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Original Article
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Chamomile Extract versus Clotrimazole Vaginal Cream in Treatment of Vulvovaginal Candidiasis: A Randomized Double-Blind Control Trial

Zahra Shiravani[1], Tahereh Poordast[1], Shaghayegh Moradi Alamdarloo[2], Fateme sadat Najib[1]*, Fatemeh Hosseinzadeh[3], Hadi Raeisi Shahraki[4]

[1]Infertility Research Center, Department of Obstetrics and Gynecology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Department of Perinatology, Maternal-fetal Medicine Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Department of Midwifery, School of Nursing and Midwifery, Estahban branch, Islamic Azad University, Estahban, Iran
[4]Department of Epidemiology and Biostatistics, School of Health, Shahrekord University of Medical Sciences, Shahrekord, Iran

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***Corresponding Author**
Fateme sadat Najib
Infertility Research Center, Department of Obstetrics and Gynecology, School of Medicine, Shiraz University of Medical Sciences, Shiraz 009871, Iran
Tel: +98-917-715-6144
E-mail: najibf@sums.ac.ir

Objectives: Vulvovaginal candidiasis (VVC) treatment is advised for all women due to its symptoms and complications. In this study, the standard treatment, clotrimazole, was compared with chamomile extract cream in outpatient clinics.
Methods: We recruited 73 women with VVC, who were randomly allocated into two groups, clotrimazole *versus* chamomile extract cream. After two weeks of treatment with the same criteria, cheese-like vaginal discharge, itching and burning sensations, strawberry cervix, and recovery percentage was evaluated.
Results: Thirty patients in each group were analyzed. There was no significant difference in age and number of pregnancies between groups ($p = 0.85$ and 0.09, respectively). Comparing before and after treatment, cheese like discharge ($p < 0.001$), itching ($p < 0.001$), burning ($p < 0.001$) had significantly improved in both groups. Further, the recovery percentage was not significantly different between groups (88.9% *vs* 75% in the chamomile vs clotrimazole groups, respectively).
Conclusion: Chamomile is as effective as clotrimazole in VVC treatment; a higher percentage of women who used this medication recovered, although this did not reach significance. In addition, no complications were reported in either group.

Keywords: vulvovaginal candidiasis, chamomile, clotrimazole

INTRODUCTION

Vulvovaginal candidiasis (VVC) is one of the most frequent infections amongst women; 75% of them encounter at least one episode of this disease during lifetime. *Candida albicans* is the predominant pathogenic species of this infection [1, 2]. Current therapy for Candida infections is limited to four major classes of antifungal drugs, including azoles, polyenes, fluoropyrimidines. Additionally, the newly generated echinocandins are widely used as an alternative for isolates that show resistance to other antifungal drugs [3, 4].

Previous studies have reported that cure rate of azole drugs is less than 100%; therefore, researchers have sought to discover another drug can be used as the standard drug [5]. *Houttuynia cordata Thunb* is a herbal plant found in Asia. It possesses various traits, including antimicrobial and anti-inflammation activities. Water extract of this plant modulates the expression of antimicrobial peptides and cytokines that are produced by vaginal epithelial cells. These play an important role in the mucosal innate immunity in the female reproductive tract [6]. A randomized clinical trial in 2019 has reported that treatment with *Salvia officinalis* tablets alone or in combination with clotrimazole, is an effective treatment for VVC [7].

Chamomile products have used for mucositis in other or-

gans, such as post chemotherapy oral mucositis, gastrointestinal microbial problems, and postpartum perineal healing. No important side effects have been reported with this treatment [8]. Components from chamomile have been used in literature for anti-microbial and anti-fungal effects [9]. The anti-inflammatory effect of chamomile reported in the studies because of decreasing IgG and IgE level [10].

The present study aimed to compare the efficacy of chamomile extract as a new line of therapy in comparison with clotrimazole; standard treatment in treating signs and symptoms of VVC.

