Comparison of Fluconazole and Clotrimazole in the Treatment of Acute Candida Albicans Vulvovaginitis

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Abstract

Objective: This study compared two antifungal drugs, fluconazole and clotrimazole for the treatment of vulvo vaginal candidiasis.

Materials and Methods: This randomized clinical trial was conducted on 120 women with vulvo vaginal candidiasis during a six month period. All patients answered a standard questionnaire containing questions about symptoms of vulvovaginal candidiasis and presence of vaginal discharge and signs of vulvar and vaginal inflammation were documented according to physical examination. Two swabs of vaginal discharge were obtained for each woman, one for direct smear, another for culture. The culture medium was Sabouraud Dextrose Agar (SDA). Patients were randomized into two groups of clotrimazole (vaginal cream for 7 days and 150 mg fluconazole in a single dose. Clinical and paraclinical responses were calculated.

Results: Clinical improvement occurred in 96 cases (80%). This value was 86.7% and 73.3%for clotrimazole and fluconazole, respectively (P-value=0.04). Paraclinical response on tenth day of treatment was observed in 87 patients (72.5% This value was 66.7% and 78.3%for clotrimazole and fluconazole groups, respectively (P-value=0.110). Mean days of treatment was 4.06 ±1.30 days for clotrimazole and 2.70 ±0.78 days for fluconazole (p value =0.031).

Conclusion: Most of the clinical and paraclinical responses to the drugs used for the treatment of vulvo vaginal candidiasis are in the favour of fluconazole.

Key words: Vulvo vaginal candidiasis, Candida albicans, Fluconazole, Clotrimazole

Introduction

Vulvo vaginal candidiasis (VVC) is a very common condition and about 75% of women experience at least one episode of candidiasis during their reproductive years (1). Some women, however; suffer from recurrent episodes of candidiasis which can signifycantly affect their quality of life and their sexual health. Vaginitis is predominantly caused by *Candida albicans* species (>90%) (2-5), only minority of cases (<10%) are caused by non *Candida albicans* species, usually *Candida glabrata*. Despite considerable debates, there is little evidence of a significant increased infection rate due to the non *Candida albicans* species (2-5). Clinical cure and negative culture results are

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two major targets of antifungal drugs. The majority of studies analyzing yeast isolates from vulvovaginitis patients have shown that the recovery of fluconazole-resistant *C.albicans* isolates is an unusual event (3-6), but isolates they often found had a small number of microorganisms. The increased consumption of over – the – counter antifungal drugs (7) and prolonged therapy for recurrent candidiasis are risk factors for the emergence of azole resistance species isolated from vulvovaginitis patients.

The purpose of this study was to determine the efficacy of two common drugs used for VVC caused by *Candida albicans* species.

Materials and methods

Sexually active women with vaginal discharge, pruritus and clinical diagnosis of vulvovaginal candidiasis were included in this study in Kosar gynecology clinic affiliated to Urmia University of Medical Sciences. This randomized clinical trial which was approved by the ethical committee of human research related to Urmia University of Medical Sciences, was conducted from 20 may to 20 October 2004. Pregnant women, patients with current antibiotic consumption, suppressive therapy, current use of oral combined contraceptive pills (ocps), recurrent candidiasis or cervicitis, menopause and BMI >30 kg/m^2 were excluded from the study. All patients (120 women) answered a standard questionnaire containing questions about symptoms of vulvovaginal candidiasis (vaginal discharge, vulvovaginal itching, vulvovaginal burning sensation, dysuria and dysparonia). On physical examination presence of vaginal discharge and signs of vulvar and vaginal inflammation were recorded. Therefore; patients included in the study were randomized upon their arrival to our clinic into two groups of clotrimazole and fluconazole. Randomization was made according to odds and even numbers given to the patients. All the participants signed a written consent in which they declared to know that the information would be used for research and the researchers made them familiar with antifungal drugs and their benefits and side effects. Two swabs of vaginal discharge were obtained for each woman, one for direct smear, another for culture. The culture medium was Sabouraud Dextrose Agar «SDA» supplemented with chloramphenicol. Smear was taken and gram staining was done for each sample. Presence of invasive forms of pseudohypha and blastospores were diagnostic. Then 0.5cc of human serum was added to fungal colony in culture media. Presence of germinal tube in this mixture was indicator for Candida albicans.

