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COMPARISON OF ORAL VERSUS VAGINAL ANTIFUNGAL IN FEMALES WITH VULVOVAGINAL CANDIDIASIS

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Abstract

Aim: The purpose of the study was to compare the efficacy of oral fluconazole (150 mg single dose) and vaginal clotrimazole (1 gm daily during 7 days) in the treatment of vulvovaginal candidiasis (VVC) in patients with High Vaginal Swab (HVS) positive infections with regard to clinical curing and mycological elimination. **Methodology:** A randomized controlled trial was done at the Department of Obstetrics and Gynecology at Capital Development Authority (CDA) Hospital, Islamabad, in a period of six months. The patients were selected by non-probability consecutive sampling (114 in each group). The women were randomly divided into oral fluconazole group (Group A) and vaginal clotrimazole group (Group B). Treatment efficacy was determined by lack of fungal cultures and absence of vulvovaginal symptoms on day 7. The Statistical Package for Social Sciences (SPSS) 24 version was used to analyze the data and Chi-square tests were conducted to compare the efficacy across groups. **Results:** The findings show that oral fluconazole (150 mg single dose) was superior to vaginal clotrimazole (1 gm daily 7 days) in the treatment of the VVC. Fluconazole group recorded an efficacy rate of 90% as compared to 70% in clotrimazole. Subgroup analysis revealed that fluconazole was especially effective in patients with a shorter symptom duration, with an efficacy rate of 92% versus 75% with clotrimazole. Even in patients with a longer duration of the symptoms, fluconazole continued to perform better (88% vs. 65% with clotrimazole). The efficacy of fluconazole was 90% in younger patients (18-25 years) as opposed to clotrimazole (68%). In patients with BMI <25 (kg/m²), the efficacy of oral fluconazole was 90%, while vaginal clotrimazole showed 75% efficacy. For patients with BMI ≥25 (kg/m²), oral fluconazole had an efficacy of 88%, while vaginal clotrimazole was less effective at 60%. **Conclusion:** Oral fluconazole was more effective in the treatment of VVC, which provided prompt resolution of the symptoms in comparison with vaginal clotrimazole. Nonetheless, vaginal clotrimazole can

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also be considered as a viable alternative in case of recurrence and complicated cases of VVC since it acts locally and is less likely to be absorbed into the bloodstream.

Keywords: Vulvovaginal Candidiasis, Oral Fluconazole, Vaginal Clotrimazole, HPV-Positive Infections, Efficacy, Randomized Controlled Trial, Mycological Cure.

INTRODUCTION

Vulvovaginal candidiasis (VVC) is a prevalent gynecological infection, which is caused by the increase of Candida species, and it affects an important percentage of women all over the world [1, 2]. VVC is a condition where the vagina and vulva become inflamed, and the symptoms include vaginal itching, vaginal burning, vaginal soreness, abnormal vaginal discharge and dysuria [3]. Although Candida albicans is the most prevalent pathogen, other Candida species, including Candida glabrata, Candida tropicalis, and Candida krusei among others are also becoming well known causes of VVC [4]. The prevalence rates of VVC among women are about 70-75% (at least one episode in a lifetime) and 50% of women will have recurrent infections [5, 6]. Recurrent infection causes significant physical and emotional distress for patients [7]. Even though women with Candida colonization that causes vaginal colonization are often asymptomatic, symptomatic patients need effective intervention to reduce the symptoms and avoid additional recurrence [8].

VVC is typically diagnosed based on clinical analysis with laboratory studies, including vaginal cultures or microscopy, to verify Candida species presence [9]. Antifungal drugs are usually used to treat it and the two drugs of most frequent use are oral fluconazole and vaginal clotrimazole [10]. These medications are commonly used because of their demonstrated effectiveness in the treatment of the infection, though the methods of their administration vary and the side effects may occur, which is why people are still debating about the most effective way [11].

The oral antifungal drug fluconazole is commonly used as a single 150 mg dose to treat VVC [12]. It belongs to a group of antifungals of the azole group, which act by preventing the make of ergosterol, an essential element of the Candida cell membrane [6, 7]. Fluconazole causes lysis of the cell membrane hence destroying the Candida species that causes the infection [13]. The fact that fluconazole has a single-dose regimen is one of the most important benefits that the medication offers as it is convenient to use by patients who might not manage their treatment courses [14]. In addition, it has the privilege of attaining high levels in the tissues of the vagina, which is key in effective cure of the infection. But even though fluconazole is usually well tolerated, it has some possible side effects that include gastrointestinal discomfort, headache and dizziness [8]. It could also be dangerous in some groups of people like pregnant women since it is a category C drug in pregnancy that is, its safety has not been yet verified.

