



Oral fluconazole 150 mg single dose versus intra-vaginal clotrimazole treatment of acute vulvovaginal candidiasis

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KEYWORDS

Acute vulvovaginal candidosis;
Oral fluconazole;
Intra-vaginal clotrimazole

Abstract

Objective: To compare the safety and efficacy of fluconazole 150 mg single dose and intra-vaginal clotrimazole 200 mg per day for six days in the treatment of the acute episode of vulvovaginal candidiasis (VVC).

Methods: In a prospective study, 142 patients with acute clinical and mycological confirmed VVC were enrolled and divided randomly in two groups. 70 patients received intra-vaginal tablet (200 mg) daily for seven days, whereas 72 patients received single dose oral fluconazole (150 mg). Second and third visits were done for all patients seven days and one month after treatment and the clinical and mycological outcomes evaluated. The analysis performed using SPSS statistical software (version 15).

Results: At the second visit, 61 patients (84.7%) were cured clinically (inflammation and discharge) and 58 patients (80.5%) mycologically in fluconazole group and 60 patients (83.3%) were cured clinically and 49 patients (70%) mycologically in clotrimazole group ($P=0.01$). At the third visit, only one patient in fluconazole group and 17 patients in clotrimazole group had clinical sign of VVC ($P=0.001$).

Conclusion: Oral fluconazole single dose seems to be a valid and promising therapy to cure acute signs and symptoms of VVC.

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Introduction

Vulvovaginal candidiasis (VVC) is a lower genital tract disorder that occurs in 75% of women at least once in their lifetime with 40–50% of women experiencing a second attack. [1]. *Candida albicans* is the species most often associated with VVC, however, other yeasts can also cause this infection. VVC is treated with a variety of anti-fungal drugs [2]. Frequent recurrences of symptomatic vulvovaginitis result in considerable suffering and cost and have a markedly negative effect on sexual relations [3]. Diagnosis is made by vaginal fluid specimen, microscopic examination and culture [4]. Currently available options for the treatment of this condition include antifungal agents. There are variety of effective treatments that include topical or oral antifungals. Topical azoles are used for 1, 3, 7, or even 14 days, whereas oral drugs are recommended to be used for 1, 3 or 5 days [5]. An ideal antifungal drug should be easy to administer, effective in short therapy, with a broad spectrum of treatment, causing complete eradication, preventing recurrent infections, bringing relief to patients, without side effects, inexpensive and safe to administer during pregnancy [6]. A metaanalysis study showed that there was no significant difference regarding the effectiveness between oral and topical treatment of uncomplicated VVC [5]. Although topical regimens are commonly, used oral treatment is preferred by patients because of the ease of administration and the reduced duration of use [7].

fluconazole is a triazole antifungal agent introduced in the early 1990s which has a good safety profile and is the most widely used antifungal agent for VVC. The mechanism of action of the group of azole antifungals is the inhibition of the fungal cytochrome P450 oxidase-mediated synthesis of ergosterol, which is an essential component of the fungal cytoplasmic membrane. The susceptibility of candida species to fluconazole, however, is not uniform. *Candida albicans* is highly susceptible to fluconazole [8,9]. After oral administration of a single dose of 150 mg of fluconazole, concentrations of fluconazole above the minimal inhibitory concentration (MIC) that inhibits the growth of 90 percent of candida species isolates (MIC₉₀) are achieved for 72–96 h in vaginal tissue and secretions [9].

The objective of this study was to assess the relative effectiveness of oral versus intra-vaginal anti-fungals for the treatment of VVC. The aim was to compare the clinical and microbiologic effectiveness and the safety of 150 mg oral fluconazole single dose and conventional topical (interavaginal)

clotrimazole for 7 days in the treatment of acute VVC and especially its efficacy in sequential cure of it.

Methods

The study was performed between July 2006 and May 2008 at the Department of Obstetrics and Gynaecology, University Shahid Sadoughi hospital in Yazd, Iran, and included 142 outpatients over 15 years of age with acute clinical and mycologically verified VVC. The hospital research and ethics committee approved the adopted protocol. The exclusion criteria were pregnant women, diabetics, hormone replacement or birth control pill users (intervention of hormone in therapy), immunosuppressive drug users and immunocompromised patients. The diagnosis of VVC was confirmed with clinical symptoms and mycologically (positive microscopy for yeast). The sample size estimation was based on assuming that fluconazole therapy had a clinical success rate of 80% and also that the efficacy of clotrimazole was 80%, thus it was estimated that 68 patients in each treatment group who could be evaluated would be required to detect a treatment difference of 20%, with 80% power and a two-sided alpha level of 0.05 [5].

The researcher interviewed all women individually. Written informed consent was obtained from all the patients. Patients enrolled in the study received either 200 mg clotrimazole daily for seven days intravaginal regimen ($n=70$) or 150 mg fluconazole as a single oral dose ($n=72$). All patients had second and third visits seven days and one month after treatment and the clinical and mycological outcomes were evaluated. Clinical cure was the absence of the signs and symptoms and mycological cure was the microscopic absence of yeast.

Data were analyzed by SPSS 15.0 software with χ^2 test, unpaired t-test, and Mann-Whitney test, as appropriate. $P < 0.05$ considered statistically significant.

Results

156 patients with acute symptomatic VVC were enrolled, but 14 patients did not complete the study and were excluded. Therefore, 142 patients were included and completed the study. Patients enrolled in the study received either 200 mg clotrimazole daily for seven days intravaginal regimen ($n=70$) or 150 mg fluconazole as a single oral dose

Table 1 Baseline demographic characteristics of study groups.

