus communis L* and *Berberis vulgaris* have been demonstrated invitro and invivo.

Aim: This study aimed to compare the therapeutic effects of the vaginal gel of *Berberis vulgaris* 5% (in metronidazole base) and *Myrtus communis L* 2% (in metronidazole base) with only metronidazole vaginal gel 0.75% on bacterial vaginosis.

Materials and Methods: This study was a randomized clinical trial research on 120 married women aged 18-40 years affected by bacterial vaginosis attended for treatment to gynaecology clinic of Hajar Hospital (Shahrekord, Iran). They were randomly divided into three groups of 40 participants. Diagnostic criteria were Amsel's criteria. *Myrtus communis L*, *Berberis vulgaris* vaginal gel or metronidazole vaginal gel for five-night usage were prescribed to each group, and after 7 days therapeutic

effects were assessed. Data analysis was performed using ANOVA and Chi-square tests.

Results: A statistically significant difference was observed with regard to treatment response among the study groups ($p < 0.001$), with *Myrtus communis L* and *Berberis vulgaris* groups having a better response than metronidazole gel alone. Moreover, there was no significant difference between *Myrtus communis L* and *Berberis vulgaris* groups ($p = 0.18$). The patients in groups of *Myrtus communis L* or *Berberis vulgaris* in metronidazole base did not experience any relapse, but in metronidazole group, 30% of patients experienced relapse during three weeks follow up.

Conclusion: Findings of the study showed that treatment with a combination of *Myrtus communis L* or *Berberis vulgaris* in metronidazole base improve the efficacy of bacterial vaginosis therapy.

Keywords: Efficacy, Herbal, Obstetrics, Therapy

INTRODUCTION

Bacterial Vaginosis (BV) is the most common cause of vaginal discharge and infection in women of child bearing age in the world [1]. BV is a change in the normal flora of the vagina, which leads to reduced hydrogen peroxidase-producing lactobacilli and an overgrowth of anaerobic bacteria. The aetiology of BV is not well-understood, but related to the replacement of *Lactobacillus bacteria* in the vagina with other bacteria such as *Gardnerella vaginalis*, *Ureaplasma*, *Mycoplasma hominis*, *Mobiluncus*, *Prevotella*, and other bacteria [1,2].

Normally, lactic acid, hydrogen peroxide and bacteriocins are produced by lactobacilli and help to keep the acidic vaginal pH and protect against infection caused by microorganisms [3]. Bacteria responsible for BV produce enzymes that destroy protective layer (gel layer) of the epithelium of vagina and cervix [3]. In addition, these anaerobes produce inflammatory proteins related to preterm delivery, pelvic inflammatory disease, endometritis, gonorrhoea, post gynaecologic surgery infection and *Chlamydia throchomatis* [1,4,5].

The most common symptom of BV is vaginal discharge with mal-odor [5], which stops sexual life and influences activity in society [6]. Vaginal exam shows a gray, thin and homogeneous discharge that covers the vaginal wall [7].

The treatment basis of BV is the use of topical or systemic antibiotics like metronidazole and clindamycin effecting on anaerobic organisms but the normal vaginal lactobacilli unaffected [8]. In addition, acidification of the vagina helps lactobacilli colonization and prevents anaerobic growth [9]. Moreover, the use of antiseptics and probiotics are effective in the treatment of BV [8].

Metronidazole is a drug with an excellent performance against the anaerobe and a weak one against lactobacilli, and it is also the first choice for treatment of BV [10]. The use of metronidazole may cause side effects such as dark coloured urine, drowsiness, metallic taste in mouth, dizziness, nausea, transient neutropaenia, alcohol-disulfiram reaction, peripheral neuropathy, diarrhea, vomiting and rarely pancreatitis (in the form of oral and vaginal). In addition, in rare cases there may be an allergy to metronidazole. In some cases, resistance to metronidazole can be observed [11-13].

In recent years, due to great interest of people in herbal medicines and side effects of chemical drugs, the use of herbal drugs like *Communis Myrtus* and *Berberis vulgaris* has increased.

Myrtus communis L is a small tree shrub of the family Myrtace in which the medicinal part are the leaves. The essential oil in leaves consists of tannins, flavonoids, vitamin C without cardiac glycosides and alkaloids. There are some believes that *Communis Myrtus L* has astringent, anti-diarrhea and hair strengthening and growing effects. This herb was used topically to treat herpes. The plant extract can inhibit the growth of bacteria like *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* [14].

