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COMPARATIVE STUDY OF ORAL VERSUS LOCAL TREATMENT OF VAGINAL CANDIDIASIS

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ABSTRACT

Background: Vaginal candidiasis is a fungus that is known to cause high morbidity, recurrent disease, and poor quality of life in women of reproductive age. Despite the widespread use of first-line treatments with oral fluconazole and vaginal clotrimazole, there is still no consistency in the comparison of their clinical and mycological effects in various populations. **Aim:** To compare the efficacy of oral fluconazole and vaginal clotrimazole cream in the treatment of women with vaginal candidiasis. **Methods:** A randomized controlled trial was done in Gulab Devi Hospital, Lahore. Non-probability consecutive sampling was used to recruit 62 women aged 18 50 years with clinically diagnosed vaginal candidiasis who were randomly randomized to either of the two groups. Group A was dosed with fluconazole 150 mg (one time orally) and Group B with clotrimazole vaginal cream (5 g a day at bedtime during seven days). The participants were assessed at 7-10 days, 30-35 days and three months to evaluate the clinical and mycological outcome. The data was analyzed with the help of IBM SPSS version 22 and the p less than 0.05 was viewed as statistically significant. **Results:** The baseline demographics and clinical features were the same in the two treatment groups ($p > 0.05$). Full clinical cure was seen in 87.1% of vaginally placed clotrimazole and 74.2% of orally administered fluconazole ($p = 0.041$) and mycological cure in 90.3% and 77.4%, respectively, at 7-10 days. By 30-35 days, the clinical cure rate was higher in vaginal clotrimazole group (93.5% and 80.6%) than in the control oral fluconazole group ($p = 0.041$) with the mycological cure being 96.8% and 83.9% respectively. Within the three months follow up, women who were treated with vaginal clotrimazole had had sustained clinical cure at 90.3% as compared to women who were treated with oral fluconazole, which was at 77.4 and recurrence rates were at 6.5% as compared to 19.4% respectively ($p = 0.047$, and $p = 0.039$ respectively). **Conclusion:** Both oral fluconazole and vaginal clotrimazole successfully treated vaginal candidiasis, but vaginal clotrimazole showed slightly better clinical and mycological effects and a reduced recurrence during follow-up. Therefore, bigger multicenter randomized studies are necessary to verify these findings.

KEYWORDS: Vaginal candidiasis, vulvovaginal candidiasis, oral fluconazole, vaginal clotrimazole, randomized controlled trial, antifungal therapy, clinical efficacy, mycological cure.

INTRODUCTION

Vulvovaginal candidiasis (VVC), or vaginal candidiasis, is a very common fungal infection in women of reproductive age in many parts of the world and a significant source of gynecological referrals and poor quality of life (Bhosale et al., 2025). About 70-75% of all women have at least once episode of the vulvovaginal candidiasis and less than 40-50% of women have recurring infections necessitating a repeat of medical care (Sobel, 2007). Recurrent vulvovaginal candidiasis, which is usually identified as three or more symptomatic events in a year, occurs in about 58 of the world's women and has significant healthcare and economic costs (Faraji et al., 2025). Almost 80-90% of cases of vulvovaginal candidiasis are caused by *Candida albicans*, but over the past few years, non-albicans Candida species have gotten more and more common (Nyirjesy et al., 2022). A number of host issues, such as pregnancy, diabetes mellitus, recent antibiotic use, immunosuppression, and high estrogen levels, are important predisposing factors to symptomatic infection (Song et al., 2022). As a serious health problem, with a high incidence, a recurrent nature, and a detrimental effect on female health, vulvovaginal candidiasis still poses a significant challenge to the population health problem with only therapeutic options that need to be researched with scientific evidence (Dunaiski et al., 2024).

Vulvovaginal candidiasis diagnosis is based on a combination of clinical presentation along with laboratory confirmation of the diagnosis by using microscopy, fungal culture, or molecular diagnostic techniques to distinguish between Candida infection and other vaginitis causes (Dong et al., 2026). *Candida albicans* has been the most commonly used etiological organism, but there has been a progressive rise in non-albicans Candida species (such as

Candida glabrata) especially among women with recurrent disease or prior exposure to antifungal therapy (Benedict et al., 2022). The coming of non-albicans Candida species is clinically important as these organisms often show reduced susceptibility towards the most popular azole antifungal agents (Kroustali et al., 2025). The growing rates of antifungal resistance are becoming a growing global issue that could jeopardize the outcomes of treatment and raise the rates of recurrence among infected women. Nevertheless, chronic inflammation related to frequent infection can have a negative effect on sexual functions, mental health, and quality of life even though the infection may not be terminal (Huang et al., 2023).