Non *C.albicans* species and non candidial vaginitis were excluded from the study. After confirming the aforementioned diagnosis, treatment of patients was performed through the described randomization method. A group of patients received single dose of 150 mg fluconazole (Pars daru co., Iran) and another group received vaginal clotrimazole cream (Pars daru co., Iran) for 7 consecutive days. Follow up visits were made ten days later. Quality of vaginal discharge, vulvovaginal inflammation, other accompanied symptoms, side effects of drugs and patient satisfaction were recorded. Improvement of vaginal discharge, vulvovaginal pruritus were considered clinical cure (outcome measure) in the follow up visit. Those with negative smear and culture were considered to have paraclinical cure. SPSS version 12 was used for statistical analysis. Chi-square test was used for comparing qualitative variables and t-test was used for quantitative variables. P-value less than 0.05 was regarded for statistical significance.

Results

One hundred and fifty patients between 20 to 50 years old were included in this study. Initial smear and culture were negative for *Candida albicans* in ten patients. Twenty patients did not continue follow up. One hundred and twenty (sixty in either group) patients took part in all phases of the study. Mean age of the patients was 34.9±4 years (35.4±2.63 and 34.5±2.17 for fluconazole and clotrimazole, respectively). Mean body mass index (BMI) was 24.1±5 kg/m^2 (35.8±2.82 and 24.5±3.27 for fluconazole and clotrimazole, respectively). Frequencies of vulvovaginal burning, dysuria and dysparonia were 39 (32.5%), 26 (21.7%) and 42 (35%), respectively (Table 1). Clinical improvement occurred in 96 cases (80%). Mean days of treatment was 4.06±1.30 days for clotrimazole and 2.70 ±0.78 days for fluconazole (P-value =0.031).

Paraclinical response on tenth day of treatment was observed in 87 patients (72.5%). This value was 66.7% and 78.3% for clotrimazole and fluconazole, respectively (P-value=0.110). Therefore post treatment evaluation revealed that 27.5 % of women were culture positive (21.7and 33.3% for fluconazole and clotrimazole, respectively). Side effects of drugs were reported in 6.6% of patients (one abdominal cramp, two vulvar or inguinal irritation in clotrimazole and 3 cases of nausea in fluconazole). Fifty seven percent

Table 1: Baseline and treatment results of the two study groups

	All patients	Fluconazole group	Clotrimazole group	P-Value
Age (year)	34.9±4	35.4±2.63	34.5±2.17	0.241
BMI (kg/m^2)	24.1±5	35.8±2.82	24.5±3.27	0.092
Improvement of vaginal-discharge	109/120 (90.8%)	53/60 (88.3%)	56/60 (93.3%)	0.343
Improvement of vaginal burning	101/120 (84.2%)	54/60 (90%)	47/60 (78.3%)	0.061
Improvement of dysuria	18/26 (69.2%)	9/12 (75%)	9/14 (64.3%)	0.555
Improvement of dysparonia	14/42 (33.3%)	7/18 (38.9%)	7/24 (29.1%)	0.503
Improvement of vulvar inflammation	5/24 (20.9%)	2/13 (15.4%)	3/11 (27.8%)	0.630
Improvement of vaginal inflammation	19/55 (34.5%)	8/30 (26.7%)	11/25 (44%)	0.178
Clinical cure	96/120 (80%)	52/60 (86.7%)	44/60 (73.3%)	0.049
Para clinical response	87/120 (72.5%)	47/60 (78.3%)	40/60 (66.7%)	0.110
Mean days of treatment	3.42±1.7	2.79± 0.78	4.06±1.3	0.031

of participants in clotrimazole group and 97% of participants in fluconazole group treated patients were satisfied from their treatment.