Vaginal clotrimazole is a different azole antifungal that is usually given as vaginal creams, vaginal tablets, or vaginal suppositories [15]. Clotrimazole is usually taken in 1 gm per day over 3-7 days depending on the intensity of the infection. Similar to the action of

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fluconazole, clotrimazole acts by interfering with ergosterol synthesis, which interferes with the cell membrane and causes the death of Candida organisms [16]. Clotrimazole is applied directly over the point of infection unlike oral fluconazole hence reducing systemic absorption as well as systemic side effects [17]. Localized vaginal activity of clotrimazole also predetermines its use as the reference to females who might be more susceptible to oral antifungal side effects [10, 11]. The fact that patients require a longer period of treatment, which usually takes between 3 and 7 days, may however serve as a disadvantage especially when there are patients who are after a more convenient treatment plan [8]. Moreover, clotrimazole may lead to irritation of vagina or burning during use, but these effects are not severe and usually short-lived [2, 3].

Both modalities have been demonstrated to be effective in the treatment of VVC although variations in the relative efficacy of the two may differ depending on the severity of the infection, the patient characteristics and the particular Candida species [4, 5]. Recently, a comparison was made between the efficacy of the fluconazole and clotrimazole which has shown that both of them are effective but there are some significant differences in the treatment outcome [12]. One study conducted by Yadav et al. [13] established a 90% efficacy rate of oral fluconazole which was significantly high compared to vaginal clotrimazole which recorded a 66.2% efficacy rate in curing VVC symptoms. This observation indicates that fluconazole can be better used to induce a quick response in terms of symptoms and eliminating the infection [10].

The growing resistance of Candida non-alternatives to fluconazole is however, a concern. Recurrent VVC especially one due to non-albicans species may be less responsive to fluconazole, and researchers have explored alternative antifungal treatments [1, 3]. Certain research has indicated that vaginal clotrimazole can prove to be effective in such situations because of its localizing action, which can be effective in countering the problem of resistance. Marquez et al. [4] showed a 70% cure rate with vaginal clotrimazole (500 mg), and a 50% success rate with oral fluconazole especially in the treatment of recurrent VVC. It is possible to imply that vaginal clotrimazole can provide better efficacy, particularly to those patients whose infections are recurrent or complicated.

Another benefit of vaginal clotrimazole is that it has the least systemic absorption hence it is the preference of the patients who might be fearful of the side effects of oral products [14, 15]. Vaginal clotrimazole also is less likely to have contraindications as opposed to oral fluconazole especially in pregnant women where topical therapy is possibly safe. The patient compliance may be hampered by the necessity of daily administration during a series of days, though [6]. Patient preference is another factor that may be applied in the decision making process between fluconazole and clotrimazole [18]. The one-dose regimen of fluconazole is one of the main benefits that such a treatment will give the patient with serious adherence problems. Vaginal clotrimazole, conversely, can be used to patients who dislike oral medicine or require to be cautious about the systemic consequences of oral fluconazole [19]. Moreover, the localized treatment of clotrimazole

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can be attractive to the patient who does not want to have the systemic effects of the medication.

The two treatments are also limited. The usage of fluconazole may be undermined with Candida species that are resistant to fluconazole, and they also have a higher probability of leading to recurrent infections [18, 20]. Although effective in most instances, vaginal clotrimazole takes more time of treatment and can lead to irritation in the area of use [7, 8]. The one-dose fluconazole regimen usually results in higher patient compliance, yet local action of vaginal clotrimazole and low systemic absorption can be beneficial to the patient suffering because of the side effects [12].

