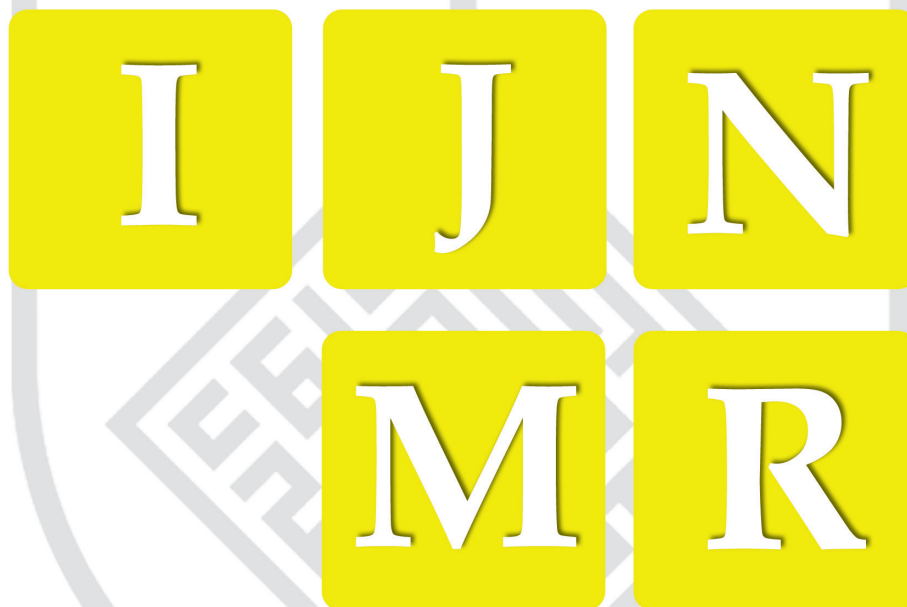


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# Comparison of the Effects of Nika Vaginal Cream with Clotrimazole Cream on Vaginal Candidiasis Symptoms: A Randomized Single-Blind Clinical Trial

## Abstract

**Background:** The prevalence of vaginal candidiasis is high in women and proper treatment is essential in this regard. **Materials and Methods:** This single-blind randomized controlled clinical trial was conducted on 120 women who were referred to Hamadan health centers in 2019. The patients were randomly divided into Clotrimazole cream and Nika vaginal cream groups each including 60 cases. The intervention group received Nika vaginal cream once a day for a week and those in the control group were given Clotrimazole vaginal cream in the same way. The clinical symptoms were studied by clinical examinations and the culture of vaginal discharge before and 7 days after the treatment to confirm the diagnosis of *Candida albicans*. The results were analyzed by SPSS 21.0 using an independent *t* test, Mann-Whitney *U* test, and Chi-square, Fisher's exact, and McNemar's tests, the significance level was set at 0.05. **Results:** Most patients in both groups reported no clinical symptoms after the intervention, and no significant difference was observed between the two groups in this regard ( $\chi^2 = 2.23$ ,  $p = 0.566$ ). Conversely, a significant difference was found in Nika and Clotrimazole groups before and after the intervention regarding improving Vulvovaginal Candidiasis (VVC) symptoms  $\chi^2 = 86.01$ ,  $\chi^2 = 99.41$ , respectively ( $p < 0.001$ ). Finally, 84.48% and 75.86% of women in the Nika  $\chi^2 = 45.02$  ( $p < 0.001$ ) and Clotrimazole cream  $\chi^2 = 40.02$  ( $p < 0.001$ ) groups had negative culture results after the intervention. **Conclusions:** In general, the Nika and Clotrimazole vaginal creams have the same effects concerning improving the symptoms of vaginal candidiasis and thus can be used to treat VVC.

**Keywords:** Candidiasis, honey, Iran, olea, propolis, vulvovaginal

## Introduction

Approximately 75% of women experience at least one period of Vulvovaginal Candidiasis (VVC) during the reproductive period. In addition, the recurrence of the disease has been observed for the second time in 40%–50% of cases. Nearly 13 million VVC cases are annually reported in the United States. Further, reports indicate that the incidence of the disease has increased over the past decade in Europe and the United States. In a study in Iran, 47.4% of women had VVC.<sup>[1]</sup> VVC is the second most common cause of vaginal infection. The diagnostic symptoms of vaginitis include white secretion, which may vary from liquid to homogeneous one, with painful vaginal lesions, dysuria, inflammation, and vaginal irritation. Furthermore, other symptoms are the edema and erythema of the lips and the skin of the

