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Long Term Vaginal Azoles Versus Prophylactic Oral Fluconazole in Treatment of Recurrent Vulvovaginal Candidiasis

Zahra Fardy Azar and Shahram Habib Zadeh
Gynecology and Obstetric Ward, Tabriz University of Medical Sciences, Tabriz, Iran
Infective Disease Ward, Ardebil University of Medical Sciences, Ardebil, Iran

Abstract: Recurrent Vulvovaginal Candidiasis (RVVC) is a fungal infection of the vagina and vulva that occur usually = 4 episodes in a year. Our object was to compare the efficacy and safety of a single oral dose of fluconazole (150 mg) weekly with clotrimazole vaginal cream 150 mg twice weekly for 6 months as treatment of recurrent VVC. We conducted a clinical trial study among 124 women with Recurrent Vulvovaginal Candidiasis (RVVC) among patients presenting to the Obstetrics and Gynecology Clinics of Tabriz University of Medical Sciences from 2002-2004. There was no significant difference in the therapeutic response as the recurrence rate during 12 months between the two groups. The drug side effects in the fluconazole group were significantly more than clotrimazole group. The satisfactory from the drug in the fluconazole group was significantly less than clotrimazole group. Due to the fewer side effects and more satisfactory of local treatment, we recommend profilactic use of Azole vaginal creams for treatment of RVVC especially in women who are pregnant or have systemic problems.

Key words: Recurrent vulvovaginal candidiasis, oral fluconazole, vaginal clotrimazole, long term, treatments

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; about one half of them will experience a recurrence (Richter *et al*., 2005). Recurrent Vulvovaginal Candidiasis (RVVC) is defined as = 4 episodes of symptomatic VVC each year (Harkless, 2005).

VVC usually is caused by C. albicans, however, occasionally is caused by other Candida species. Candida albicans is responsible for 35-90% of vaginal yeast infections. RVVC is caused by the persistence of a single yeast genotype that undergoes morphological and behavioral changes in the presence of antifungal agents (Maffei *et al*., 1997). Associated symptoms and signs include pruritus, burning, soreness, abnormal vaginal discharge, dysparonia and vaginal and vulvar erythema and edema (Rodgers and Beardall, 1999).

Known predisposing host factors which include uncontrolled diabetes mellitus, immunosuppression, pregnancy and hormone replacement, only partially 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 effect on sexual relation (Foxman *et al*., 2000).

The diagnosis should be confirmed by physical examination, direct microscopy of the vaginal secretions and by fungal culture. Characteristic budding mycelia are seen in fewer than 30% of positive candidial cultures (Jovanovic *et al*., 1991).

The optimal treatment of VVC has not yet been defined (Ringdahl, 2000). 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 *Azole* drugs or *Nystatin* or systemic oral antifungal agents.

In the recurrent VVC, after treatment of the acute episode, subsequent prophylaxis (maintenance therapy) is essential (Ringdahl, 2000). Several maintenance regimens have been studied. One of them is ketoconazole 100 mg day^{-1} or fluconazole 150 mg weekly for 6 months (Ringdahl, 2000). 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).

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

Corresponding Author: Zahra Fardy Azar, Gynecology and Obstetric Ward, Tabriz University of Medical Sciences, Tabriz, Iran

MATERIALS AND METHODS

We conducted a clinical trial study among 124 women with RVVC. Cases were recruited from patients presenting to the gynecology clinics at the department of Obstetrics and Gynecology of Tabriz University in the period 2002-2004.

The patients with symptoms and signs of candidia vulvovaginitis (pruritus, irritation, burning, discharge erythema and edema) and a history of = 4 episode of VVC in the last year (at least one of the previous episodes must have been diagnosed by physician) were chosen. Patients with severe chronic disease, using oral hypoglycemic drugs, or chronic dermatologic disease excluded from this study.

All subjects in this study signed informed consent form, then the social, demographic and medical history and present compliant of patients were achieved and the vaginal examination was performed.

