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Original Research Article.

Therapeutic Efficacy of Voriconazole in Fluconazole Resistant Vaginal Candidiasis

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ABSTRACT

Background: *Candida* species is known as the most common opportunistic yeast affecting the genitourinary tract. The triazoles are commonly used for the treatment of candidiasis. But the increasing resistance of *Candida* to different azoles created a demand for newer drugs.

Objective: Voriconazole is a second generation azole antifungal agent that shows excellent in vitro activity against a wide variety of yeast and moulds. This study was done to assess the therapeutic efficacy of Voriconazole in Fluconazole resistant vaginal candidiasis.

Material and Methods: This one-group pretest-posttest quasi-experiment was conducted in a specialized private chamber of Faridpur, Bangladesh from January 2018 to July 2019. Vaginal candidiasis was diagnosed by clinical features, microscopic examination, culture and sensitivity of high vaginal swab. Voriconazole was used only in Fluconazole resistant vaginal candidiasis.

Results: During the study period, 568 patients were presented with vulvovaginitis. Among them, in 267 (47%) patients, *Candida albicans* were isolated. All patients were treated by Fluconazole as first-line treatment. 160 (60%) of those patients did not improve clinically and were treated by Voriconazole. Success rate was 93% (149). Regarding side effects of Voriconazole, transient visual disturbance occurred in 35% of the patients, nausea and vomiting in 20% of the patients.

Conclusion: Due to wide species variety of *Candida* and increasing resistance, Voriconazole may be the second line treatment of vaginal candidiasis.

Key words: Vaginal Candidiasis, Drug Resistance, Fluconazole, Voriconazole.

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INTRODUCTION

Vulvovaginitis is one of the most common fungal infections in women of reproductive age. This condition is often ignored or treated as an insignificant problem.[1] Candida is an opportunistic pathogenic yeast. Mycotic vaginitis is a common mucosal infection caused mainly by the yeast *Candida albicans*, which is about 85-90%.[2] There is a balance between Candida, normal bacterial flora and immune defense mechanism in vagina.[3]

When the balance is disturbed, colonization is replaced by infection. During vaginal candidiasis, vagina remains in normal pH range (pH 4-4.5), but in mixed infection (bacterial, Trichomonas), pH level rises.[4] Vaginal candidiasis may be associated with reduced immunity, prolonged antibiotic therapy, use of contraceptives, malnutrition, pregnancy, diabetes, obesity, use of immunosuppressive agents, psychological and emotional stress.[5]

Sexual intercourse with an infected person is the commonest mode of spread of genital candidiasis.[6] *Candida* species may produce systemic infection specially esophageal candidiasis in immunocompromised patients.

Vaginal candidiasis is commonly treated with the trizoles, namely Fluconazole, Itraconazole and Ketoconazole, which specifically inhibit fungal ergosterol biosynthesis.[7] The azoles are generally fungistatic rather than fungicidal and some members of azole group are toxic.[3] On the other hand, significantly high resistance of *Candida albicans* to various azole groups have been reported in an Indian study and by other studies.[8-10]

In the 1990s, Fluconazole and Itraconazole were widely used. But neither was an ideal agent. Itraconazole was plagued by absorption problem; Fluconazole had a limited spectrum of antifungal activity, and resistance was soon noted especially in immunocompromised hosts.[11] A second generation trizole agents have been in development in the past decade. The first of these new agents got approval from the US Food and Drug

Administration (FDA) is Voriconazole, a synthetic deviation of Fluconazole. Replacement of the trizol rings with a fluorinated pyrimidine and addition of an α-methyl group resulted in expanded activity, compared with that of Fluconazole. The development of Voriconazole was emphasized because of its broadened antifungal spectrum.[11] The mechanism of action of Voriconazole is almost similar to other azole groups, that is inversion of cytochrome P450 dependent 14α-lanosterol demethylation, which is a vital step in cell membrane ergosterol synthesis by fungi.[12] In addition to the fungistatic effect, Voriconazole and other 2nd generation azoles are fungicidal for some filamentous organisms.[13] Voriconazole is active against all Candida species, including *Candida krusei*, strains of *Candida glabrata* that are inherently Fluconazole resistant and *Candida albicans* that have acquired resistance to Fluconazole.[14] Voriconazole is broadly activate against many species of *Aspergillus* which is often resistant to Amphotericin B.[15-17] Voriconazole is formulated as an oral tablet, an oral suspension, and intravenous solution. The bioavailability for oral formulation is quite high, greater than 90%. Absorption is not affected by gastric acidity. Loading dose for the first 24 hours is recommended to achieve therapeutic levels rapidly. Due to its shorter half-life (6 hours), Voriconazole is dosed twice daily.[12]

