

The effect of curcumin-based and clotrimazole vaginal cream in the treatment of vulvovaginal candidiasis

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ABSTRACT

Background: Vulvovaginal candidiasis (VVC) is the second most common infection of the lower female genital among women passing through their productive age. Furthermore, *Candida albicans* is the most common VVC agents followed by, non-*albicans* *Candida* species. Nowadays, extensive studies are being conducted on alternative therapies and the use of herbal medicines. **Objectives:** The present study was conducted to compare the effect of curcumin and clotrimazole vaginal cream in the treatment of VVC. **Methods:** The present randomized controlled trial study was performed on 94 women passing through their productive age after their being diagnosed with VVC. The subjects were randomly divided into two groups, with one receiving curcumin-based vaginal 10% cream and the other receiving clotrimazole vaginal 1% cream. The treatment period was 1 week and a full 5 g applicator was used every night. Required follow-up was implemented 4-7 days after the end of treatment. **Results:** The results showed no significant differences between the two groups in terms of vaginal discharge, itching, vulvovaginal irritation, and vulvovaginal erythema ($P > 0.05$); however, the number of negative cultures in the group receiving curcumin was significantly lower in comparison with the other group, which received clotrimazole ($P = 0.002$). **Conclusion:** It seems that although curcumin could be effective in the treatment of clinical symptoms of VVC, it, quite similar to clotrimazole vaginal cream, did not affect vaginal culture.

Keywords: Clotrimazole, curcuma longa, curcumin, vulvovaginal candidiasis

Introduction

Vulvovaginal candidiasis (VVC) is one of the most common gynecologic problems in reproductive aged women; after bacterial vaginosis, it is considered as the second most common cause of vaginitis. This condition is characterized by the presence of *Candida* species in the mucous membrane of the lower genital system.^[1] Though VVC is the second most common cause of

vaginitis, incidence of this disease is increasing significantly.^[2,3] Kiasat *et al.* reported the prevalence of 39.76% for VVC and 4.6% for recurrent VVC in Ahvaz, Iran.^[4] The prevalence of VVC in Zanjan was 4.8%.^[5] The affected women's lack of admittance to health centers and the arbitrary use of azoles have made it difficult to quantify the incidence of candidate vaginitis accurately.^[6] Patients with associated symptoms, such as itching and vaginal discharge, experience feeling of dissatisfaction and reduced self-confidence, the ultimate result of which is reluctance to have sex and reduces sexual satisfaction in the couples.^[7]

Azole antifungal compounds are currently the most commonly used standard treatment agents. It is worth mentioning that the

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widespread use of a specific group of medication, like ketoconazole, increases the possibility of resistance to that medication through time.^[8] The major concern regarding this disease is the increase in *C. glabrata* instead of *C. albicans* in the vaginal environment, justifying the fact that many patients complain of nonrelief of clinical symptoms of illness after completing the course of treatment.^[9] However based on a study carried on Ahvazian women, *C. albicans* was the most common species among the isolates followed by *C. glabrata*, *C. dubliniensis*, and *Candida* species.^[10,11]

Recent studies show the antifungal effects of curcumin, the effective ingredient found in the rhizome of turmeric. Curcumin inhibits the release of hydrogen ion from fungal cells significantly (in the absence or presence of peripheral glucose) and decreases the level of cellular ergosterol, leading to a significant decrease in the secretion of proteinase from fungal cells which, ultimately, breaks down the membrane, causes intracellular fluid leakage, and brings about the death of fungal cells.^[12,13] Karaman *et al.* and Dovigo *et al.* suggested that the antifungal activity of curcumin is effective in improving oral candidiasis in the rats.^[14,15] A pilot study by Patil *et al.*, which was conducted on 25 chemotherapy patients, reported improvement of oral mucositis through mouthwash-containing curcumin.^[16]

Given the antifungal effects of curcumin proven in *in vitro* and animal studies and since no clinical trial studies have been conducted to evaluate the effect of curcumin on the treatment of VVC, the present study was carried out to compare the effect of curcumin-based vaginal cream and clotrimazole vaginal cream in the treatment of VVC.

