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ORIGINAL ARTICLE

Vaginal azoles versus oral fluconazole in treatment of recurrent vulvovaginal candidiasis

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ABSTRACT

Background: Vulvovaginal candidiasis (VVC) is a fungal infection of the vagina and vulva. It is usually caused by Candida albicans, however, occasionally other candida species are responsible. The optimal treatment of VVC has not yet been defined. The present study was designed to compare the efficacy and safety of a single oral dose of fluconazole with clotrimazole vaginal cream as the treatment of choice for recurrent VVC.

Materials and methods: We conducted a clinical trial study on 124 women with RVVC. Sampling of vaginal discharge was achieved for clinically suspected patients, then, observed with KOH for vaginal candidiasis. Sample culture was performed for cases in whom the result of direct examination was negative but there was high clinical suspicion of the disease. For laboratory examination, swab specimens were placed on sabourauds agar plus chloramphenicol and cyclohexamide with natural PH. For treatment, patients were randomized systematically in 2 equal groups, one receiving clotrimazole vaginal cream 5g/day for 7 days for acute episode and 5g twice a week for 6 months as a prophylaxis. The second group was prescribed single oral dose of fluconazole capsule 150 mg for acute episode followed by prophylactic regimen of 150 mg weekly for 6 months.

Results: A total of 124 women with RVVC were enrolled and assigned in 2 groups of fluconazole and clotrimazole with the mean age of 32±5 years (a range, 18-50 years) and 32±2 years (a range, 19-49 years), respectively. Of 117 cases, the recurrence rate was 8.6% in fluconazole and 8.5% in clotrimazole group. Recurrence rate in follow up period (second 6 months) was 38.3% and 40%, respectively (NS).

Conclusion: Response to treatment and reduction in recurrence rate of VVC were similar among fluconazole and long-term users of azole vaginal creams.

Keywords: V*ulvovaginal candidiasis, Fluconazole, Clotrimazole*.

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INTRODUCTION

Vulvovaginal candidiasis (VVC) is a fungal infection of the vagina and vulva. An estimated of 75% of all women experience at least one episode of VVC in their lifetime, of whom one half will experience a recurrence (1). Recurrent vulvovaginal candidiasis (RVVC) is defined as ≥ 4 episodes of symptomatic VVC each year (2).

VVC is usually caused by Candida albicans, however, occasionally other candida species are responsible. C. albicans is responsible for 35%-90% of vaginal yeast infections. RVVC is caused

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by the persistence of a single yeast genotype that undergoes morphological and behavioral changes in the presence of antifungal agents (3). Associated symptoms and signs include pruritus, burning, soreness, abnormal vaginal discharge, dysparonia, and vaginal and vulvar erythema and edema (4).

Known predisposing host factors which include uncontrolled diabetes mellitus, immunosuppression, pregnancy, and hormone replacement therapy, could partly explain RVVC. Broad spectrum antibiotic use has been suggested as a risk factor for both acute and recurrent VVC. Frequent recurrences of symptomatic vulvovaginitis result in considerable suffering and have a markedly negative influence on sexual relation (5).

The diagnosis should be confirmed by physical examination, direct microscopy of the vaginal secretions and, of course, fungal culture. Characteristic budding mycelia are seen in fewer than 30% of positive candida cultures (6).

The optimal treatment of VVC has not yet been defined (7). Consequently, treatment must be individualized based on a comparison of effectiveness, convenience, potential side effects, and costs. Treatment of the acute episode usually involves topical application of Azoles drugs or nystatin or systemic oral antifungal agents. However, for recurrent VVC, after treatment of the acute episode, subsequent prophylaxis (maintenance therapy) is essential (7). Several maintenance regimens have been proposed, like ketoconazole 100 mg/day or fluconazole 150mg weekly for 6 months (7). Oral treatment carries a greater potential for systemic toxicity and drug interaction for pregnant women, diabetic patients, and for whom it is contraindicated (such as those with renal or hepatic insufficiency).

The present study was designed to compare the efficacy and safety of a single oral dose of fluconazole (150mg) weekly with clotrimazole vaginal cream 150 mg twice weekly for 6 months as the treatment of choice for recurrent VVC.

PATIENTS and METHODS

We conducted a clinical trial study on 124 women with RVVC. Cases were recruited from patients presenting to the Gynecology and Obstetrics Clinic at Tabriz Medical University between 2002–2004.

Patients with signs and symptoms of candidia vulvovaginitis (pruritus, irritation, burning, discharge, erythema and edema) and a history of more than 4 episodes of VVC during the past year (at least one of the previous episodes must have been diagnosed by physician) were included. The following exclusion criteria were applied at baseline: severe chronic disease, use of oral hypoglycemic drugs, chronic dermatologic disease.

All subjects were requested to sign an informed consent, then, social, demographic and medical features as well as the present complaint of the patient were inquired and vaginal examination was performed.