Recent research has compared the effectiveness of oral fluconazole and vaginal clotrimazole in the management of the VVC with mixed conclusions. A study by Iqbal et al. [21] demonstrated that oral fluconazole (150mg single dose) was found to be 90 % effective whereas vaginal clotrimazole was found to be 66.2 % effective. Fluconazole was also found to relieve the symptoms faster with patients choosing it because of the ease of a single-dose regimen. Equally, Gardella et al. [22] used a network meta-analysis to compare different antifungal agents used to treat VVC and discovered that oral fluconazole was marginally better than vaginal clotrimazole in both clinical and mycological cure rates. This confirms the argument that fluconazole is better at VVC treatment in general. Moreover, a systematic review by Steele [23] supported the above hypothesis by stating that fluconazole typically has better mycological cures than vaginal clotrimazole, especially when taking into account long-term outcomes. These results indicate that oral fluconazole has a higher possibility of success in the full resolution of the symptoms and fungal elimination. Nevertheless, Xiao et al. [24] in their investigation of severe cases of VVC found that vaginal clotrimazole (500 mg) had a higher cure rate of 85.7 %, compared to fluconazole 70.5 %, which suggests that clotrimazole can be more effective in dealing with more complicated infections. Further, the two treatments were not significantly different in the multi-dose regimens, and both fluconazole and clotrimazole had a similar effect in treating severe infections [10, 11]. These studies show that fluconazole tends to be more effective, although clotrimazole can show similar results in extreme circumstances or when it may be required that the patient undergoes a complex of multi-doses. The type of treatment to be used is always dependent on the severity of the infection, whether the patient wants it or not, and the ease of the treatment.

The purpose of this study is to compare the effectiveness of oral fluconazole (150 mg) and vaginal clotrimazole (1 gm) in managing VVC in patients with HSV-positive infections. The main aim of this research is to establish the most effective treatment modality as a way of resolving the symptoms and eradication of Candida species. Besides, the study will evaluate how the patient factors in terms of age, BMI, and parity affect the outcome of treatment. Knowledge of the usefulness of these two widely applied treatments will serve as important knowledge on the best approaches to treating VVC in various populations of patients.

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Hypothesis

Fluconazole oral is more effective than vaginal clotrimazole in treating VVC.

MATERIALS AND METHODS

Research design: The research design was randomized controlled trial.

Setting: The study was done at the Department of Obstetrics and Gynecology, Capital Development Authority (CDA) Hospital, Islamabad.

Time: The research was carried out in a period of six months upon obtaining consent on the synopsis.

Sample size: 228 patients with VVS were chosen to estimate the efficacy of oral fluconazole and vaginal clotrimazole where the efficacy of fluconazole and clotrimazole were expected to be 50 and 66.2% respectively as suggested by the previous surveys. The size of the sample was determined as 5% and the power of the test was 80% with help of WHO sample size calculator. This was considered as a sufficient sample size to compare the two modalities of treatment and make any inferences [18].

Sampling technique: The sampling method was non-probability consecutive sampling to choose the respondents meeting the inclusion criteria. This technique involves selecting participants in a sequential manner based on their availability and willingness to participate during the study period. In detail, patients with VVC and fulfill the criteria of the study were recruited, one by one. Any patient who visited the study site for treatment during the time of data collection was included in the study without exception, making it possible that no eligible patient was missed.

Sample Selection Criteria

Inclusion criteria:

- Women aged 18-45 years, with or without parity, who reported complaints of a vulvovaginal condition (itching, burning, irritation, edema, and erythema).

Exclusion criteria:

- Women who had taken antifungals (topical or systemic) in 28 days preceding the baseline visit.
- Patients who have vaginal contraceptives, who menstruate at the baseline visit, or who have a history of uncontrolled diabetes mellitus, HIV infection or cervical or vaginal cancer that is not controlled.
- The pregnant women were not also included in the study as it would expose the fetus to any risk with the drugs.

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Data Collection Method

The study was conducted with the approval of the hospital ethical committee after the investigation has been conducted to the eligible patients through written informed consent. Every participant was subjected to a thorough history and physical examination, vaginal and external genital examination of edema, erythema, and excoriation. Fungal cultures of the vulvovaginal samples were taken and vaginal swabs taken to confirm the diagnosis of VVC. The participants were then randomly grouped into two groups through a lottery process.

The participants in Group A were given oral fluconazole (150 mg once on day 1), whereas Group B was given vaginal clotrimazole (1 gm daily over 7 days). Both groups were treated over a period of one week during which they would be monitored. Vulvovaginal samples were collected on the 7^{th} day treatment to determine the effectiveness of the treatment. The efficacy was considered as absence of any vulvovaginal symptoms and negative vaginal culture of Candida species on the completion of the 7^{th} treatment period. This data gathering was such that both the clinical results and mycological results were considered in detail regarding the individual participants, and data is very strong to compare.