vagina, normal cervix, normal pH (<4.5), fungal components whether budding yeast or mycelium, and a negative Whiff test result.<sup>[2]</sup> VVC symptoms often appear just before the beginning of menstrual bleeding. Clear erythema in the vagina and small lesions surrounding the erythematous zones in the vagina are diagnostic criteria for VVC in the examination.<sup>[3]</sup> Food and Drug Administration-approved medicine for the treatment of vaginal candidiasis is an azole-class group such as Fluconazole and Clotrimazole, but recently, there have been reports on the side effects of these medicines, including metallic taste in the mouth, headache, dizziness, and the like.<sup>[4]</sup> The side effects of itching include vaginal irritation, redness, and scaling.<sup>[5]</sup> Such cases highlight the necessity of finding alternative treatments for vaginitis candidiasis.<sup>[6]</sup> In a systematic review study, the use of herbal

Hamideh Parsapour<sup>1</sup>,  
Seyede Zahra Masoumi<sup>2</sup>,  
Arezoo Shayan<sup>2</sup>,  
Shirin Moradkhani<sup>3</sup>,  
Seyed Amir Ghiasian<sup>4,5</sup>,  
Mohammad Kazem Rashidi<sup>6</sup>

<sup>1</sup>Department of Gynecology,

Clinical Research Development Unit of Fatemeh Hospital,

Hamadan University of Medical Sciences, Hamadan, Iran,

<sup>2</sup>Department of Midwifery and Reproductive Health, Mother and Child Care Research Center, School of Nursing and Midwifery, Hamadan University of Medical Sciences, Hamadan, Iran,

<sup>3</sup>Department of Pharmacognosy, School of Pharmacy, Medicinal Plants and Natural Products Research Center, Hamadan University of Medical Sciences, Hamadan, Iran, <sup>4</sup>Medical Parasitology and Mycology Department, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran, <sup>5</sup>Psoriasis Research Center, Department of Dermatology, Farshchian Hospital, Hamadan University of Medical Sciences, Hamadan, Iran, <sup>6</sup>Nika Research and Traditional Medicine Production Company, Hamadan, Iran

### Address for correspondence:

Dr. Seyede Zahra Masoumi, Fahmideh Ave, Hamadan, University of Medical Sciences, School of Nursing and Midwifery, Department of Midwifery and Reproductive Health, Hamadan, Iran.  
E-mail: zahramid2001@gmail.com

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drugs, along with routine ones is recommended for the treatment of VVC.<sup>[7]</sup> The vaginal cream Nika containing honey, olive oil, and bee propolis (black wax) is completely organic. This combination has created a product that has extraordinary effects in addition to antioxidant, anti-analgesic, and anti-inflammatory properties. Honey in combination with olive oil creates miracles for relieving skin problems. Honey has antibacterial effects as well.<sup>[8]</sup> Propolis bee wax is a matter with medicinal properties, and nowadays, its alcoholic solution is used to treat gynecological problems in some countries.<sup>[9]</sup> The ethanol extract of propolis has also antibacterial, antifungal, and anti-inflammatory properties.<sup>[10,11]</sup> Furthermore, the daily use of topical olive oil has been reported to be effective in improving the clinical and paraclinical aspects of the treatment of patients with VVC.<sup>[12,13]</sup> These compounds have antioxidant, antimicrobial, anti-cancer, anti-platelet aggregation, and antihypertensive properties.<sup>[14]</sup> However, no study has so far evaluated the effect of the combination of honey, olive, and propolis on VVC treatment. The combined cream vaginal of honey, olive, and propolis (i.e., Nika cream) is a completely natural and organic medicine that contains no essential oils or preservatives and can be used during lactation. Considering that the treatment of VVC is highly important due to its high prevalence in women.<sup>[15]</sup> The present study sought to compare the Nika cream with Clotrimazole cream on the treatment of VVC.