MATERIALS AND METHODS

1. Study design

This is a double-blind randomized clinical trial in women who were referred to outpatient clinics affiliated with the Shiraz University of Medical Sciences. The study was conducted over a 15-month period, from January 2017 to March 2018. The Medical Ethics Committee of Shiraz University of Medical Science approved the study (IR.SUMS.MED.REC.1397.8186). Written informed consent was obtained for all participants. The trial registered at the Iranian registry of clinical trials (registration number, IRCT2016051118655N2).

Study participants were divided into two groups using simple

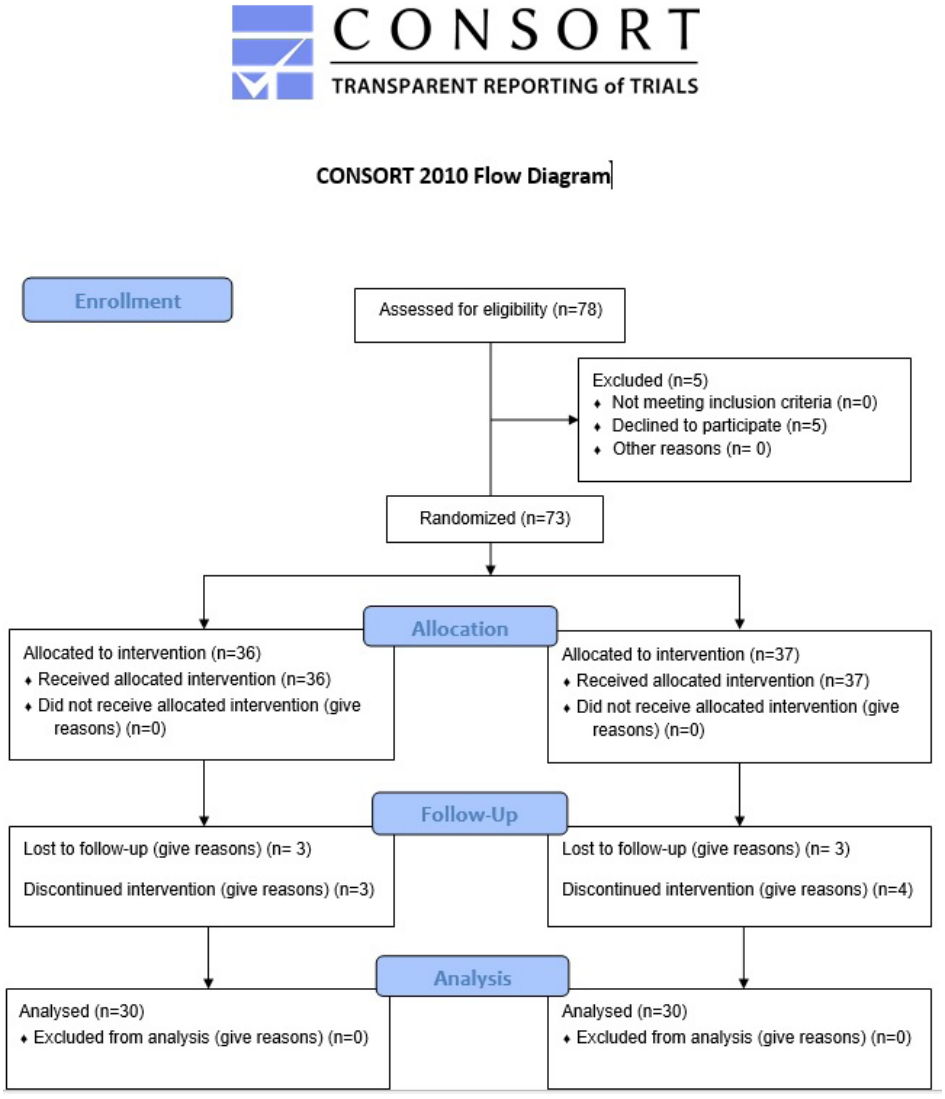

Figure 1. CONSORT 2010 flow diagram.