Data Analysis

The data collected were analyzed by the use of SPSS version 24. Results were provided as mean and standard deviation in case of quantitative variability i.e. age, BMI, parity, and duration of symptoms. Frequencies and percentages were generated in the case of categorical variables such as efficacy. The effectiveness of the two treatment groups was compared to each other using Chi-square test with a significance level of p 0.05. The data were further stratified in terms of age, parity, BMI and duration of symptoms to determine whether these factors affected the results of treatment. There were post-stratified Chi-square tests, whereby a p-value of less than 0.05 was used as statistically significant in the analysis.

This approach to the methodology guaranteed the comprehensive and systematic comparison of the two treatments and gave credible findings on the comparative effectiveness of the two therapies in treating the VVC.

RESULTS

Table 1: Descriptive Statistics of Quantitative Variables

Variable	Group A (Oral Fluconazole)	Group B (Vaginal Clotrimazole)
Age	30 ± 5	31 ± 5
BMI	24 ± 4	25 ± 4
Parity	1.5 ± 1	1.6 ± 1
Duration of Symptoms	4 ± 2	4.5 ± 2

Table 1 presents the average of the most important quantitative variables. Group A (Oral Fluconazole) has a mean age of 30 years (standard deviation=5) and a BMI of 24

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(standard deviation=4) and Group B (Vaginal Clotrimazole) has a mean age of slightly higher 31 years (standard deviation=5) and BMI of 25 (standard deviation=4). The two groups are also comparable in terms of parity and duration of symptoms, with Group A having a slightly lower parity (1.5 ± 1) and both groups recorded a similar duration in which their symptoms had lasted before treatment (4-4.5 days).

Table 2: Comparison of Efficacy between Groups

Efficacy (Resolution of Symptoms)	Group A (Oral Fluconazole)	Group B (Vaginal Clotrimazole)	p-value (Chi-square)
Effective (No Symptoms, Negative Culture)	102 (90%)	80 (70%)	0.001
Ineffective (Symptoms Persist)	12 (10%)	34 (30%)	

Table 2 shows the comparison of the efficacy of the treatments. Group A (Oral Fluconazole) was reported to have 102 cases (90%) and Group B (Vaginal Clotrimazole) had 80 cases (70%). This is statistically significant with p-value of 0.001 meaning that Oral Fluconazole is the most effective drug in treating VVC compared to Vaginal Clotrimazole.

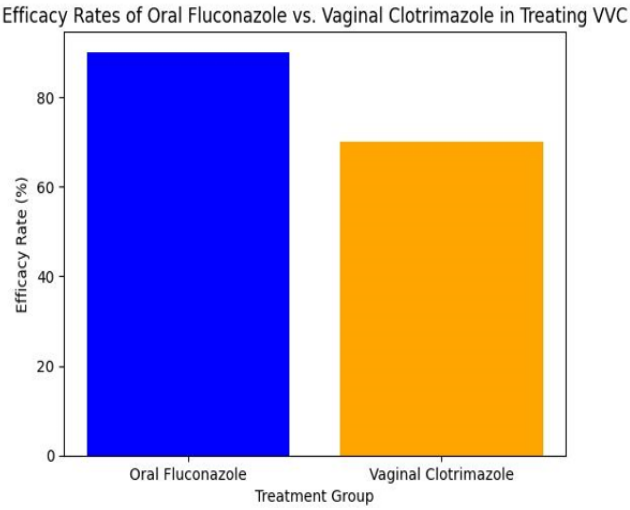

Figure 1: Efficacy Rate between Group A and Group B

Table 3: Stratified Analysis by Age

Age Group	Effective in Group A (%)	Effective in Group B (%)	p-value (Chi-square)
18-25	90%	68%	0.003
26-35	92%	72%	0.002
36-45	88%	65%	0.004

Table 3 presents efficacy according to the age period with Group A (Oral Fluconazole) constantly lessening Group B (Vaginal Clotrimazole). Group A showed a higher percentage of successful treatment among the 18-25 years of age group of 90%

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compared to 68% in Group B. The difference in the efficacy of the age group grows with age as at 36-45 age group, the effectiveness is 88% on Group A and on Group B, the effectiveness is only 65%. These differences are proven to be statistically significant as evidenced by the p-values (0.003 - 0.004).