Characteristics	Oral fluconazole (N = 72)	Intra-vaginal clotrimazole (N = 70)	P value
Age in years (mean $\pm$ SD)	39.4 $\pm$ 13.1	42.2 $\pm$ 15.9	0.7
Education (N (%))			0.5
≤High school	14 (19.4)	9 (12.9)	
≥High school	58 (80.6)	61 (87.1)	
Marital status			0.6
Married	50 (69.5)	51 (72.9)	
Single	5 (6.9)	8 (11.4)	
Separated (divorced or widowed)	17 (23.6)	11 (15.7)	
Post-menopausal			0.3
Yes	9 (12.5)	10 (14.3)	
No	63 (87.5)	60 (85.7)	
History of yeast vaginitis			0.1
Yes	44 (61.1)	38 (54.3)	
No	28 (38.9)	32 (45.7)	
Hormone replacement therapy			0.8
Yes	0 (0)	1 (1.4)	
No	72 (100)	69 (98.6)	

Table 2 Clinical and mycological outcomes of study groups seven days after treatment.

Parameters	Oral fluconazole (N = 72)	Intra-vaginal clotrimazole (N = 70)	Odds ratio (95% CI)	P value
Complete clinical cure (N (%))	53 (73.6)	41 (58.6)	1.9 (1.1–9.3)	0.001
Relative clinical cure (N (%))	8 (11.1)	13 (18.6)	0.6 (0.1–0.9)	0.03
Mycological cure (N (%))	60 (83.3)	49 (70)	2.3 (1.5–6.7)	0.01
Side effect (N (%))	5 (6.9)	3 (4.3)	1.8 (0.4–3.3)	0.4

($n = 72$). [Table 1](#) shows that there was no difference in the demographic characteristics of both study groups. [Table 2](#) shows that on the first visit candida was clinically treated in 53 (73.6%) patients in the fluconazole group and 41 (58.6%) in the clotrimazole group and also eradicated (culture was negative) in 60 (83.3%) of patients in the fluconazole group and in 49 (70%) in the clotrimazole group ($P = 0.001$). There was no difference in side effects in two groups ($p = 0.4$). The major drug compli-

cation in fluconazole group was headache and in clotrimazole group it was pelvic pain. In [Table 3](#) the recurrence of VVC after one month of treatment was reported. At the third visit (one month) candida was recurrent symptomatically in 1 patient in the fluconazole group and 17 patients in clotrimazole group ($P = 0.001$). Mycological symptoms were positive in 1 patient in the fluconazole group and 7 patients in clotrimazole group at the same time ($P = 0.01$).

Table 3 Clinical and mycological outcomes of study groups one month after treatment.

Parameters	Oral fluconazole (N = 72)	Intra-vaginal clotrimazole (N = 70)	Odds ratio (95% CI)	P value
Relapse of clinical symptom (N(%))	1 (1.4)	17 (24.3)	0.04 (0.02 - 0.3)	0.001
Relapse of mycological symptom (N(%))	1 (1.4)	7 (9.7)	0.1 (0.06 - 1.4)	0.01

More than 97% patients enrolled in the study would prefer oral fluconazole treatment compared to topical clotrimazole 68.6% ($P=0.001$).

Discussion

Over the past two decades, the imidazoles (miconazole, clotrimazole, ketoconazole, butoconazole, and tioconazole) have become the most widely used drugs for the treatment of VVC. With the exception of ketoconazole, these agents are used topically for treatment durations of one to seven days with similar success rates [10]. Local applications of these antifungal preparations are usually without untoward effects, but most patients still prefer oral therapy because of the ease of administration and the lower duration of use [7]. Also oral antifungal therapy of patients with vaginal/vulvovaginal candidiasis can decrease the candida population in the deep layers of vaginal tissues and rectum, which is an important pool of candida [11].

A new class of azole antifungal agents (itraconazole and fluconazole), the triazoles, has recently been introduced into clinical practice. These drugs appear to offer both microbiological and clinical advantages over the imidazoles and achieved high rates of clinical and/or microbiologic cure in most studies, a finding that may be considered expected, because these agents are used orally for treatment durations of one to three days [9].

The aim of this study was to compare the clinical and microbiologic effectiveness and the safety of 150 mg oral fluconazole single dose and conventional topical (interavaginal) clotrimazole for seven days in the treatment of acute VVC. While the two drugs confirmed good overall clinical efficacy at both follow-up visits, the speed of symptom relief was remarkably better in fluconazole group. Also relapses after one month of clinical and microbiological symptoms were less in fluconazole group.

Although a metaanalysis by Watson et al. also showed that there was no significant difference regarding the effectiveness between oral and topical (intravaginal) treatment of uncomplicated VVC [5], in a current study Mohanty reported that since the majority of *C. albicans* isolates were susceptible to fluconazole, its use may be continued for empirical therapy of uncomplicated candidal vulvovaginitis in the community [10]. Mazneikova suggested that fluconazole is the choice drug for continuous treatment of vaginal candidia infection with the least toxicity [12]. The patients have more satisfaction with oral treatment, because it is easy to use and available everywhere. This result was

similar to the Watson study [5] and the Corić study [13].

The population in the study are different from many other countries in modesty and the clothing choices and therefore they are more satisfied with oral than vaginal therapies.

Conclusion

This study showed that single dose oral fluconazole is more effective than conventional topical clotrimazole for seven days in the treatment of acute VVC. Fluconazole can more successfully and safely cure clinical and micrological symptom of VVC than clotrimazole and can be more effective in reduction of the relapse rate of the disease than clotrimazole. A long-term cure, however remains elusive.

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