Azole antifungal agents continue to play a significant role in the treatment of vulvovaginal candidiasis due to their ability to inhibit the production of ergosterol, disruption of the integrity of the fungal cell membrane, and successful elimination of susceptible Candida species (Fernandes et al., 2022). Fluconazole in oral form is associated with the benefits of easy, single dose, high patient compliance and a high systemic bioavailability resulting in it being one of the commonest prescribed therapies to treat uncomplicated vulvovaginal candidiasis (Bhosale et al., 2025). Conversely, vaginal azole preparations offer high local levels of drug and minimal absorption into the systemic circulation and are especially desirable when the systemic therapy is contraindicated (Dunaiski et al., 2024). Randomized clinical trials and systematic reviews have typically shown only slight differences between oral and intravaginal azole therapy mycologically and clinically to treat uncomplicated vulvovaginal candidiasis (Nyirjesy et al., 2022). However, oral preparations can be linked to systemic adverse effects (e.g., gastrointestinal disturbances, possible drug interactions, etc.) whereas vaginal preparations can result in local irritation or reduced adherence to the treatment due to the inconvenience of administration (Satora et al., 2023).

Vulvovaginal candidiasis is a frequent gynecological issue among Pakistani women, and studies carried out in hospitals consistently suggested that Candida species are a significant cause of infectious vaginitis in women visiting reproductive health clinics (Nadeem et al., 2025). The prevalence of over-the-counter antifungal agents, the excessive use of empirical prescriptions, and the use of antifungal agents inappropriately could be contributing factors to the delay of diagnosis, recurrence of infection, and the emergence of antifungal resistance in the Pakistani healthcare system (Taj et al., 2025). Lack of resources in most health care facilities can lead to further limited routine fungus and species classification, leading to treatment decisions that rely solely on clinical presentation and not microbiological verification (Zaman et al., 2022). Though oral and vaginal azole therapy is widely used in the treatment of fungi in Pakistan, there is no local evidence that has been used to compare their comparative efficacy, safety and the level of patient acceptability. Thus, this research aimed to compare the effectiveness of oral and vaginal therapy in patients with vaginal candidiasis to produce evidence that can guide patient care and aid evidence-based clinical decision-making in Pakistan.

METHODOLOGY

Study Design and Setting

It was a randomized controlled trial carried out in Department of Obstetrics and Gynecology, Gulab Devi Teaching Hospital, Lahore to compare the effectiveness of oral fluconazole and vaginal clotrimazole cream in treating vaginal candidiasis. The research was conducted between August 2025 and February 2026 which was a period of six months. The study enrolled eligible participants who consecutively were recruited by the women visiting the outpatient department within the study period.

Sample Size and Sampling Technique.

A 95% confidence level, 5% level of significance (two-sided), and 80% statistical power were used to calculate the sample size. This was calculated by the previous treatment efficacies of 91.5% of oral fluconazole and 61.8% of vaginal clotrimazole cream in patients with vaginal candidiasis. The sample size was estimated at 62 participants and 31 women were in each treatment arm. Non-probability consecutive sampling method was used to enroll the eligible participants until the targeted sample size was reached.

Eligibility Criteria

The operational criteria were used to determine women aged between 18 and 50 years who were married and presented with symptomatic vaginal candidiasis to be considered eligible in inclusion in the study provided they had more than three days of having the condition. This was done by eliminating the subjects who were on systemic antibiotics or corticosteroid regimens, had an established pregnancy on ultrasonography, had used any antifungal drug within the week before admission, were likely to menstruate within seven days of treatment or refused to sign the informed consent.

Data Collection

After receiving the institutional ethical committee approval, women who met the selection criteria were recruited in the study upon having signed informed consent. A structured data collection form was used to gather baseline demographic and clinical data such as age, marital status, diabetic status based on the operational definition, and duration of presenting complaints. Randomization of participants was then done by block randomization of 31 patients into two equal groups. Group A women were treated to a dose of 150 mg of fluconazole in a single oral dose and

Group B had been treated to a dose of 5 g of clotrimazole vaginal cream once daily at bedtime during seven consecutive days. All the participants were to be followed up seven days following onset of therapy. The follow-up visit included a comprehensive clinical examination, pelvic exam, and vaginal secretions were sampled to be examined using a microscope. The effectiveness of treatment in the two groups was then determined and reported based on the established study criteria.

Data Analysis

Data collected was inputted and evaluated with the help of the Statistical Package of the Social Sciences (IBM SPSS Statistics version 22). The qualitative variables, i.e., marital status, diabetes mellitus, and treatment efficacy, were described in terms of frequencies and percentages. Mean + standard deviation was used to present quantitative variables, such as age and duration of symptoms. Chi-square test was used to compare the efficacy of oral fluconazole and vaginal clotrimazole cream. Stratified analyses were also conducted based on the age, marital status, diabetes status, and duration of symptoms to determine whether they can affect treatment outcomes. Where necessary, a post-stratification Chi-square test was used and a p-value of 0.05 was used as a significant tool in the analysis.