## Materials and Methods

The present single-blind randomized controlled clinical trial (IRCT20120215009014N290) was conducted on 120, 18–44-year-old women in 2019. After obtaining a license from Hamadan University of Medical Sciences, the researcher referred to comprehensive health centers. The

sample size was calculated based on the study by Rasooli *et al.*<sup>[11]</sup> In this study, the test reliability, test power, and the amount of sample loss were 95, 90, and 20%, respectively. The minimum required sample size in each group was then determined to be 60 cases (a total of 120 samples for both groups). Moreover, the purposeful sampling method was used, and participants were randomly assigned to two groups of Nika vaginal cream (Group A) and 1% Clotrimazole vaginal cream (Group B). Before starting the study, the aims of the study and the advantages of using herbal and combined vaginal creams were explained to the participants, and written consent was obtained from women who volunteered to participate in this study. Moreover, they were asked to report the side effects of medications. It is noteworthy that visiting patients and medicines had no costs, and women were ensured of data confidentiality.

Then, the participants and the researcher completed the demographics form and the checklist, respectively. Next, VCC was examined before and after the intervention by taking a history and evaluating clinical symptoms, clinical examinations, and the culture of vaginal discharge. Clinical signs included vulvitis, vaginitis, itching, and the secretions of cheese, and the pH level of the vaginal secretion was measured by paper pH gauges. The inclusion criteria included married women aged 18–44 years, vaginal secretion culture positive for vaginal candidiasis, symptoms of candidiasis in clinical examinations, lack of receiving any vaginal treatment or oral fluconazole for VVC during the last month, immunosuppressive and vaginal medicines, and oral contraceptive pill during the past 2 weeks. In addition, other inclusion criteria were the non-use of oral or intravenous antifungal medication since 1 month before the study, no abnormal uterine bleeding, no recurrent vaginitis (four or more per year), no pregnancy, no breastfeeding, absence of specific diseases such as liver and kidney diseases, central nervous system abnormalities, blood dyscrasias, diabetes lack of a history of azole sensitivity, absence of abnormal pap smear tests over the past 12 months. The exclusion criteria were taking any medication affecting the symptoms and treatment of vaginal candidiasis concurrently during the intervention, and the patient's unwillingness to continue treatment. To collect samples Hamadan was geographically divided into four districts. Two health centers were randomly selected from each of the north, south, east, and west districts using the draws, that finally eight health centers were selected accordingly. Then, a list of the eligible women of these centers was obtained, and allocation sequences were determined using the fourth randomized blocking [Figure 1]. Blinding was because the main researcher was unaware of how individuals were divided into two groups.

The cream vaginal was patented by Nika Traditional Medicine Products Research and Production Company and licensed by the Ministry of Health (No. 7177482515095332)

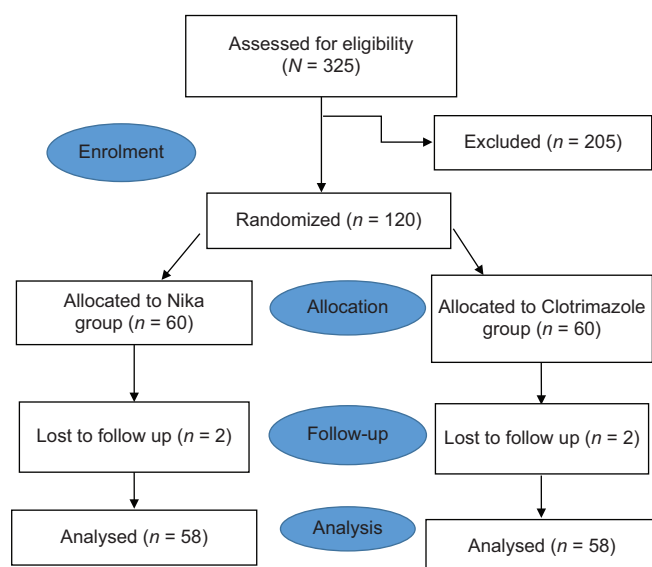


Figure 1: Consort flowchart of selected samples

and has been marketed in pharmacies since 2015. This product has been mass-produced in Nazarabad Pharmaceutical Company of Karaj. The important effects of Nika include healing wounds from scratches and cuts, sutures, bed sores, diabetic wounds, burns, inflammation and allergies, and fungi. The subjects in group A were asked to use Nika vaginal cream by a full applicator for seven nights, and group B was given 5 g Clotrimazole 1% as vaginal cream using the same method. The two groups were asked to be followed up for 7 days after starting the treatment. At this time, checklists were completed again and clinical symptoms were examined by the researcher at the time of examination. Vaginal discharge was cultured again.