Sampling of vaginal discharge was achieved for clinically suspected patients, then, observed with KOH for vaginal candidiasis. Sample culture was performed for cases in whom the result of direct examination was negative but there was high clinical suspicion of the disease. For laboratory examination, swab specimens were placed on sabourauds agar plus chloramphenicol and cyclohexamide with natural PH. The specimens were stored at 37°C and subsequently identified by smooth white colony formation. FBS (fasting blood sugar) test was requested to confirm the unknown diabetes mellitus, and Pap smear was also performed to rule out pre-cancer lesion of the cervix.

For treatment, patients were randomized systematically in 2 groups with 62 cases in each. The first group received clotrimazole vaginal cream 5g/day for 7 days for acute episode and 5g twice a week for 6 months as a prophylaxis. The second group was prescribed single oral dose of fluconazole capsule 150 mg for acute episode

followed by prophylactic regimen of 150 mg weekly for 6 months.

Patients were visited a week following the initiation of therapy and then monthly for one year. At each visit, a detailed clinical history was inquired, a pelvic examination was performed, and a vaginal sample was obtained for microscopic examination. Patients had to discontinue the assigned study treatment if they had severe complication, missed two or more consecutive doses of the drug or had irregular control visits. The recurrence of VVC was determined by patient complaint, physical examination, and laboratory finding (microscopic findings or fungal culture). Patients' satisfaction with drug use was evaluated by interview using a Likert spectrum.

Data were analyzed by SPSS for Windows (version 10.5, USA) and Mann-Withney U-test, Kaplan-Mayer method and chi-square test were used, when appropriate.

RESULTS

A total of 124 women with RVVC were enrolled and assigned in 2 groups of fluconazole and clotrimazole with the mean age of 32±5 years (a range, 18-50 years) and 32±2 years (a range, 19-49 years), respectively. The main socio-demographic characteristics of patients are presented in table 1. These variables showed no significant difference between the two groups.

As shown in table 2, the frequency of antibiotic use in the past 6 months, contraception method, the history of diabetes, and results of laboratory findings were more or less the same in both groups. None of the patient was pregnant.

The main symptoms of disease were vaginal burning (82.3%), and vaginal pruritus (78.2%), however, vulvovaginal erythema (87.9%), mucosal edema (79.8%), and white caseouse discharge (68.5%) were more commonly found during physical examination. Having followed the prescribed regimens, the cure rate at first visit was 99%.

Table 1. *Sociodemographic characteristics of patients with Vulvovaginal candidiasis*

	Group*	
	Clotrimazole (n=59)	**Fluconazole (n=58)**
Literature status		
Illiterate	32(54.2)	26(44.8)
Diploma	21(35.5)	23(39.6)
Graduated	6(10.3)	9(15.6)
Occupation		
Housekeeper	44(74.6)	44(76.0)
Employee	15(25.4)	14(24.0)

* Groups showed no significant difference

Table 2. *Medical characteristics of patients with Vulvovaginal candidiasis*

	Group*	
	Clotrimazole (n=59)	**Fluconazole (n=58)**
Contraceptive method		
OCP	12(20.3)	18(31)
IUD	9(15.2)	12(20.6)
Barrier	5(8.5)	5(8.8)
Withdrawal	33(56)	23(39.6)
Antibiotic use during the last 6 months	17(28)	15(25)
Diabetes mellitus	6(10)	7(11.6)
Laboratory results		
Direct smear with KOH	55(91.6)	57(95)
Candida culture	5(8.3)	3(5)
Pap smear		
Normal	41(69.4)	35(60.3)
Positive for candida	12(19)	8(13.8)
Cervicitis	6(11.6)	15(25.9)

* Groups showed no significant difference

During the third visit, 2 patients of fluconazole group were excluded because of irregular visits while 2 other patients were excluded during the 4th and 5th visit because of more than 3 times missing drug use. On the other hand, in the clotrimazole

group, 3 patients were excluded in the 2nd and 3rd visit because of local sensitivity to the drug.

Of remaining 117 cases, as presented in table 3, the recurrence rate was 8.6% in fluconazole group and 8.5% in clotrimazole group. Recurrence rate in follow up period (second 6 months) was 38.3% and 40%, respectively (NS).