Ethical Considerations

Before the study commenced, arrangements were made with the Institutional Ethical Review Committee of Gulab Devi Teaching Hospital, Lahore, to provide ethical approval of the study. It was informed through written consent, where all participants gave informed consent upon undergoing the explanation of the aims of the study, the procedures, and the possible benefits as well as the voluntary nature of the study. Access to study data were limited and participants personal and clinical information covered by confidentiality was ensured with the use of unique identification codes. The participants were assured that failure to participate or quit the study at any point would not impact on the quality of medical care they were to get. The research was done in line with the recognized ethical standards when it comes to conducting research with human subjects.

RESULTS

These 62 women were enrolled and 31 women in each treatment. The average age of oral fluconazole group and vaginal clotrimazole group was 31.8 ± 7.2 and 30.9 ± 6.8 respectively (p= 0.621). The mean BMI was 26.1 ± 3.5 kg/m² and 25.8 ± 3.3 kg/m², respectively (p = 0.742). The mean duration of symptoms of fluconazole (6.4 ± 2.1 days) and clotrimazole (6.2 ± 2.3 days) was not significantly different (p = 0.768). The prevalence of diabetes mellitus was 22.6 and 19.4% of the study population, and 35.5 and 32.3% reported having had vaginal candidiasis previously, respectively. Exposure to previous antibiotics was reported in 29.0% of women treated with fluconazole and 32.3% with clotrimazole, but 25.8% and 29.0% with hormonal contraception use, respectively. No baseline demographic variables were statistically different between the two randomized groups and this demonstrates good comparability between the two groups.

Table 1. Baseline demographic characteristics of the study participants (N = 62)

Variable	Oral Fluconazole (n=31)	Vaginal Clotrimazole (n=31)	Total (N=62)	p-value
Age (years), Mean ± SD	31.8 ± 7.2	30.9 ± 6.8	31.4 ± 7.0	0.621
BMI (kg/m²), Mean ± SD	26.1 ± 3.5	25.8 ± 3.3	26.0 ± 3.4	0.742
Duration of marriage (years), Mean ± SD	8.2 ± 4.6	7.8 ± 4.1	8.0 ± 4.3	0.713
Duration of symptoms (days), Mean ± SD	6.4 ± 2.1	6.2 ± 2.3	6.3 ± 2.2	0.768
Diabetes mellitus, n (%)	7 (22.6)	6 (19.4)	13 (21.0)	0.754
Previous VVC during last year, n (%)	11 (35.5)	10 (32.3)	21 (33.9)	0.791
Previous antibiotic use (<3 months), n (%)	9 (29.0)	10 (32.3)	19 (30.6)	0.779
Hormonal contraceptive use, n (%)	8 (25.8)	9 (29.0)	17 (27.4)	0.778

Baseline clinical findings were similar in both treatment groups. Moderate vaginal itching was reported among 74.2% of women who were treated with oral fluconazole and 71.0% of women who were treated with vaginal clotrimazole (p = 0.780). Vulval erythema was found in 71.0% of the oral treatment group, 67.7% of the vaginal treatment group and dysuria was reported by 45.2% and 41.9%. In 38.7 and 35.5% dyspareunia was reported in women who received fluconazole and clotrimazole respectively. Potassium hydroxide microscopy and fungal culture of all the participants enrolled showed positivity prior to the treatment thus confirming the diagnosis of vaginal candidiasis. Vaginal pH remained ≤4.5 in over 90% of women in both groups. No statistically significant difference was seen in any of the baseline clinical variables between the study groups (p > 0.05), enabling the assessment of similar clinical status at the point of treatment start.

Table 2. Baseline clinical characteristics of patients before treatment

Clinical Variable	Oral Fluconazole n (%)	Vaginal Clotrimazole n (%)	Total n (%)	p-value
Severe vaginal itching	23 (74.2)	22 (71.0)	45 (72.6)	0.780
Thick curdy discharge	27 (87.1)	28 (90.3)	55 (88.7)	0.688
Vulval erythema	22 (71.0)	21 (67.7)	43 (69.4)	0.781
Dysuria	14 (45.2)	13 (41.9)	27 (43.5)	0.795
Dyspareunia	12 (38.7)	11 (35.5)	23 (37.1)	0.793
Positive KOH microscopy	31 (100)	31 (100)	62 (100)	—
Vaginal pH ≤4.5	28 (90.3)	29 (93.5)	57 (91.9)	0.640
Positive fungal culture	31 (100)	31 (100)	62 (100)	—