Materials and Method

Patients and criteria

Ninety four women were randomly recruited to participate in the present randomized controlled trial study. Required data were collected from selected healthcare centers affiliated to the Ahvaz Jundishapur University of medical sciences and Bushehr University of medical sciences from April to October, 2017. Being aged 18–45 years, presence of, at least, one of the symptoms of VVC in the interview and it's being observed and confirmed by laboratory tests, being monogamous, body mass index less than 30, nonuse of cream, suppository or vaginal shower in the last 48 hours, and completing the informed consent were the man inclusion criteria. The exclusion criteria were as follows: being pregnant, breast feeding, menopause, consumption of oral contraceptive pills, medical disorder, frequent VVC, consumption of corticosteroids, broad-spectrum antibiotics in the past two weeks, and systemic antifungal medicines in the last four weeks. A sociodemographic questionnaire and a checklist were used to collect data.

Sampling and identification

Two samples of vaginal discharge were taken from the lateral and posterior side of vagina using sterile cotton swabs. The first

swab used for slide preparation and slides were stained using blue methylened. Smear test considered positive if pseudohyphae and/or yeasts and budding cells were observed. The second swab was inoculated onto CHROMagar *Candida* culture medium. All culture media were incubated at 30–35°C for 48–96 h and the number of colonies was counted daily. Each colony color represents a candidate species.

Preparation of vaginal cream

Curcumin vaginal cream was produced in the laboratory of the Faculty of Pharmacy at Ahvaz Jundishapur University of Medical Sciences. The vaginal plant cream was prepared by incorporation of dissolved curcumin, with registration number 820354, in a suitable base composed of Vaseline, mineral oil, acetyl alcohol, benzyl alcohol, monobasic sodium phosphate, and dibasic sodium phosphate. According to the minimum inhibitory concentration (MIC) of curcumin on *Candida* species,^[14,15] 10% concentration was chosen for preparation of vaginal curcumin creams. According to a clinical study, vaginal tablet of curcumin was more similar to the calculated dose for a longer period than the period selected as treatment duration in the present study; thus, 10% was approved as safe concentration.^[17] The prepared vaginal creams were tested for stability, uniformity, diffusion, acidity, release rate, and standardization for control and optimization. Finally, curcumin vaginal cream tubes were packed under clean conditions. Clotrimazole vaginal 1% cream was provided by Pars Daru Company.

Intervention

Women diagnosed with VVC participated in the present study. The first researcher (NA), who was totally aware of the process of the implementation of the study, asked participants to administer either curcumin vaginal 10% cream or Clotrimazole vaginal 1% cream as a full applicator for one week during bedtime. Every participant received a phone call weekly regarding correct consumption of curcumin or clotrimazole vaginal cream. The subjects were excluded if they did not want to continue the study, in case of emergency use of antibiotics, or allergy to the drug and forgetting drug use more than one night. Since curcumin vaginal cream was yellow, the individuals in the intervention group received ten daily sanitary pads to prevent the change of the color of the underwear. In order to determine the rate of recovery, the subjects referred again 4–7 days after the completion of one-week treatment; they, completed posttreatment form and necessary laboratory and clinical examinations were repeated in order to assess the extent of recover, including negative smear and culture and loss of signs and symptoms.

Statistics analysis

Continuous data were screened to determine normality using Kolmogorov–Smirnov test. Mann Whitney test was used for nonparametric quantitative values between two groups; Kruskal–Wallis test was used to accomplish this objective within the groups. Moreover, Chi-square test was used to compare

qualitative variables between two groups; $P < 0.05$ was considered as significance level.

Results

About 359 women were screened regarding inclusion and exclusion criteria; 98 women were diagnosed with VVD; they were randomly divided in two groups. A total number of 231 patients were excluded from the study due to various causes, including mixed infection (92 subjects), absence of candidate vaginitis in laboratory tests (54 subjects), or simple refusal to enter the study (85 subjects).

All subjects categorized in two groups continued to cooperate up to the end of the study [Figure 1].

The mean age of women was 27.57 ± 4.86 and 28.06 ± 2.35 years in two groups of curcumin and clotrimazole ($P > 0.05$). The two groups did not show any significant differences in childbirth and pregnancy number, BMI, and contraceptive methods ($P > 0.05$) [Table 1].

As one can clearly observe in Table 2, the frequency of discharge of women in both groups decreased significantly in 4–7 days after treatment (from 91.5 to 34% in curcumin and from 87.2 to 31.9% in clotrimazole group) ($P < 0.001$). Differences

between the groups were not significant ($P = 0.82$). Vulvovaginal itching decreased from 85.1 to 12.8% after treatment in the curcumin group ($P = 0.001$). In case of the clotrimazole group, this significant decline was from 87.2 to 19.1% after treatment ($P = 0.001$). After intervention, there was no significant difference between the two groups ($P = 0.76$).