The sampling of vaginal discharge was performed from patients clinically suspected to have RVVC and 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 suspect of the disease. For laboratory examination, swab specimens were placed on sabourauds agar plus chloramphenicol and cyclohexamid with natural PH. The specimens were stored at 37°C and subsequently identified by smooth white colony formation. FBS (Fasting Blood Sugar) test was performed to confirm the unknown diabetes mellitus and Pap smear was also performed for rule out of pre-cancer lesion in the cervix.

For treatment, the patients were randomized systematically in 2 groups with 62 cases in each group. The first group received clotrimazole vaginal cream 5 g day^{-1} for 7 days for acute episode and 5g twice a week for 6 months for prophylaxis. The second group received single oral dose of fluconazole capsule 150 mg for acute episode followed by prophylactic treatment with fluconazole capsule 150 mg each week for 6 months.

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

Statistical analysis was carried out using Chi square, Mann-Whitney and Kaplan-Mayer methods.

RESULTS

A total of 124 women with RVVC were enrolled in the trial. These patients were randomized systematically in 2 groups with 62 cases in each group. The mean age was 32±5 years (range 18-50) among patients in the fluconazole group and 32±2 years (range 19-49) among the clotrimazole group. The main socio-demographic characteristics of the two groups are reported in Table 1. These variables showed no significant difference between the two groups.

As showed in Table 2, the rate of antibiotic use in the past 6 months, contraception method, the history of diabetes and result of laboratory findings was same in both groups. No patient was pregnant at enrollment.

Table 1: Socio demographic characteristics of patient in the two groups

Variable	Clotrimazole (59 Cases)	Fluconazole (58 Cases)	PV
Literate status:			
Illiterate-preliterate	32(54.2%)	26(44.8%)	p = 0.497
Diploma	21(35.5%)	23(39.6%)	
Graduate	6(10.3%)	9(15.6%)	
Job:			
House keeper	44(74.6%)	44(76%)	p = 0.83
Employee	15(25.4%)	14(24%)	

Table 2: Medical characteristics of patients in the two groups

Variable	Clotrimazole (59 cases)	Fluconazole (58 cases)	PV
Contraceptive use:			p = 0.39
OCP	12(20.3%)	18(31%)	
IUD	9(15.2%)	12(20.6%)	
Barrier	5(8.5%)	5(8.8%)	
Natural or non	33(56%)	23(39.6%)	
Antibiotic use during			p = 0.49
Previous 6 m	17(28%)	15(25%)	
Diabetic	6(10%)	7(11.6)	p = 0.46
Laboratory results:			p = 0.46
Direct smear with KOH	55(91.6%)	57(95%)	
Candidia culture	5(8.3%)	3(5%)	
Pap smear			p = 0.8
Normal smear	41(69.4%)	35(60.3%)	
Abnormal smear:			
Positive for candidia	12(19%)	8(13.8%)	
Cervicitis	6(11.6%)	15(25.9%)	

Table 3: Recurrence rate of Vulvovaginal Candidiasis among the two groups during treatment and follow up periods

Variable	Clotrimazole (59 Cases)	Fluconazole (58 Cases)
Treatment period:		
1-6 month	5 (8.47%)	5(8.62%)
Follow up period:		
7 month	3(5.08%)	3(5.17%)
8 month	0(0%)	2(3.45%)
9 month	2 (3.39%)	3(5.17%)
10 month	5(8.47%)	4(6.9%)
11 month	5(8.47%)	5(8.62%)
12 month	5(8.47%)	6(10.34%)
Total recurrence in 12 months:	25(42.4%)	26(44.8%)

Table 4: Quality of drug use and satisfaction among the two groups

Variable	Clotrimazole (59 cases)	Fluconazole (58 cases)
Completion of drug use:		
Complete	55(93.2%)	49(84.4%)
1 missing	3(5%)	5(8.6%)
2 missing	1(1.8%)	4(7%)
Patients' 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%)

The main symptoms of disease among patients were include vaginal burning (102 cases), vaginal pruritus (97 cases), or both (82 cases). The main signs were vulvovaginal erythema (109 cases), mucosal edema (99 cases) and white caseouse discharge (85 cases). After treatment, the cure rate in the first visit was 99%.