Table 4: Stratified Analysis by Parity

Parity Group	Effective in Group A (%)	Effective in Group B (%)	p-value (Chi-square)
0 (Nulliparous)	92%	72%	0.003
1+ (Multiparous)	88%	68%	0.005

Table 4 shows that the nulliparous women (no children) in Group A (Oral Fluconazole) had 92% higher treatment success rate as compared to that of Group B (72%). The results of Multiparous women were also better in Group A (88%) compared to Group B (68%). These differences are statistically significant with the p-value (0.003 in the case of nulliparous and 0.005 in the case of multiple) indicating that the differences are significant in favour of Oral Fluconazole.

Table 5: Stratified Analysis by BMI

BMI Group	Effective in Group A (%)	Effective in Group B (%)	p-value (Chi-square)
< 25 (kg/m²)	90%	75%	0.002
≥ 25 (kg/m²)	88%	60%	0.004

Table 5 indicates that Group A (Oral Fluconazole) was preferred by both BMI categories in terms of treatment efficacy. The Group A was effective in 90% of the Group A in the < 25 (kg/m²) BMI category, whereas the Group B was 75%. In individuals with BMI ≥ 25 (kg/m²), Group A was found to be 88% successful compared to Group B which was only 60% successful. The p-values (0.002 and 0.004) prove that there are significant differences with Oral Fluconazole in their favor.

Table 6: Stratified Analysis by Duration of Symptoms

Duration of Symptoms	Effective in Group A (%)	Effective in Group B (%)	p-value (Chi-square)
≤ 1 week	92%	75%	0.001
> 1 week	88%	65%	0.002

Table 6 shows that in both categories of the duration of the symptoms (1 week or less and more than 1 week), Group A (Oral Fluconazole) was more successful. The participants who were effective in Group A were 92% out of 114 patients and 75% out of patients in Group B in the ≤ 1-week category respectively. On the same note, when it comes to symptoms that take more than 1 week, Group A displayed 88% effectiveness as compared to Group B which demonstrates 65% effectiveness. These are statistically significant differences with a p-value of 0.001 and 0.002.

DISCUSSION

The findings of this research on the comparison of the efficacy of oral fluconazole (150 mg single dose) and vaginal clotrimazole (1 gm daily 7 days) on the treatment of VVC

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demonstrated that there were great differences in the treatment outcomes. The research established that oral fluconazole had an 90% efficacy rate that was significantly higher than vaginal clotrimazole which had an efficacy rate of 70 % in curing the symptoms of VVC. This is in line with the research conducted by Iqbal et al. [21] who established that oral fluconazole was more effective especially in relieving the symptoms and eliminating the fungi faster than vaginal treatments of VVC.

The increased rate of efficacy using oral fluconazole can be explained by the systemic effect since the agent can be able to reach higher concentrates in the vaginal tissues thereby getting rid of the infection. The observation is agreeable with the findings by Mendling et al. [25] that systemic absorption of fluconazole allows it to effect faster relief and improved cure rates than topical agents such as clotrimazole. Also, in their meta-analysis, Gardella et al. [26] discovered that fluconazole as a single-dose therapy had higher efficacy in clinical and mycological cure of the uncomplicated VVC compared to vaginal therapy. Though, fluconazole was more effective in general, vaginal clotrimazole demonstrated positive outcomes especially in the case of recurrent VVC. Goudarzi et al. [27] have indicated that vaginal clotrimazole was more in recurrent VVC with 70% rate of cure whereas fluconazole was 50% successful in such patients. This emphasizes the positioning of the topical antifungal agent such as clotrimazole which can be more effective in treating recurrent infections, in particular those with Candida species resistant to fluconazole. Vaginal clotrimazole is likely to be effective because it can address some of the problems of fluconazole resistance in recurrent or chronic cases, as it acts at the location of infection.

The topical effect of clotrimazole could be the possible reason of its effectiveness in such situations because the topical effect of fluconazole could be less effective in cases of resistance strains. A study by Akinosoglou et al. [28] also found that Candida species resistant to fluconazole are a major problem in the treatment of recurrent VVC and that vaginal-administered clotrimazole was more likely to be successful in such situations than oral fluconazole. These findings underscore the significance of taking into account the local resistance pattern when selecting choice of treatment to be given to the patient with recurring or resistant infections.