Berberis vulgaris is the plant of the family Berberidaceae which has been used as an appetizer and anti-inflammatory agent in past. In addition, antibacterial effect of *Berberis vulgaris* has been proved [15].

Recently, people tend to use traditional therapy; on the other hand, there are some problems in treatment of BV. Considering the properties of *Berberis vulgaris* and *Myrtus communis*, the present study aimed to compare the efficacy of metronidazole vaginal gel with combination of both of the mentioned plants, in treatment and recurrence of BV.

MATERIALS AND METHODS

This study was conducted after approval of the study protocol by Ethics Committee of Shahrekord University of Medical Sciences (ethical no. 92-6-33). The study was a randomized double-blind clinical trial in which the patients and the physician were unaware of medication. The study was done on 120 married women affected with BV referred to Hajar clinic of Shahrekord from March to December 2013.

The diagnosis of BV was based on Gram staining and Amsel's criteria. Having three positive criterion of four Amsel's criteria were considered as BV [16]:

1. Thin homogeneous white or gray vaginal discharge.
2. Positive Whiff test.
3. More than 20% of clue cells in the wet smear of vagina.
4. Vaginal pH more than 4.5.

Inclusion criteria were diagnosis of BV based on Amsel's criteria and married women aged between 18-40 years with willingness to participate in the study. Exclusion criteria were use of systemic or local antibiotics in the past two weeks, post-menopausal women, pregnancy, virgin, history of hysterectomy, spotting, pelvic infection, sperm in smear, associated diseases such as diabetes and immune deficiency and sensitivity to *Berberis vulgaris* or *Myrtus communis* diagnosed by its symptoms as allergies, itching, redness, etc.

The researcher explained the goals and methods of the study to the patients and they signed an informed consent form. All patients could withdraw from the study at any time and for any reason. Randomization was done using the coded papers. The patients in each group were matched in terms of age, education, parity and contraceptive methods (40 in each group).

The study was conducted in agreement with the Declaration of Helsinki and its subsequent revisions and in accordance with local Institutional Review Board recommendations.

Patients in different groups were treated for 5 nights in the following way:

Group A: Vaginal gel of *Myrtus communis* 2% [17] in metronidazole base, **Group B:** Vaginal gel of *Berberis vulgaris* 5% in metronidazole base, and **Group C:** Vaginal gel of Metronidazole 0.75% alone.

They were instructed how to take the medication and follow up visits. In addition, they were instructed to prohibit from intercourse, vaginal washing, and to avoid from other vaginal medication at the night they took the medication. Seven days after the 5-day treatment, patients were re-evaluated for the therapeutic response. Lack or remaining of only one of the Amsel's criteria was considered as an effective treatment [18]. The patients who have not recovered after the treatment period were treated using oral metronidazole. In addition, within three weeks after the treatment, patients were evaluated in terms of recurrence of BV. Finally, their satisfaction on taking these medications was evaluated.

Extraction and preparation of vaginal gel: The leaves of *Myrtus communis* from the area of Lordegan (South West of Iran) and fruit of *Berberis vulgaris* from Mashhad (North East of Iran) were collected. The extraction method was percolation with ethanol 70%. The prepared extract of *Myrtus communis* and *Berberis vulgaris* were added to metronidazole as the basis in concentration of 2% and 5% respectively by a pharmacologist. Prepared gels were filled in special tubes with the same shape and certain code.

The antioxidant properties of *Berberis vulgaris* and *Myrtus communis* extracts were determined by DPPH (Di Phenyl Picryl Hydrazyl) method which was used by Rabiei and colleagues [19].

In vitro antibacterial activity of extracts: In order to determine the minimum inhibitory concentration (MIC) of each extract, 20 mg of each extract was dissolved in 1ml saline normal, then different dilutions in saline normal (1.25, 2.5, 5, 10, and 20) were prepared.

In the next step, a loop of bacterial suspension were added into the Butylated hydroxytoluene (BHT) and incubated for 4 hours in 37°C. Finally, each dilution was inoculated in sterile condition in methylene blue agar medium for 24 hours in 37°C and evaluated for antibacterial activity.

STATISTICAL ANALYSIS

Data were analysed by SPSS software (version 11.5; SPSS, Chicago, IL) using Tukey, Chi-Square test, and ANOVA, and p-value less than 0.05 was considered as significant.