Discussion

Epidemiologic studies show a constant increase in the prevalence of vulvovaginal candidiasis (8). The majority of cases are caused by *Candida albicans*; however, episodes due to non-albicans species of *Candida* appear to become increased (9-11). In the present study, the prevalence of *C.albicans* (88.3%) was predominant, similar to the findings obtained in a North American population by Sobel (8) and by Kent (12), but less than Tiene et al (13), Abu-Elteen et al (14) and Buscemi et al(6).

Twenty seven percent (27.5%) of women have positive culture or smear after the treatment (21.7% and 33.3% for fluconazole and clotrimazole, respectively). Karimian (15), Mikamo (16) and O-Praserts (17) reported positive culture after the treatment with fluconazole about 8.4%, 27.7% and 30.2% for fluconazole and 22.9%, 33% and 32% for clotrimazole, respectively. These results are similar to those in our study except for fluconazole in Karimian study. Despite this, clinical cure was 86.7% in the fluconazole and 73.3% in clotrimazole group, a finding that was similar to those recent studies mentioned above for fluconazole and clotrimazole drugs; (77.1% vs 74.2%) (76% vs 72%) (88.7% vs 90%), respectively, but greater than what was reported in Vacheva□s study (18).

In the recent years information on the susceptibilities of *Candida* isolates responsible for symptommatic vaginitis has been made available (19). Houang et al. (20) measured the fluconazole levels in vaginal secretions of patients following administration of a single 150-mg dose of fluconazole. The peak concentration of fluconazole in vaginal secretions was 2.43 μg/ml 8 to 24 hours later and persisted in concentrations greater than the MIC (minimum inhibitory concentration) for most strains of *C.albicans* for at least 3 days. Saporiti and her coworkers found 13.5% of species were resistant to fluconazole in candida albicans volvovaginitis (21). In Richter study (19), resistance to fluconazole was 3.7% which was observed only among *C.glabrata* isolates (15.2%) and *C.krusei*, but resistance to the fluconazole was not observed in *Candida albicans* species. Sobel et al (22) studied 556 women with either severe or recurrent *Candida vaginitis* and treated them with fluconazole. They measured clinical improvement and culture at baseline and 14 and 35 days later. They observed that in the baseline evaluation, 93% of *Candida albicans* isolates were highly sensitive to the drug (MIC of ≤1 μg/ml) and would theoretically be inhibited by the predicted fluconazole concentrations. In fact, more than 90% of these patients responded excellent from clinical point of view. The majority of

women who failed clinically at both follow-up visits did so as a result of infection with *Candida albicans* strains which were highly susceptible to fluconazole. Similarly, in this study most women who had persistently culture-positive, were infected with fluconazole-susceptible strains, emphasizing the limitation of azoles as fungistatic agents in the management of *Candida vaginitis* (23). Both systemic and topical azole agents appear to be similarly limited in their abilities to eradicate vaginal candida, despite impressive clinical success rates. But the limitation of their study was studying only severe or complicated women, not mild or moderate vulvovaginitis candidiasis. In the present study, some patients in both groups did not respond to drugs (21.7% in fluconazole and 33.7% in clotrimazole groups). Although 27.5% of women were observed to have positive culture, only 20% of them did not show clinical improvement.

We didn't conduct in vitro susceptibility testing, which could limit our study. As Sobel said" It is reasonable to perform susceptibility tests for women who have poor clinical and mycological responses in individual episodes for those receiving maintenance suppressive azole regimens who have breakthrough infections" (23). Also as Li J and et al showed identification of specific genotypes that correlate with severity of VVC has diagnostic and therapeutic significance (24).

So, it seems that usual antifungal drug is not effective for all VVC cases due to *Candida albicans*. Probably resistant species and over- the- counter use of drugs are responsible for this problem. It is reasonable that antifungal drugs used with prescription, and susceptibility testing for non-responder patients is recommended.

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