The data collection tools were a demographics form and a checklist including 11 and 9 questions, respectively. The prepared checklist was used to record the result of culture and signs in addition to symptoms such as vaginal white secretion, occasional itching (Both inside the vagina and the vulva), cervical vertebrae, vaginal erythema, dyspareunia, and dysuria before and after the treatment. Finally, SPSS21 was used to analyze the data by independent *t*-test, Mann-Whitney, Chi-square, Fisher's exact, and McNemar's tests, and  $p < 0.05$  was considered as the level of significance. Two people from each group were unwilling to continue participating in the study, and 58 people in each group were examined accordingly.

### Ethical considerations

The study was approved by the Research Ethics Review Committee of Hamadan University of Medical Sciences (UMSHA.REC.1398.347). In addition, written informed consent was obtained from all participants in both groups, and they were assured of the confidentiality of their personal information.

### Results

In this study, randomization was performed on 120 eligible individuals who were placed in two groups each including 58 cases as two people in each group showed

unwillingness to continue the treatment. The Mean (SD) of age and body mass index of the Clotrimazole and Nika groups were 30.36 (7.52) and 29.24 (6.91) years, as well as 24.74 (4.11) and 24.83 (3.62) kg/m<sup>2</sup>, respectively. Based on the obtained data [Table 1], no significant difference was observed between the two groups regarding demographic information and they were homogenous ( $p > 0.05$ ).

Before the intervention, symptoms such as itching, burning, edema of the vulva, urinary irritation, cheese discharge, and dyspareunia were evaluated in the two groups. Accordingly, 43.15 and 37.90% of all symptoms were observed in the Nika and Clotrimazole groups, respectively. There was a significant difference in terms of all symptoms in both groups before and after the intervention  $\chi^2 = 86.01$  ( $p < 0.001$ ). Conversely, no symptoms were observed in 79.30 and 67.20% of people in the Nika and Clotrimazole groups after the intervention, respectively. Based on the results, there was no statistically significant difference between the two groups regarding VVC symptoms before and after the intervention ( $p > 0.05$ ). After taking the medicines 20.70% and 32.80% of individuals in taking Nika and Clotrimazole cream reported at least one clinical symptom. Thus, Nika cream was more effective in reducing clinical symptoms [Table 2]. Most women in Nika and Clotrimazole groups had negative *Candida albicans* culture results after the intervention although the results were more negative (84.48 and 75.86%, respectively) in the Nika group [Table 3].

### Discussion

Based on the results, the two groups showed similar clinical symptoms (e.g., itching, burning, edema of the volva, urinary irritation, cheese discharge, and dyspareunia) before the study. However, the clinical symptoms showed a significant decrease after the intervention so that most participants of Nika and Clotrimazole groups were completely asymptomatic. In each group, a significant difference was observed before and after the intervention

**Table 1: Comparison of demographic characteristics in Nika and Clotrimazole groups**

Characteristics	Nika Group Mean (SD)	Clotrimazole Group Mean (SD)	Test statistic	<i>p</i>
Age (in year)	29.24 (6.91)	30.36 (7.52)	$t_{114} = -0.83$	0.405**
BMI*	24.83 (3.62)	24.74 (4.11)	$t_{114} = 0.12$	0.903**
Parity	1.54 (0.86)	1.5 (0.71)	$u_{114} = -0.19$	0.845***
Education <i>n</i> (%)				
Illiterate	3 (5.00)	4 (6.67)	$\chi^2 = 1.41$	0.842****
Primary	8 (13.33)	7 (11.67)		
High school	6 (10.00)	7 (11.67)		
Diploma	31 (51.67)	34 (56.67)		
Academic	12 (20.00)	8 (24.99)		
Occupation <i>n</i> (%)				
Employed	4 (6.67)	8 (13.33)	$\chi^2 = 2.14$	0.143****
Unemployed	56 (93.33)	52 (86.67)		

\*Body mass index; \*\*Independent *t*-test; \*\*\*Mann-Whitney *U* test; \*\*\*\*Chi-square test



**Table 2: Comparison of the symptoms of VVC\* in Clotrimazole and Nika groups before and after the intervention by Fisher's exact test**