Voriconazole is generally well tolerated. The most common side effect, one not previously noticed in other azoles is a reversible disturbance of vision (photopsia). This occurs in about 30% of patients.[18-20] Visual disturbances include altered colour discrimination, blurred vision, the appearance of bright spots and wavy lines, and photophobia. Skin rash is the second most common adverse effect. Other less common side effects are headache, nausea, vomiting, diarrhea, and abdominal pain. Symptoms tend to occur during the first week of therapy and decrease or disappear in spite of continued therapy in most patients.[11]

The primary objective of this study was to assess the therapeutic efficacy of Voriconazole in Fluconazole resistant vaginal candidiasis. At the same, time risk factors associated with vaginal candidiasis were analysed. We also evaluated the side effects of Voriconazole and recurrence of the disease was noted.

MATERIALS AND METHODS

The one-group pretest-posttest quasi-experiment was carried out in a specialized private chamber at Faridpur, Bangladesh from January 2018 to July 2019 (1 year 6 months). Married and sexually active women between 18-50 years of age who attended the clinic with the features of the vulvovaginitis (vaginal discharge, itching, burning sensation during micturition, genital burning, dyspareunia) were included in this study. Written informed consent from patients was taken. An in-depth history was taken in a preformed questionnaire. During the clinical examination, high vaginal swab was collected and sent for microscopic examination along with culture and sensitivity.

Vaginal candidiasis was diagnosed from clinical examination (card like discharge, vaginal soreness, and itching) and microscopic identification of *Candida albicans*. As first-line treatment, all patients got Fluconazole for 14 days. Associated comorbidities were treated simultaneously. Those patients did not improve clinically, and culture sensitivity reports showing resistant to Fluconazole were diagnosed as Fluconazole resistant vaginal candidiasis. They were then selected for treating with Voriconazole. Before prescribing, the side-effects were informed to the patients. We used Voriconazole in the dose 400 mg twice on 1st day, then 200 mg twice for the next 13 days. All patients were re-examined after 21 days for therapeutic efficacy and any toxicity. The patients were then kept in follow up for the next three months for any recurrence.

We excluded pregnant lady, women aged below 18 years or more than 50 years, postmenopausal lady, and patients who had the evidence of bacterial or protozoal infection in vaginal swab.

Voriconazole was first time marketed by General Pharmaceuticals Ltd. in Bangladesh with the name Voricon. We used Voricon (200 mg) in tablet form. There was no conflict of interest. We took permission from the ethical committee of Faridpur Medical College, Bangladesh for this study.

RESULTS

During the study period, 568 patients were presented with the features of vulvovaginitis. Among them, 267 (47%) were diagnosed as vaginal candidiasis after microscopic examination of the high vaginal swab. Pregnancy with vaginal candidiasis was excluded from this study as there is no study in favour of the safety of Voriconazole in pregnancy. After 14 days, all patients (267) were examined for clinical improvement. Among them, 160 (60%) patients did not improve, and they got the second-line treatment with Voriconazole for another 14 days.

Associated comorbidities specially diabetes or urinary tract infection were treated simultaneously. They were also consulted for the improvement of personal hygiene. They were informed about the toxicity of the drugs. All patients were re-examined after 21 days. Among 160 patients, 93% (149) patients showed improvement both clinically and by microscopic examination.

Table I: Predisposing Factors for Vaginal Candidiasis.

Predisposing factors	N (%)
Pregnancy	136 (50.9%)
Diabetes mellitus	112 (41.9%)
Obesity (BMI >30)	103 (38.6%)
History of antibiotic	73 (27.3%)
Urinary catheter within 1 year	35 (13.1%)
Intrauterine contraceptive device	5 (1.9%)
Immunosuppression	2 (0.7%)

Table II: Age Distribution of Patients

Age	N (%)
20-29	57 (20.9%)
30-39	136 (51.2%)
40-49	74 (28.9%)

Table III: Treatment Related Adverse Effects

Adverse effects	N (%)
Abnormal vision	56 (35.0%)
Nausea and vomiting	32 (20.0%)
Rash	13 (8.1)%
Headache	8 (5%)
Abdominal pain	3 (1.9%)