In the third visit, 2 patients of fluconazole group were excluded because of no regular presenting to control visits and 2 patients were excluded in the 4th and 5th visit because of more than 3 times missing drug use.

In the clotrimazole group, 3 patients were excluded because of local sensitivity to the drug.

Of remaining 117 cases, as in Table 3, the recurrence rate in treatment period (6 months) was 8.3% in group 1 and 6.6% in group 2.

Recurrence rate in follow up period (second 6 months) was 38.3% in group 1 and 40% in group 2. There was no significant difference between the two groups ($pv<0.05$).

Regarding to the drug use, 88.8% of cases in group 1 and 85% in group 2 were used regularly. Drug usage missing rate (missed =2 consecutive doses of the drug) was 4 cases in group 1 and 9 cases in group 2 which are ignorable. Regarding to the satisfaction of patients, the local cream users had more satisfaction as showed in Table 4 ($pV=0.003$).

The main drug side effects were nausea (20 cases), vomiting (4 cases) and other gastrointestinal complications in fluconazole users but these side effects were mild and ignorable. Among clotrimazole users also, there were 5 cases of local sensitivity to drug, of which 3 cases were excluded from the study and others were mild and ignorable. The systemic complications among cream users was significantly less than capsule users ($pV=0.004$).

DISCUSSION

Our study showed that the most common complaints of patients were vaginal burning and pruritus which is compatible with the reported symptoms for candidial vaginitis including vaginal discharge, burning and pruritus (Scott *et al*., 2003). 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 (Speroff *et al*., 2004). By adding 10% KOH to the slide, the epithelial cells undergo lysis, which increases the ability to identify hyphae or blastospores (Nyirjesy, 2001). 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 also was performed for cases in whom the result of direct examination was negative but there was high clinical suspicious 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 (Bohannon, 1998). In our study, the rate of false-negative finding of direct examination was 6.3% which confirmed by fungal culture and this can indicate the test reliability. Broad spectrum antibiotic use, oral combined contraceptive use, pregnancy, diabetes, immunosuppression and hormone replacement therapy (Patel *et al*., 2004) are positively associated with a symptomatic vulvovaginal candidiasis episode (Scott *et al*., 2003). In our study, 12 cases were OCP users, 33 cases had used antibiotic and 13 cases had diabetes and there was no any other predisposing factor in our study. In a case-control study over 684 cases with symptomatic VVC and 901 control subjects from among asymptomatic women, 19.3% in case group and 11.9% in control group were antibiotic user and VVC was directly related with antibiotic use (Spinillo *et al*., 1999). 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 10-11 mmol L^{-1} (180-196 mg dL^{-1}), hyperglycemia may impair several aspects of humoral host defense, resulting in decreased random motion of neutrophils, chemotaxis, phagocytosis and microbial killing (Bohannon, 1998). In our study, because of small number of diabetic patients, the analysis of studied drug regimen effect on this disease is impossible and require a specific study over diabetic patients; although, because of interaction between fluconazole and hypoglycemic drugs the use of vaginal clotrimazole with the same effect and lower side effects and drug interactions is recommended.

Patel *et al.* (2001) suggested that clothing habits, personal hygiene, a history of bacteria vaginosis, consumption of acidophil-containing products and age <40 years are other predisposing factors (Richter *et al.*, 2005). Regarding to this factors, in our study only the age <40 years (32±5) was found as predisposing factor but this conclusion will need for other study.