Studied Groups	Itching n (%)	Burning n (%)	Edema of Volva n (%)	Urinary Irritation n (%)	Cheese Discharge n (%)	Dyspareunia n (%)	$\chi^2$	p
Nika								
Before	15 (29.50)	5 (8.60)	0 (0)	1 (1.70)	10 (17.20)	2 (3.40)	86.01	<0.001
After	9 (15.50)	2 (3.40)	0 (0.00)	0 (0.00)	4 (6.90)	0 (0.00)		
Clotrimazole								
Before	20 (34.50)	3 (5.20)	1 (1.70)	1 (1.70)	11 (19.00)	0 (0.00)	99.41	<0.001
After	6 (10.30)	3 (5.20)	0 (0.00)	0 (0.00)	7 (12.10)	0 (0.00)		

\*VolvoVaginal Candidiasis. Statistical test (before and before); Exact test=4.28, df=6,  $p=0.705$ ; Statistical test (After and after); Exact test=2.23; df=3;  $p=0.566$

**Table 3: Comparison of culture results from vaginal discharge in terms of the existence of *Candida albicans* before and after the intervention in Clotrimazole and Nika groups by the McNemar's test**

Groups	Before Intervention	After Intervention Negative n (%)	Positive n (%)	$\chi^2$	p
Nika	Negative	0 (0.00)	0 (0.00)	45.01	<0.001
	Positive	49 (84.48)	9 (15.52)		
Clotrimazole	Negative	0 (0.00)	0 (0.00)	40.02	<0.001
	Positive	44 (75.86)	14 (24.14)		

with regard to improving VVC symptoms. In line with the findings of our study, Seifi Nader Goli *et al.*<sup>[16]</sup> found that the level of lactobacilli significantly increased in the honey group after the treatment, and improvements were observed in the clinical symptoms. Based on their results, honey did not change normal vaginal flora compared with Clotrimazole. Similarly, Fazel *et al.*<sup>[17]</sup> used honey, Clotrimazole-honey combination, and Clotrimazole to treat candidiasis vaginitis and reported that the patient's symptoms reduced significantly after treatment with a combination of honey and Clotrimazole. This study partly similar to our study comparing Clotrimazole with honey. Although our study compared honey in combination with olive and propolis with Clotrimazole in different doses. In another study, Rasooli *et al.*<sup>[11]</sup> compared cinnamon and honey vaginal cream with Clotrimazole vaginal cream in the treatment of candidiasis and concluded that irritation was significantly lower in the group using cinnamon and honey vaginal cream compared to the Clotrimazole group.<sup>[11]</sup> Which is consistent with the results of the present study regarding the effects of honey in the treatment of candidiasis. Likewise, Abdelmonem *et al.*<sup>[18]</sup> indicated that using honey and yogurt is effective in treating candidiasis vaginitis. In their review study, Gümüş and Yurttaş<sup>[19]</sup> investigated the effects of olive oil on wound care and showed that it was a high-quality nutrient oil and was used for wound healing due to its antibacterial and anti-inflammatory effects. In this study, olive oil was used, and the results were due to the anti-candida or inflammatory effects of olives. Furthermore, Peña-Jiménez *et al.*<sup>[20]</sup> evaluated the therapeutic effects of

the topical ozonated olive oil on healing acute cutaneous wounds and its therapeutic mechanism in the guinea pig model. Based on the results, the ozonated olive oil group had a significantly smaller wound size and area, a higher number of fibroblasts, increased intensity of collagen fibers, and higher amounts of growth factors. They also concluded that the topical use of the ozonated olive oil can heal acute skin ulcers. The above-mentioned results corroborate with the results of the present study on the efficacy of Nika herbal cream including honey, propolis, and olive. This is probably due to the anti-candida effects of Nika vaginal cream in reducing the symptoms of candidal vulvovaginitis. In the study by Mousavi, intravaginal propolis cream had a similar effect to Clotrimazole on cheesy discharge and itching of candidiasis,<sup>[21]</sup> which is in line with the finding of our study. The strength of our study was that it used a combination of honey, olives, and propolis in the treatment of VVC, whereas other studies examined each of these compounds alone. In addition, the use of Nika combination cream in the treatment of VVC is an innovation. However, the limitation of our study was the small sample size due to the time limit in sampling and follow-up of women with VVC was performed for a short time. Accordingly, there is a need for further studies in this field in order to obtain definitive results regarding the effect of Nika in the treatment of VVC.

## Conclusion

In our study, both drugs were effective in treating the symptoms of VVC. Although Nika cream was more effective. Thus, Nika cream is recommended for the treatment of VVC.

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## Conflicts of interest

Nothing to declare.

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