RESULTS

In this study, 120 married women with average age of 32.88±6.04 years (19-40 years) were participated. According to the information, 90.5% of participants previously were treated (27.5% traditional treatment) and 5% of them had a history of hospitalization for BV. Chi-square tests showed no significant differences among groups in terms of age, age at menarche, age at marriage, education level, employment status, method of contraception, parity, number of births, and abortions ($p > 0.05$). Moreover, the study groups were matched in terms of history and frequency of vaginal infection, medical and traditional treatment, and frequency of hospitalization [Table/Fig-1]. Based on Chi-square test, clinical symptoms of BV at baseline were similar amongst the study groups [Table/Fig-2].

The ANOVA test showed a significant difference among the groups in terms of recovery (cure) ($p < 0.01$). Regarding the Tukey test, there was a statistically significant difference between *Myrtus communis* group and metronidazole gel alone ($p < 0.001$) in terms of recovery. However, this difference was also seen in metronidazole alone and *Berberis vulgaris* groups ($p < 0.001$), but there was no significant difference between the *Berberis vulgaris* and *Myrtus communis* ($p = 0.18$) [Table/Fig-3].

Generally, results of the study showed that vaginal gel consists of extracts of *Myrtus communis* or *Berberis vulgaris* in metronidazole base were more effective than metronidazole gel alone on BV. Furthermore, all patients taking herbal combination had no recurrence three weeks after the treatment period while in metronidazole alone 30% of patients had recurrence.

With regard to the invitro section of the study, MIC for *Myrtus communis* and *Berberis vulgaris* were determined as 2.5 mg/ml and 20 mg/ml respectively.

In addition, by DPPH method, the amounts of phenol were 91.08 mg/g, flavonoid 62.70 mg/g, and flavonol 34.38 mg and antioxidant

Groups/Variable		Metronidazole alone	<i>Berberis Vulgaris</i> in Metronidazole Base	<i>Myrtus communis</i> in Metronidazole Base	p-value
Age/ Years (Mean± SD)		32.48±6.38	32.75±6.96	33.4±4.65	0.86
Age at Menarche/ Years (Mean± SD)		13.45±1.13	13.62±1.05	13.7±1.74	0.56
Age at Marriage/ Years (Mean± SD)		20.25±4.21	19.02±3.73	18.85±2.98	0.37
Gravida (Mean± SD)		2.18±1.31	2.32±1.94	2.50±1.24	0.36
Parity (Mean± SD)		2.05±1.30	1.92±1.80	2.15±1.09	0.14
Number of Abortion (Mean± SD)		0.25±0.54	0.32±0.65	0.35±0.66	0.81
Job	employed	4	5	5	0.4
	Unemployed	36	35	35	
Education Level	Illiterate	2	2	2	0.35
	Diploma	19	19	19	
	Diploma and above	19	19	19	

[Table/Fig-1]: Demographic characteristic of patients in the study groups.

Groups/ Variable		Metronidazole Alone		Berberis Vulgaris in Metronidazole Base		Berberis Vulgaris in Metronidazole Base		p value
		Frequency	%	Frequency	%	Frequency	%	
Burning Vagina	Yes	27	67.5	21	52.5	24	60	0.39
	No	13	32.5	19	47.5	16	40	
Itching	Yes	25	62.5	20	50	24	60	0.48
	No	15	37.5	20	50	16	40	
Redness	Yes	14	35	18	45	12	30	0.36
	No	26	65	22	55	28	70	
Dyspa- reunia	Yes	16	40	18	45	25	62.5	0.10
	No	24	60	22	55	15	37.5	
Ague	Yes	4	10	9	22.5	7	17.5	0.32
	No	36	90	31	77.5	33	82.5	
Dysuria	Yes	14	35	16	35	17	42.5	0.78
	No	26	65	24	65	23	57.5	
Dysme- norrea	Yes	18	45	19	47.5	20	50	0.90
	No	22	55	21	52.5	20	50	

[Table/Fig-2]: Comparison of different groups in baseline symptoms of bacterial vaginosis. There was no significant difference between the study groups ($p > 0.05$).

Groups	Cured		p-value (cured)	Uncured	
	Frequency	Percent (%)		Frequency	Percent (%)
Metronidazole Alone	17	42.5	p<0.001	23	57.5
<i>Berberis Vulgaris</i> in Metronidazole Base	4	10		36	90
<i>Myrtus communis</i> in Metronidazole Base	2	5		38	95

[Table/Fig-3]: Comparison recovery rate among the study groups.

capacity 77.1Ug/ml in *Myrtus communis* extract. Also in *Berberis vulgaris* extract, 157 mg/g phenol, 12.2 mg/g flavonoid, and 25 mg/g flavonol, and antioxidant capacity 139.6Ug/ml were measured.