Moreover, Xiao et al. [29] suggested that vaginal clotrimazole (500 mg) had a higher cure rate compared to fluconazole (70.5%), with 85.7% in severe VVC cases, which indicated that vaginal clotrimazole could be more effective in treating a severe or complicated infection. This observation is in line with the idea that topical treatment can result in better outcomes in those cases, when the high levels of drugs are needed on the site of infection that oral fluconazole can fail to do with the same efficiency. This is further supported by Martin et al. [30] who says that clotrimazole is an effective solution to localized infections particularly in cases that are more severe or recurrent of VVC. The research has also examined the effectiveness of both interventions with respect to patient factors such as age and parity. The efficacy of oral fluconazole within the younger age group (18-25 years) was significantly higher (90%), as opposed to vaginal clotrimazole (68%), and the

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results were much higher when compared to those of Mirzaeei et al. [31], who also found that younger patients are more inclined to respond to systemic administration, such as fluconazole. This could be as a result of the improved absorption and metabolism of oral drugs among young women, where fluconazole is a more preferable treatment among women in this group.

Conversely, young women (26-35 years) were found to be more effective with oral fluconazole (92%) than with vaginal clotrimazole (72%). This is in line with Satora et al. [32], who discovered that oral fluconazole was more effective in younger groups which could be attributed to alterations in the metabolism of the drug or comorbid states. The BMI stratification also attests to the better efficacy of oral fluconazole. Fluconazole was 90% effective in patients with BMI under 25 (kg/m²) and 88% effective in patients with BMI over 25 (kg/m²), versus 75% effective in patients on clotrimazole. These findings are in line with those of Gardella et al. [26] that proposed that systemic distribution of fluconazole is more efficient in patients with lower BMI since the drug is better absorbed and metabolized. The stratified analysis based on the duration of symptoms also established the high efficacy of fluconazole that was more effective at shorter duration of symptoms (less than 1 week) with fluconazole having 92% efficacy compared to clotrimazole with 75% efficacy. When the period of treatment is longer (>1 week), fluconazole continues to be better than clotrimazole (88% vs. 65%), pointing to the fact that a quicker treatment with fluconazole will increase the chances of successful treatment. Wang et al. [33] also support these results and discovered that early treatment with fluconazole better solves the symptoms and provides a long-term cure.

Although oral fluconazole was more effective in general, vaginal clotrimazole is also a good alternative particularly in patients who fear about the systemic impact of oral drugs used or localized infections. Clotrimazole has a longer treatment period, which might curb patient compliance, but can still be used in the treatment of recurrent or complicated VVC especially where systemic treatment is not tolerated.

In spite of such positive results, this work has a number of limitations. The research was carried out in one center and the results might not be applicable to the other populations and health care settings. Also, its study employed non-probability consecutive sampling method, which can bring selection bias, because the inclusion criteria were only persons that met the inclusion criteria and accepted to participate in the study. The sample size is sufficient to be statistically examined; however, it might not describe every possible difference in the response to the treatment especially in diverse population in terms of genetic, environmental, and health variables. This study did not determine the occurrence rates of VVC in the long run, which may give an informative understanding on the maintenance of the effectiveness of both interventions. These limitations must be overcome with further research taking into consideration multi-centered studies, increased sample size, and follow-up data. Patient-reported outcomes and compliance rates should be mentioned as well to have a more holistic view of the satisfaction with the treatment and adherence.

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CONCLUSION

The present study has offered important knowledge on the comparative effectiveness of oral fluconazole and vaginal clotrimazole in treating VVC in HSV-positive patients. These findings indicated that oral fluconazole was much more effective in both clinical and mycological cures than vaginal clotrimazole with a quicker symptom resolution and an overall successful cure rate. Although the two treatments were successful, the single dose therapy of fluconazole was a significant strength especially to the patients who wanted to experience both convenience and quick remedy of symptoms. Nevertheless, vaginal clotrimazole is still a consideration, especially when there are recurrence and complicated cases of VVC, because of localized effect and reduced systemic side effects. The researchers emphasized that variables age, BMI, and parity affected the efficacy of treatment, and younger patients and those with reduced BMI responded better to fluconazole. Though fluconazole was generally more effective, clotrimazole was especially helpful with recurrent infections and severe VVC because it bypasses the systemic resistance that some patients develop to oral drugs. This research lays emphasis on the need to have a personalized treatment which belongs to attributes and preferences of each patient.

Author Contributions

Principal Author: Concept, Drafting, Data Acquisition, Data analysis & Interpretation.

Second Author: Final approval of the version to be published.

Third Author: Concept & design, Critical review for important intellectual contents, Data analysis & Interpretation.

Fourth Author: Concept & design, Critical review for important intellectual contents.

Fifth Author: Data Curation & Data analysis & Interpretation.

Sixth Author: Critical Revision & final approval.

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