The frequency of burning, erythema and vaginal smear results also decreased significantly in both groups after 4–7 days of treatment ($P < 0.001$); however, this difference was not significant between the groups. The results indicated a lower negative cultures after treatment in 59.6% cases of the curcumin group vs. 76.6% cases in the clotrimazole group ($P = 0.002$).

Also, complete recovery was observed in 66% of subjects in the curcumin group vs. 48.9% subjects in the clotrimazole group. The results showed no significant differences between groups in terms of complete recovery after intervention ($P = 0.09$) [Table 3].

Vulvovaginal burning sensation seen in 6.4% subjects was the main adverse effect of curcumin cream, observed with a comparative rate of 2.1% between two groups. 8.5% of subjects in the curcumin and 4.3% of subjects in the clotrimazole group experienced vulvolar itching; in case of vulvovaginal discomfort, this comparative rate was 2.1 to 4.3% among subjects in curcumin and clotrimazole groups in order. Vulvar itching was the most frequently observed side effects in curcumin group. However, there was no significant difference between two groups in terms of side effects ($P = 0.3$).

Discussion

The results of the present study showed that, despite higher frequency of negative culture in clotrimazole group, curcumin and clotrimazole vaginal cream can be effective in the treatment and complete recovery of symptoms of VVC. In fact, curcumin turned out to have similar effects on the improvement of vulvovaginal discharge, itching, burning, erythema, and smear results of vaginal discharge compare to clotrimazole vaginal cream; however, it was not as effective as clotrimazole in regard with vaginal discharge culture.

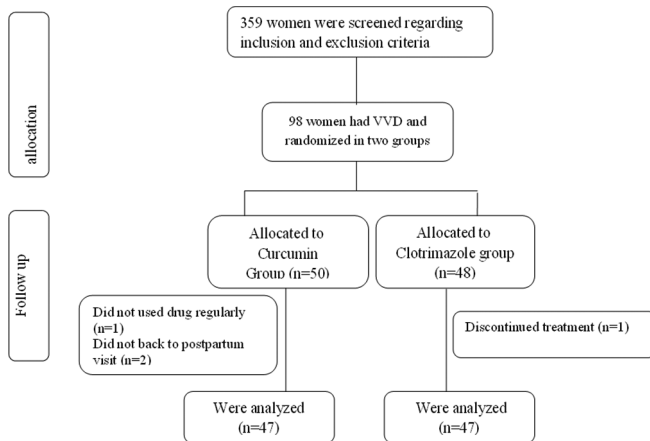


Figure 1: Flow diagram of recruitment and retention of participants

Table 1: Characteristics of women, before and 7 days after treatment in curcumin and clotrimazole groups

Characteristics	Curcumin group n=47	Clotrimazole group n=47	P
Age, mean (SD)	27.57±4.86	28.06±2.35	0.61
Childbirth, n	1.76±1.02	2.06±1.07	0.25
Pregnancy, n	1.87±1.09	2.14±1.10	0.25
BMI, w/m ²	Normal Overweight	15 (31.9%) 32 (68.1%)	0.28
Contraceptive method, n (%)	No contraception Coitus interrupts Condom IUD Progesterone methods TL, vasectomy	10 (21.3%) 11 (23.4%) 15 (31.9%) 5 (10.5%) 3 (6.4%) 1 (2.1%)	0.6
	20 (42.6%) 27 (57.4%)	15 (31.9%) 32 (68.1%)	
	13 (27.7%) 10 (21.3%) 16 (34%) 5 (10.6%) 1 (2.1%) 2 (4.3%)	10 (21.3%) 11 (23.4%) 15 (31.9%) 5 (10.5%) 3 (6.4%) 1 (2.1%)	

Table 2: Comparison of symptoms sings and laboratory tests in women before and 7 days after treatment in curcumin and clotrimazole groups