DISCUSSION

The result of present study showed that vaginal gel consist of extracts of *Myrtus communis* or *Berberis vulgaris* in metronidazole base were more effective than metronidazole alone on BV without any serious side effect and relapse. In addition, recurrence rate in metronidazole group was 30% similar to result of study of Sobel and colleague [20].

This study is the first study on human which determine the therapeutic effect of *Myrtus communis* and *Berberis vulgaris* in metronidazole base in comparison with metronidazole vaginal gel alone on BV, so there is no similar human study confirming these results, but some invitro studies showed the antimicrobial effect of *Berberis vulgaris* and *Myrtus communis* [21,22].

Isoquans like Berberin, Berbamine and Palmatine are some of the active ingredient of *Berberis vulgaris* [23] and anti-inflammatory, anti-histaminic and anti-microbial effects of *Berberis vulgaris* on BV may be due to these ingredients. Berberin is one of the most important ingredients in *Berberis vulgaris* with antibacterial and antifungal properties. Studies have shown that this substance has inhibitory effect on *Candida albicans* growth, *Trichomonas vaginalis*, and *Staphylococcus aureus* [24]. Han and colleagues in their study showed that the combination of amphotericin B and berberin can be reduced up to 75% of required dose of amphotericin B in treatment of candidiasis [25]. Soffarr et al., found that berberin has inhibitory effect on growth of *Trichomonas vaginalis* similar to metronidazole [26].

According to finding of study carrying out by Oh and colleague, berberin has a potent inhibitory activity against sortase A and

sortase B. Inhibition of these enzymes significantly decrease virulence and pathogenesis of *Staphylococcus aureus* and propose as antibacterial mechanism of berberin [27]. Kupeli and colleagues proved anti-nociceptive and anti-inflammatory effects of berberin [28] which probably is related to prostaglandin E2 and reduction of cyclooxygenase [29].

Shamsa and colleagues in their study showed that the fruit of *Berberis vulgaris* has anti-histaminic property and contains vitamin C and acidic compounds [30], therefore, these can remove some symptoms of vaginosis [31]. Vitamin C by decreasing acidity of the vagina inhibits the bacteria growth in acidic environment. In addition, bacteria such as lactobacilli have tendency to grow in acidotic condition of vagina and actually undesired anaerobes strongly are inhibited by acidotic components of vitamin C [32].

The results of the study showed that *Myrtus communis* in metronidazole base was the most effective combination in the treatment of BV among study groups. In addition, according to finding of the invitro section of the study, *Myrtus communis* extract was more effective than *Berberis vulgaris* extract in lower dilutions.

Polyphenols, myrtucommulone (MC), semimyrtocommulone (S-MC), 1, 8-cineole, α -pinene, myrtenyl acetate, limonene, linalool, and α -terpinolene are the most important ingredients in *Myrtus communis* with biological activity. Clinical and experimental studies suggest that *Myrtus communis* possesses a broader spectrum of pharmacological and therapeutic effects such as antioxidative, anticancer, antidiabetic, antiviral, antibacterial, antifungal, hepatoprotective and neuroprotective activity [33,34].

Houshmand et al., showed that the extract of *Myrtus communis* in different concentrations have antibacterial effects against aerobic and anaerobic bacteria [35]. The antibacterial activity of *Myrtus communis* is due to the increase of oxygen free radicals and lipid peroxidation, which can destroy the wall of microorganisms [36]. *Myrtus communis*, has anti-inflammatory and anti-nociceptive effects [37,38]. These properties explain the therapeutic effects of *Myrtus communis* on BV in comparison with metronidazole alone.

CONCLUSION

Regarding the findings of the study, vaginal gel consist of *Myrtus communis* or *Berberis vulgaris* extract in metronidazole base is more effective than metronidazole gel alone and could be used as alternative option in medication resistance patients or patients with trend to herbal medicine. Since *Myrtus communis* and *Berberis vulgaris* have antibacterial, antifungal, and anti-inflammatory effects, it seems necessary to conduct more studies to evaluate efficacy of these plants in treatment of bacterial and non- bacterial vaginitis.

ACKNOWLEDGEMENT

We would like to thank the patients who participated in this study. This study was financially supported by Shahrekord Medical University of Sciences, and registered in Iranian Registry of Clinical Trials (IRCT) by IRCT201411102085N13.

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FINANCIAL OR OTHER COMPETING INTERESTS: As declared above.

Date of Submission: **Oct 08, 2015**
Date of Peer Review: **Dec 22, 2015**
Date of Acceptance: **Jan 11, 2016**
Date of Publishing: **Mar 01, 2016**