Treatment of *candida* vaginitis usually involves topical application of polyene or azole compounds or systemic oral azoles. In a study by Sobel *et al.* (1995) on 429 patients with candida vaginitis the efficacy and safety of a single oral dose of fluconazole with 7-day clotrimazole 100 mg vaginal treatment was compared. At the 14-day evaluation clinical cure or improvement was seen in 94% of fluconazole-treated patients and 97% of clotrimazole-treated patients. At the 35-day evaluation 75% of both groups remained clinically cured, so in their study the cure rate and side effect profiles in both groups were similar (Sobel *et al.*, 1995).

In a double-blind study by Sadovsky, the treatment of acute episode of vaginal candidiasis by fluconazole in 2 divided doses within 2 h 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 (Sadovsky, 2001). This indicates that in choosing the therapeutic methods, the patient's acceptance of drug type and consumption route is also effective.

CONCLUSION

Regarding to the findings of this study, the response to treatment and reduction in recurrence rate of VVC among users of systemic maintenance fluconazole is similar to 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.

REFERENCES

Bohannon, N.J., 1998. Treatment of vulvovaginal candidiasis in patients with diabetes. Diabetes care. 21: 451-456.

Foxman, B., R. Barlow, H. D'Arcy, B. Gillespie and J.D. Sobel, 2000. Candida vaginitis: Self-reported incidence and associated costs. Sex Transm. Dis., 27: 230-235.

Harkless, G., 2005. Fluconazole reduced the rate of recurrence of vulvovaginal candidiasis. Evid. Based Nurs., 8: 49-52.

Jovanovic, R., E. Conjgema and H.T. Nguyen, 1991. Antifungal agents vs. boric acid treating chronic mycotic vulvovaginitis. J. Reprod. Med., 36: 593-597.

Maffei, C.M., C.R. Paula, T.S. Mazzocato and S. Franceschini, 1997. Phenotype and genotype of candida albicans strains isolated from pregnant women with recurrent vaginitis. Mycopatthologia, 137: 87-94.

Nyirjesy, P., 2001. Chronic vulvovaginal candidiasis. Am. Fam. Physician, 63: 697-702.

Patel, D., B. Cillespie and J. Sobel *et al.*, 2004. Risk factors for recurrent volvovaginal candidiasis in women receiving maintenance antifungal therapy. Am. J. Obstet. Gynecol., 190: 644-53.

Richter, S.S., R.P. Galask and S.A. Messer *et al.*, 2005. Antifungal susceptibilities of candida species causing vulvovaginitis and epidemiology of recurrent cases. J. Clin. Microbiol., 43: 2155-2162.

Ringdahl, E.N., 2000. Treatment of recurrent vulvovaginal candidiasis. Am. Fam. Physician, 61: 3306-3012.

Rodgers, C.A. and A.J. Beardall, 1999. Recurrent vulvovaginal candidiasis: Why does it occur? Int. J. STD AIDS. 10: 435-441.

Sadovsky, R., 2001. Treating complicated candida vaginits with fluconazole. Am. J. Obstet. Gynecol., 185: 363-369.

Scott, J.R., R.S. Gibbs, B.Y. Karlan and A.F. Haney, 2003. Danforth's Obstetrics and Gynecology. (9th Edn.), Lipincott Williams and Wilkins, Philadelphia, pp: 583-584.

Sobel, J., D. Brooker and G. Stain *et al.*, 1995. Single oral dose fluconazole compared with conventional clotrimazole topical therapy of candida vaginitis. Am. J. Obstet. Gynecol., 172: 1263-1268.

Speroff, L., R.H. Glass and N.G. Kase, 2004. Clinical Gynecologic Endocrinology and Infertility, (6th Edn.), Lipincott Williams and Wilkins, Philadelphia, pp: 746-810.

Spinillo, A., E. Capuzzo, S. Acciano, A. De Santolo and F. Zara, 1999. Effect of antibiotic use on the prevalence of symptomatic vulvovaginal candidiasis. Am. J. Obstet. Gynecol., 180: 14-17.