		Curcumin group n=47		Clotrimazole group n=47		P
		Yes	No	Yes	No	
Discharge	Before	43 (91.5%)	4 (8.5%)	41 (87.2%)	6 (12.8%)	0.75
	After	16 (34%)	30 (66%)	15 (31.9%)	32 (68.1%)	0.82
	P between two groups	0.001		0.001		
Itching	Before	40 (85.1%)	7 (14.9%)	41 (87.2%)	6 (12.8%)	0.40
	After	6 (12.8%)	41 (87.2%)	9 (19.1%)	38 (80.9%)	0.76
	P between two groups	0.001		0.001		
Burning	Before	26 (59.6%)	19 (40.4%)	31 (66%)	16 (34%)	0.52
	After	20 (42.6%)	27 (57.4%)	19 (40.4%)	29 (59.6%)	0.83
	P between two groups	0.001		0.001		
Erythema	Before	38 (80.9%)	9 (19.1%)	37 (74.5%)	12 (25.5%)	0.46
	After	12 (25.5%)	35 (74.5%)	7 (14.7%)	40 (85.1%)	0.20
	P between two groups	0.001		0.001		
Smear		Positive	Negative	Positive	Negative	
	Before	32 (68.1%)	15 (31.9%)	35 (74.5%)	12 (25.5%)	0.49
	After	12 (25.5%)	35 (74.5%)	6 (12.8%)	41 (87.2%)	0.18
	P between two groups	0.001		0.001		
Culture		Positive	Negative	Positive	Negative	
	Before	47 (100)	0	47 (100)	0	1
	After	19 (40.4%)	28 (59.6%)	11 (23.4%)	36 (76.6%)	0.002
	P between two groups	0.001		0.001		

Table 3: The frequency and percentage of total recovery after treatment

	Curcumin group n=47	Clotrimazole group n=47	P
Complete Yes	31 (66%)	23 (48.9%)	0.09
recovery No	16 (34%)	24 (51.1%)	

The possible mechanism of anti-fungal effects of curcumin may due to the fact that curcumin inhibits the release of hydrogen ion from fungal cells significantly and decreases the level of cellular ergosterol, leading to a decrease in the secretion of proteinase from fungal cells, which ultimately breaks down the membrane, causes intracellular fluid leakage and brings about the death of fungal cells.^[12,13] Shabaniyan *et al.* study indicated that the mean of itching, irritation, and cheesy discharge in the group using clotrimazole ginger cream was lower than the control group after treatment.^[18] Also, in a study Curcumin vaginal cream was incorporated in three concentrations (0.01%, 0.1%, and 1.0%) in an immunosuppressed rat model. After 6 days of preclinical study, the number of infected animals was 1/6 in all groups treated with curcumin and the fungal burden showed a progressive reduction in the inflammatory infiltrate in the group treated with 1.0% cream.^[19] Patil *et al.* evaluated the effect of curcumin mouthwash on radiochemical healing induced by oral mucositis in 20 adult patients with cancer. The subjects were randomly divided into two groups of intervention (mouthwash-containing 0.004% curcumin) and control (chlorhexidine 0.2% mouthwash). The results showed a significant difference between two groups in regard to erythema.^[16] Also, the results of the present study indicated that there was a significant decrease in stained positive smear in each group, but there was no significant difference

between the two groups after the intervention. However, the negative culture was observed in 76.6% of subjects in the clotrimazole and 59.6% of subjects in the curcumin group after the treatment; on the other hand, the negativity of vaginal cultures after treatment was lower in curcumin group compared to clotrimazole group ($P = 0.002$).

Medicinal methods, including topical treatments with azoles, such as clotrimazole, removed the symptoms and negative culture in 80–90% of cases. Usual symptoms disappear within 2–3 days.^[20] In the present study, azole compounds (clotrimazole) yielded the same results in regards to negative culture; curcumin, also, caused a 59.6% rate of negative cultivation. Although the effect of curcumin did not turn out to be as optimum as clotrimazole, further investigations can be conducted on this substance as an herbal remedy for treatment of vaginal symptomatic candidiasis. The results, also, showed no significant difference between two groups in regard with total score of symptoms, including burning, erythema, itching, and vaginal discharge. These symptoms may prolong the course of treatment. Duration of treatment for curcumin requires more extensive studies. The results of the present study are consistent with Shabaniyan *et al.* and Patil, *et al.* researches.^[16,19]

Conclusions

The results of the present study showed that, despite higher frequency of negative culture in clotrimazole group, curcumin and clotrimazole vaginal cream can be effective in the treatment and complete recovery of symptoms of VVC. Thus, further studies are required in this domain.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Ethical consideration

The protocol of the present study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ref No: IR.AJUMS.REC.1395.511); it was also registered in the Iranian registry for randomized controlled trials (Ref No: IRCT2016111330874N1).

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Nil.

Conflicts of interest

The authors declare that they have no financial interests related to the material in the manuscript.

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