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EFFICACY OF ITRACONAZOLE VERSUS FLUCONAZOLE IN VULVOVAGINAL CANDIDIASIS: AN IN VIVO STUDY

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ABSTRACT: AIMS: To compare the efficacy of itraconazole 200mg twice for one day and fluconazole 150mg single dose in the treatment of acute vulvovaginal candidiasis. **METHODS:** The study was carried out at the Department of Obstetrics & Gynaecology, K.P.C. Medical College & Hospital, Jadavpur, Kolkata, from August 2011 to July 2012 on 80 women with clinical and mycological diagnosis of vulvovaginal candidiasis. Diagnosis was based on history, clinical examination and relevant investigations. The women were divided into two equal groups. After initial assessment, Group 1 was treated with capsule itraconazole 200mg twice for one day, and Group 2 with capsule fluconazole 150mg single dose. They were assessed clinically for cure and relapse on day 7 and 21 respectively. **RESULTS:** The overall clinical evaluation showed 70% (n=28) cure rate with itraconazole and 50% (n=20) with fluconazole. In Group-1, 9 (22.5%) and in Group-2, 10 (25%) showed some improvement, while 3 (7.5%) in Group 1, and 10 (25%) in Group 2 failed to respond. At the 7th day follow up, Clinical success rates (cure and improvement) were 92.5% in the itraconazole group and 75% in the fluconazole group ($P < 0.05$). Relapse was observed in 5 (18%) and 8 (40%) of the cured cases in Group 1 and Group 2 respectively on day 21. **CONCLUSION:** Itraconazole was found to be more effective in the treatment of vulvovaginal candidiasis compared to fluconazole with high cure and low relapse rate.

KEYWORDS: Itraconazole, Fluconazole, Vulvovaginal candidiasis.

INTRODUCTION: Vulvovaginal candidiasis (VVC) or Candida vaginitis is a common fungal infection among adult women during reproductive ages. It has been estimated that 75% of all adult women experience at least one period of vulvovaginal candidiasis in their lifetime.¹ Vulvovaginitis is the inflammation of the vagina and the vulva. The majority of cases of vulvovaginal candidiasis are caused by *Candida albicans*, other etiologic agents are *C. glabrata*, *C. tropicalis* and *C. krusei*.^{1,2,3}

Candida species are commonly found in small amount in a healthy vagina. However, when an imbalance occurs, such as change in normal acidity of a vagina or the change in hormonal balance, *Candida* multiplies and symptoms of candidiasis like non-specific vulvovaginal pruritus, soreness, thick vaginal discharge, vulval pain and dyspareunia appears.⁴ Effective management of *Candida* infection depends on accurate diagnosis; selection and administration of specific therapy and good compliance of the patient.⁵

There are a variety of local and systemic antimycotic agents available for the treatment of vulvovaginal candidiasis.⁶ The systemic drugs are more expensive than topical preparations, but the latter can cause irritant contact dermatitis and are sometimes messy. In contrast, systemic therapy is easy to administer and patient compliance is better.⁷ Furthermore, if the vulva is very inflamed topical preparations are painful to administer.⁸

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Fluconazole and itraconazole are both triazole antifungals. They have been licensed for the short-term oral treatment of vulvovaginal candidiasis and have been proved to be safer than both amphotericin B and ketoconazole.⁷ Fluconazole is the first line of management for treatment of localized and systemic vulvovaginal candidiasis. In the past, antifungal drug resistance was not known to exist, but today primary and secondary antifungal drug resistance has been proved by extensive multicentre studies.⁹ Thus, an alternative wider spectrum antifungal such as itraconazole can be more effective.

Although in vitro resistance to drug almost always mean a high rate of failure in the treatment, but in vitro sensitivity of the *Candida* species to antifungal drugs does not always mean successful treatment.⁹ Thus, in vivo response of the antifungal drug has earned importance and therefore, was the basis of this study.

The objective of the current in vivo study was to provide comparative data of the single-dose regimen of fluconazole versus the single-day dosage of itraconazole in vulvovaginal candidiasis.

MATERIALS AND METHODS: The present study was conducted at the Obstetrics and Gynaecology OPD, K.P.C. Medical College & Hospital, Jadavpur, Kolkata, from August 2011 to July 2012. A total of 80 married women aged 18 years or above with symptomatic acute vulvovaginal candidiasis were included in this study. Non-pregnant women who had clinical signs and symptoms of vulvovaginal candidiasis (pruritis, burning, and discharge) and pseudohyphae present on microscopic examination of a KOH smear were considered for enrollment in this study.

Women with any of the following conditions were excluded from the study: women who had abnormal Papanicolaou smear cytology, allergy to azole drugs, or chronic vaginal candidiasis; women who were known to have diabetes or immunosuppression; women receiving antifungal chemotherapy; women who were known to have impaired renal or hepatic function; and women who had a concurrent bacterial, viral, or trichomonal vaginal infection. In all patients, the diagnosis was confirmed by direct microscopy and KOH test.

After establishing the diagnosis, the subjects were randomly divided into two groups of 40 each. Patients in Group 1 were prescribed capsule itraconazole (200mg twice oral dose for 1 day) and those in Group 2 were given capsule fluconazole (150 mg single oral dose). After treatment, they were followed up on day 7 and day 21, each sign and symptom was assessed separately. Clinical effectiveness was recorded as cure, improvement, failure and relapse as follows:

Cure: Complete disappearance of all signs and symptoms; Improvement: Improvement or partial disappearance of signs and symptoms; Failure: No change or worsening of signs and symptoms; and Relapse: Reappearance of signs and symptoms after documented cure had occurred. Chi-square test was used for studying the statistical significance of association between different attributes with 5% significance level.