Figure I: Clinical Improvements of Patients Treated with Fluconazole

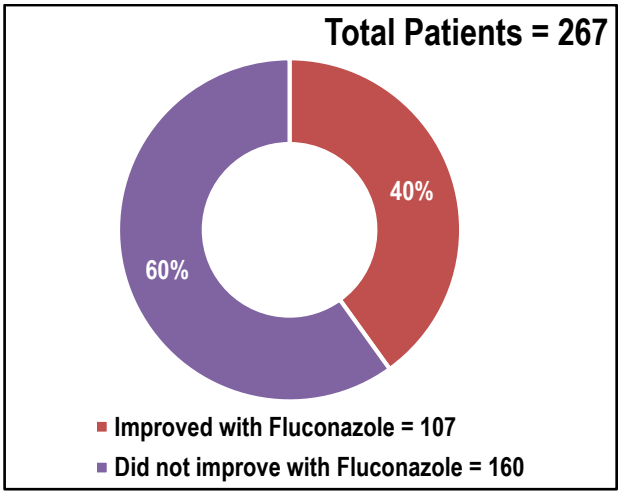
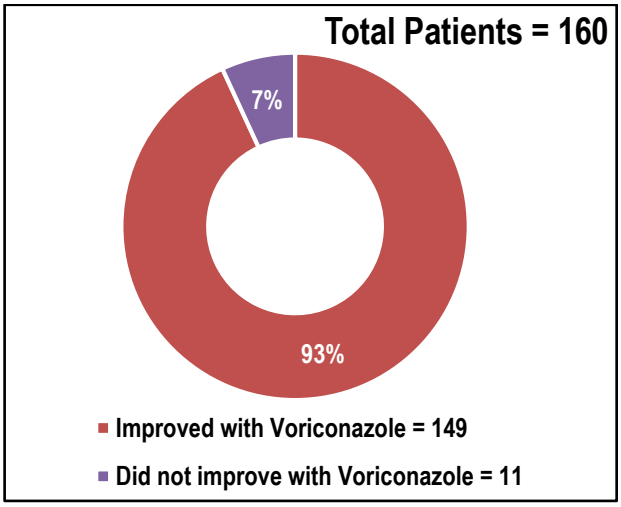


Figure II: Clinical Improvements of Fluconazole Resistant Patients Treated with Voriconazole



After completion of treatment, all patients were kept in follow up for the next 3 months. Among 160 patients, 105 came back after 3 months for follow up. Among them only 8 patients complained about recurrence. And among the 8 patients, 5 were suffering from uncontrolled diabetes mellitus.

DISCUSSION

Vaginal candidiasis is an extremely common infection in 60-70% of the women during their reproductive age and at least once in their lives.[21,22] Worldwide many studies have revealed that candida species can switch over from commensal state into a pathogen causing infection of the oral mucosa, gastrointestinal lining, and genital tract epithelium. In our study, among all patients attending with some sorts of vulvovaginitis, 47% were suffering from candidiasis which was comparable to 48.4% in Babin D et al.[10] One study demonstrated the overall prevalence of vaginal candidates is 25%.[23] The prevalence rate is parallel to 26% recorded in Ibadan[24] and is more or less two folds to that reported in Burkina Faso (14%) and approximately half of that in Cameroon (55.4%).[25]

In our study, the highest frequency of vaginal candidates was observed between the age group 30-39 (51.2%). Among the 40-49 age group, it was 28.9% and lowest in the 20-29 age group (20.9%). Babin D et al. found the highest frequency in the age group 26-35 (49.58%), followed by the age group of 18-25 (35.55%), and lowest frequency was obtained in the age group above 40 years (14.87%). Another study showed prevalence was more in the age group 20-29 years (33.8%), followed by the age group 30-39 years (24.3%).[23]

We analysed the predisposing factors for vaginal candidiasis. Diabetes mellitus was the frequently associated risk factor (41.9%), followed by obesity (38.6%), history of antibiotic use (27.3%), urinary catheter within 1 year (13.1%), intrauterine contraceptive device (1.9%) and immunosuppression (0.7%).

In this study, 60% of the patients did not respond to the treatment with Fluconazole.

Our study was not a comparative study between 1st generation and 2nd generation azoles. We did the clinical trial of Voriconazole in Fluconazole resistant cases. We did not find any other clinical trial like this to compare. But antifungal susceptibility testing in Babin D et al. revealed that for Fluconazole the overall resistance was detected in 16.27% followed by Itraconazole (13.95%) and Voriconazole (9.3%) respectively.

After treatment with Voriconazole 93% of our patients improved clinically and microscopically they were found negative of fungi.

Voriconazole has unique toxicity. We were concerned about the adverse effects and counselled well before the application of the drugs. In our study, the most common side effect was abnormal vision (35%) then nausea and vomiting (20%), skin rash (8.1%), headache (5%) and abdominal pain (1.9%).

Another study by Perfect JR et al. showed abnormal vision in 22.8%, then rash in 7.5%, nausea, and vomiting in 11.3% cases.

If the patients are well explained about the adverse effects, they usually can tolerate it and continue the treatment. None of the patients discontinued the treatment.

CONCLUSION

Voriconazole is being used more for systemic fungal infection specially for immunocompromised patients or hospital infections. Comparatively lower dose and shorter duration of treatment with this 2nd generation azole can effectively cure the Fluconazole resistant vaginal candidates and improve the quality of life of a woman.

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