Table 3. *Recurrence rate of vulvovaginal candidiasis among the two groups during treatment and follow-up period*

	Group*	
	Clotrimazole (n=59)	**Fluconazole (n=58)**
Treatment period (first 6 months)		
1-6 months	5(8.5)	5(8.6)
Follow-up period		
7th month	3(5.1)	3(5.2)
8th month	0	2(3.5)
9th month	2(3.4)	3(5.2)
10th month	5(8.5)	4(6.9)
11th month	5(8.5)	5(8.6)
12th month	5(8.5)	6(10.3)
Total recurrence (during a 12-month period)	25(42.4)	26(44.8)

* Groups showed no significant difference

Table 4. *Quality of drug use and satisfaction in both groups*

	Group*	
	Clotrimazole (n=59)	**Fluconazole (n=58)**
Completion of regimen protocol		
Complete	55(93.2)	49(84.4)
1 missing dose	3(5.0)	5(8.6)
2 missing doses	1(1.8)	4(7.0)
Patient's satisfaction		
Very good	19(32.2)	10(17.2)
Good	15(25.4)	14(24.4)
Relatively good	13(21.7)	9(15.5)
Relatively bad	8(13.3)	9(15.5)
Bad	2(3.3)	8(13.7)
Very bad	2(3.3)	8(13.7)

Totally, 88.8% of cases in fluconazole group and 85% of cases in clotrimazole group used their drug regularly. Drug usage missing rate (missed ≥2 consecutive doses of the drug) was 4 cases in fluconazole and 9 cases in clotrimazole group, respectively. Local cream users were more satisfied with their regimen ($p<0.003$) (table 4).

In fluconazole group, the main drug side effects were nausea (34.5%), and vomiting (6.9%), however, local sensitivity to drug (8.5%) was the only significant side effect. Systemic complications among cream users was significantly less than capsule users ($P<0.004$).

DISCUSSION

Our study showed that the most common complaints of patients were vaginal burning and pruritus which is compatible with the reported symptoms for vaginal candidiasis including vaginal discharge, burning and pruritus (8). The most prevalent signs in this study were white caseouse discharge and erythema.

Direct observation of fungal mycelia by using KOH under light microscope is the simplest and the most available test for diagnosis of VVC (9). By adding 10% KOH to the slide, the epithelial cells undergo lysis, which increases the ability to identify hyphae or blastospores (10). Although microscopic evaluation is the best office tool to diagnose vulvovaginal candidiasis, it lacks accuracy, as demonstrated by data showing that up to 50% of patients with culture-proven symptomatic vulvovaginitis have negative microscopic findings. In our study, Sample culture was also performed for cases in whom the result of direct examination was negative but there was high clinical suspicion of the disease. In addition, a larger proportion of false-negative finding may result from cases of C. glabrata infections, possibly because of the lack of hyphae formation by this organism, which makes microscopic identification

more difficult (11). In our study, the rate of false-negative finding of direct examination was 6.3% which was confirmed by fungal culture, indicating the test reliability.

Broad spectrum antibiotic use, use of combined oral contraceptives, pregnancy, diabetes, immunosuppression, and hormone replacement therapy (12) are positively associated with symptomatic vulvovaginal candidiasis episodes (8). In our study, OCP use (12 cases), antibiotic use (33 cases), and diabetes mellitus (13 cases) were the predisposing factors. In a case-control study over 684 cases with symptomatic VVC and 901 controls (asymptomatic women), 19.3% of cases and 11.9% of controls were antibiotic users while VVC was revealed to be directly related with antibiotic use (13). Bohannon suggested that hyperglycemia is the major cause of increased susceptibility of diabetic patients to VVC. Increased glucose levels in genital tissues enhance yeast adhesion and growth. Beginning at levels of 10-11mmol/L (180-196 mg/dl), hyperglycemia may impair several aspects of humoral host defense, resulting in decreased random motion of neutrophils, chemotaxis, phagocytosis, and microbial killing (11). In our study, because of small number of diabetic patients, the analysis of studied drug regimen effect on this disease is impossible, although, because of interaction between fluconazole and hypoglycemic drugs, use of vaginal clotrimazole with the same efficacy and lower side effects is recommended.

Patel et al. suggested that clothing habits, personal hygiene, a history of bacterial vaginosis, consumption of acidophil-containing products, and age <40 years are other predisposing factors (1). Bear in mind their findings, in our study, only age <40 years (32±5) was found as a predisposing factor.

Treatment of vaginal candidiasis usually involves topical application of polyene or azole compounds or systemic oral azoles. In a study by Sobel et al. on 429 patients with vaginal candidiasis, the efficacy and safety of a single oral dose of fluconazole was compared with a 7-day clotrimazole (100/mg) regimen. At day 14^{th}, clinical cure or improvement was found in 94% of fluconazole- and 97% of clotrimazole-treated patients, however, after 35 days, 75% of both groups remained clinically cured, therefore, the cure rate was similar in both groups (14).

In a double-blind study by Sadovsky, the treatment of acute episode of vaginal candidiasis by fluconazole in 2 divided doses within 2 hours was compared with fluconazole single dose therapy. In this study, the more cure rate achieved by divided doses, but because of popularity of single dose method, the authors reported that this method is more effective (15). Thus, patient's acceptance of drug type and consumption route is of utmost importance.

In conclusion, response to treatment and reduction in recurrence rate of VVC were similar among fluconazole and long-term users of azole vaginal creams. Furthermore, the local treatment has fewer side effects and is more satisfactory. We recommend periodic and long-term use of azole creams for treatment of RVVC in women who are pregnant or have any systemic problem.

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