RESULTS: All the 80 patients completed the study and there were no dropout. Disease severity was similar for the both the groups. Other demographic and epidemiologic parameters of these patients were also comparable for both the groups. The ages ranged from 18 to 57 years in Group 1 and from 23 to 54 years in Group 2. The duration of the disease (enquired through history) varied from 7 to 35 days in the former and from 10 to 42 days in the latter. At the 7th day follow up, 28 (70%) of the total in Group 1, and 20 (50%) of Group 2 had been cured completely; 9 (22.5%) patients in Group 1 and

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10 (25%) in Group 2 showed clinical improvement; 3 (7.5%) in Group 1 and 10 (25%) in Group 2 showed no response. At the 21 day follow up, Clinical success rates (cure and improvement) were 92.5% in the itraconazole group and 75% in the fluconazole group ($P < 0.05$). Relapse was seen in 5 (18%) of the 28 cured patients in Group 1, and 8 (40%) of the 20 cured patients in Group 2 on day 21. Response to treatment, as such, was significantly better in Group 1 compared to Group 2 (Table 1).

DISCUSSION: Vulvovaginal candidiasis is the second most common cause of vaginitis after anaerobic bacterial vaginosis. It is observed that *C. albicans* accounts for 70–90 % of VVC cases, with a recent emergence of non-*albicans* species (Paulitsch and Weger et al. 2006, Austria).²

Itraconazole and fluconazole are safe, broad-spectrum antifungal drugs which have gained an important place in the treatment of vulvovaginal candidiasis. Their safety and efficacy have been evaluated in a number of comparative and non-comparative trials conducted in different areas of the world.^{10, 11}

Eradication rate observed in our study was similar to that in the literature. Our results with itraconazole (70% cures) and fluconazole (50% cure) are in accordance with the study of Woolley PD and Higgins SP.¹² It compared three treatment groups as topical treatment with clotrimazole (500mg vaginal pessary and 1% cream), oral treatment with itraconazole (200mg twice a day for one day) and fluconazole (150mg single dose) in separate groups of acute vulvovaginal candidiasis and reported clinical cure of 80%, 80% and 62% respectively for each regimen.

Clinical cure was significantly lower in fluconazole group than that in the itraconazole group or the clotrimazole group.

We had given the clinical trial of single-day 200mg twice therapy of itraconazole, while an earlier study showed that the treatment with a daily 200mg oral dose of itraconazole for 3 days and a single 150mg oral dose of fluconazole proved to be equally effective in the treatment of vaginal candidiasis.¹³ The Clinical cure rate was significantly high in the itraconazole group compared to the fluconazole group. Results of these studies are similar to our study results.

Another study established the relationship of clinical outcome of candidal infection and in vitro results by the determination of minimum inhibitory concentration (MIC) of itraconazole and fluconazole.⁴ Clinically, itraconazole was effective in 64.3% of the cases, while fluconazole was effective in 71.0%. The mycological cure rates (negative culture) were 64.3% with itraconazole and 78.9% with fluconazole. In clinical and mycological evaluation, the responses were statistically significant at the end of the treatment for both regimens.^{4, 5}

A meta analysis¹⁶ on various studies conducted on the efficacy of single-day dose of fluconazole comprising 3279 patients, found a positive clinical response in 94% with a range of 88–100% and mycological cure in 85% (range 76–98%) of patients at first follow up visit. Furthermore, in a similar European multicentre study, 70% patients were cured clinically during therapy and 24% improved clinically.¹⁶ Our findings do not coincide with the results of above-mentioned studies.

This difference between the efficacy of itraconazole and fluconazole could be explained by the fact that in our local setup, women might be suffering from fluconazole-resistant strain of *Candida* species. Identification of different strains of *Candida* was not included in our study. Literature also suggests that *Candida Glabrata* and *Candida Krusie* are often non-responsive to fluconazole, but are susceptible to itraconazole. Primary resistance of local candida species to fluconazole and secondary drug resistance to fluconazole, a commonly prescribed drug in our population for vulvovaginal

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candidiasis, cannot be ruled out. However, more local studies are required to be done for the evaluation of therapeutic efficacy of these antifungal drugs.^{14,15}

Our results regarding high relapse rate with fluconazole compared to itraconazole were also consistent with international data reported earlier.¹² This is probably, because that itraconazole is highly active against most common fungi. It stays in the vaginal mucosa longer than ketoconazole and fluconazole because of its high lipophilicity and high affinity for keratin. The highly lipophilic character of itraconazole results in favorable tissue blood ratio.¹⁷

It has been found in the vaginal tissue for four days after a single-day treatment with 200mg twice a day.¹⁷ Therefore, recurrence rate with itraconazole is low as suggested by a comparative study wherein the recurrence rate after 28 days of treatment was 7% with itraconazole, and 23% with fluconazole.¹²

CONCLUSIONS: Itraconazole was found to be more effective in the treatment of vulvovaginal candidiasis compared to fluconazole, and might represent a better choice in treating the condition. Failure and relapse rates were significantly higher with fluconazole. The small sample size of our study necessitates further studies to validate the findings.

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Post treatment response	No. of patients (%) for the following treatment groups	
	Itraconazole	Fluconazole
1 wk		
Total no. of patients	40	40
Clinical response		
Cure	28(70%)	20(50%)
Improvement	9(22.5%)	10(25%)
Failure	3(7.5%)	10(25%)
3 wk*		
Total no. of patients	28	20
Relapse	5(18%)	8(40%)

TABLE: Efficacy evaluation of the two treatment groups

* Based on patient being cured at 1 week.

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