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randomization with a randomization table. The sample size was calculated with α = 5% and power = 80. According to a pilot sample, the sample size required to reach the objectives of our study was at least 60 subjects. However, considering a possible dropout rate of 18%, the minimum sample size was determined to be 36 cases per group. The CONSORT flow diagram for the study is shown in Fig. 1.

2. Participants

We recruited women who had been referred to outpatient clinics affiliated with Shiraz University of Medical Sciences and had positive signs and symptoms for VVC, such as vulvovaginal itching, burning sensations, malodor discharge, and strawberry cervix.

Inclusion criteria were women who provided informed consent, sexually active, aged between 18-44 years, had intercourse > 3 days previously, and consented to examination 2 weeks later.

Exclusion criteria were recurrent candidiasis (RVVC, which refers to confirmed symptomatic VVC for ≥ 4 times within 1 year) [11], pregnancy, menopausal status, menstruation time, any sign or symptoms of other vaginal infections, allergy to chamomile byproducts, or having another diagnosis, such as diabetes mellitus and immunosuppressive conditions.

3. Intervention

The double-blind nature of the study was explained to the participants. A trained physician examined the participants who were clinically diagnosed with VVC. All participants were anonymized and given a code after being assigned to their groups. Clotrimazole and chamomile vaginal creams were administered to the appropriate women in identically shaped packages; both treatments were packaged in tubes without names that were numbered using the random allocation method. The pharmacy staff distributed clotrimazole or chamomile based on the randomized table. Participants and the physician who prescribed the drugs were blind to the study protocol. The clotrimazole group were prescribed a vaginal cream with 2% clotrimazole (Sinapishgam Darou Co., Iran) once per day for 5 days. The chamomile group were prescribed Camillin, a chamomile extract cream, once per day for 5 days (Ahoora Daroo Co., Iran). This cream was standardized to 0.14 mg/ml total flavonoid and hydroalcoholic extract of German chamomile. Two weeks later, all participants underwent further examination to assess symptoms.

4. Statistical analysis

Statistical analysis was performed using SPSS 18.0. and $p < 0.05$ was considered as statistically significant. Descriptive statistics were reported as median and interquartile range (IQR). Chi square or Fisher's exact tests were used to compare qualitative variables between groups. The McNemar test was conducted to compare changes before and after the intervention in each group.

RESULTS

Of the 78 patients who were assessed for eligibility, 73 were randomized into treatment groups. None of the eligible women had an allergy to chamomile. Five patients did not accept the double-blind nature of the study. Therefore, the final participant numbers were 36 and 37 in the Camillin and clotrimazole groups, respectively. Three women in each group were lost to follow-up. Three and 4 patients in the Camillin and clotrimazole groups, respectively, did not use the drugs for 5 days and were excluded from the study. Therefore, 30 patients in each group were finally assessed. Table 1 shows the participant demographics, including age, number of pregnancies and abortions.

The chi-square test was used to compare the effect of clotrimazole or chamomile on cheese-like vaginal discharge, itching and burning sensations, the presence of strawberry

Table 1. Demographic data in clotrimazole and chamomile extract groups

Variable	Chamomile extract cream (30)		Clotrimazole cream (30)		p-value
	Median	IQR	Median	IQR	
Age	35.0	30.0-38.0	35.5	31.2-38.0	0.85
Gravid	2.0	1.0-2.0	2.0	2.0-3.75	0.09
Abortion	0.0	0.0-1.0	0.0	0.0-0.75	0.70

Table 2. Effect of clotrimazole and chamomile on candidiasis before and after treatment

Variable	Group	Before		After		p-value (MC Nemar test)
		No	Yes	No	Yes	
Cheese like discharge	Chamomile	12 (44.4)	15 (55.6)	25 (92.6)	2 (7.4)	< 0.001
	Clotrimazole	9 (32.1)	19 (67.9)	22 (78.6)	6 (21.4)	< 0.001
p-value (chi square test)		0.35		0.14		
Burning	Chamomile	6 (22.2)	21 (77.8)	24 (88.9)	3 (11.1)	< 0.001
	Clotrimazole	11 (39.3)	17 (60.7)	24 (85.7)	4 (14.3)	< 0.001
p-value (chi square test)		0.17		0.72		
Itching	Chamomile	6 (22.2)	21 (77.8)	24 (88.9)	3 (11.1)	< 0.001
	Clotrimazole	6 (21.4)	22 (78.6)	22 (78.6)	6 (21.4)	< 0.001
p-value (chi square test)		0.94		0.47		
Strawberry cx	Chamomile	25 (92.6)	2 (7.4)	23 (82.1)	5 (17.9)	0.99
	Clotrimazole	26 (96.3)	1 (3.7)	25 (89.3)	3 (10.7)	0.69
p-value (chi square test)		0.42		0.61		
Recovery percentage	Chamomile	-		88.9%		-
	Clotrimazole	-		75.0%		-
p-value (chi square test)				0.29		

cervix, and recovery percentage. Moreover, Mc-Nemar test was conducted to compare changes before and after the intervention for each sign and symptoms in each group (Table 2). No adverse effects were reported in either group.

In each group number of patients absolute and relative effect sizes is reported.

DISCUSSION

This study assessed the effect of chamomile extract treatment on vulvovaginal candidiasis (VVC) sign and symptoms when compared with the standard treatment, clotrimazole. No complications with this drug were reported in any participants.

Treatment with vaginal clotrimazole has shown some adverse reactions, such as vulvovaginal burning, polyuria, pruritus vulvae, vulvar pain and swelling, burning sensation of the penis (of the sexual partner). Some studies have sought a new approach to treat VVC because medications, such as azoles, polyenes and fluoropyrimidines, cannot cure this disease in all patients. New treatments include the ATP-infrared bio-effect technique, biofilm production, and antifungal drug resistance [12]. Herbal drugs are good replacements for these antifungal and antimicrobial drugs.

Previous studies have shown the anti-inflammatory, spasmolytic, antiviral, and anti-fungal effect of chamomile. Agusti [13] has reported that chamomile can be used to effectively treat *Candida Albicans*. Alfa-bisabolol, luteolin, and quercetin are the components of chamomile that are anti-bacterial, especially against gram positive species at 25 mg/ml [9]. Another component of chamomile is apigenin. This interferes with intermolecular adhesion in response to cytokines, which leads to its anti-inflammatory effects [10]. Another anti-inflammatory component of chamomile is azelon. This induces hypophysis, causing an increased release of cortisol and decreased histamine [6, 8]. Furthermore, chamomile has wound healing properties, which can improve eczema [14, 15].

In this study, the qualitative criteria of vulvovaginal candidiasis were evaluated. One limitation of this study is that we did not also assess objective criteria, like PH and mycelium cultures. Allergies, possible unexpected side effects, and no specified safety zones are other limitations of this study. By contrast, herbal medications are dependent on plant quality and influenced by weather, soil, and altitude. Herb extraction and the concentration required for treatment are other limitations for using these drugs. Moreover, different forms of herbal medications may affect the study results.

CONCLUSIONS

Taken together, our study showed that chamomile has

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the same effect as vaginal clotrimazole treatment for VVC in women of child-bearing age. This is a suitable alternative to clotrimazole because it has no reported side effects. However, further studies are required to confirm these data.

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CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest.

ORCID

Zahra Shiravani, https://orcid.org/0000-0001-5796-2954
Tahereh Poordast, https://orcid.org/0000-0003-0151-978X
Shaghayegh Moradi Alamdarloo, https://orcid.org/0000-0002-4064-4906
Fateme sadat Najib, https://orcid.org/0000-0003-3396-145X
Fatemeh Hosseinzadeh, https://orcid.org/0000-0001-6240-9483
Hadi Raeisi Shahraki, https://orcid.org/0000-0003-3071-5587

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