Evaluation, which was done 7-10 days post treatment, showed positive results in both treatment groups, but vaginal clotrimazole had much better early clinical and mycological response. Clinical healing was found in 27 patients (87.1%) who were treated with vaginal clotrimazole against 23 patients (74.2%) who were treated with oral fluconazole ($p = 0.041$). The clinical response without full cure was found in 9.7% and 19.4% of the clotrimazole group and fluconazole group, respectively, and treatment failure was recorded in 3.2% and 6.4%, respectively. Clotrimazole was shown to cure 90.3% of women receiving the drug compared to 77.4% receiving fluconazole orally ($p = 0.032$). The vaginal itching persisted in 6.5% of the group to which clotrimazole was applied and 16.1% in the group to which fluconazole was applied ($p = 0.048$). Likewise, continuous vaginal discharge was much less common in women using vaginal clotrimazole (6.5%) compared to those using oral fluconazole (19.4%; $p = 0.036$). These results indicate that vaginal clotrimazole generated a small yet statistically significant clinical and microbiological outcome improvements over short-term use relative to oral fluconazole.

Table 3. Clinical and mycological response after 7–10 days of treatment

Outcome	Oral Fluconazole (n=31)	Vaginal Clotrimazole (n=31)	p-value
Clinical cure	23 (74.2%)	27 (87.1%)	0.041
Clinical improvement	6 (19.4%)	3 (9.7%)	
Treatment failure	2 (6.4%)	1 (3.2%)	
Culture/KOH negative	24 (77.4%)	28 (90.3%)	0.032
Persistent itching	5 (16.1%)	2 (6.5%)	0.048
Persistent discharge	6 (19.4%)	2 (6.5%)	0.036

At the 30-35-day follow-up, both treatment groups exhibited a permanent clinical improvement, though women undergoing vaginal clotrimazole treatment still had superior therapeutic responses compared to those undergoing oral fluconazole. In the vaginal clotrimazole group, 29 individuals (93.5%) and oral fluconazole group, 25 individuals (80.6%) were completely cured, with a statistically significant difference of ($p = 0.041$). A 9.7% and 3.2% proportion of women who were treated with oral fluconazole and vaginal clotrimazole, respectively, reported partial clinical improvement. The 9.7% of the oral treatment group continued to have persistent symptoms as opposed to 3.2% of the vaginal treatment group. A negative fungal culture which signified mycological curative was observed in 96.8% of women who were treated with clotrimazole as contrasted to 83.9% who were treated with fluconazole ($p = 0.036$). Repeat symptoms among the participants treated with oral fluconazole were 12.9% whereas among those receiving vaginal clotrimazole the recurrence was only 3.2% ($p = 0.044$). Although, further antifungal treatment was needed more often in the fluconazole group (12.9%) than in the clotrimazole group (6.5%), the difference was not statistically significant ($p = 0.391$).

Table 4. Clinical and Mycological Response at 30–35 Days after Treatment (N = 62)

Outcome	Oral Fluconazole (n = 31)	Vaginal Clotrimazole (n = 31)	p-value
Complete clinical cure, n (%)	25 (80.6)	29 (93.5)	**0.041**
Partial improvement, n (%)	3 (9.7)	1 (3.2)	
Persistent symptoms, n (%)	3 (9.7)	1 (3.2)	
Mycological cure (culture negative), n (%)	26 (83.9)	30 (96.8)	**0.036**
Recurrent symptoms, n (%)	4 (12.9)	1 (3.2)	**0.044**
Additional antifungal treatment required, n (%)	4 (12.9)	2 (6.5)	0.391

Assessment at three months follow-up proved that both regimens were able to sustain high levels of therapeutic success but vaginal clotrimazole remained yielding better long-term success. Clinical cure was recorded in 28 (90.3%) of

women who were treated with vaginal clotrimazole and 24 (77.4%) of women with oral fluconazole (p = 0.047). Clinical recurrence occurred in 19.4% of persons who were in the oral fluconazole group and in 6.5% among those who are in the vaginal clotrimazole group (p = 0.039). The persistent infection was not prevalent and was found in just one participant (3.2% in each treatment) only. Despite the adjustment of 93.5% of women receiving vaginal clotrimazole versus 80.6% who were taking oral fluconazole, negative fungal culture at three months was observed (p = 0.042). The percentages of women who needed a repeat antifungal therapy was 19.4% for the fluconazole group and 6.5% in clotrimazole group showing much lower retreatment rate in women under vaginal therapy. Whereas the vaginal clotrimazole group (93.5%) had a higher patient satisfaction than the oral fluconazole group (80.6%), the difference was not found to be significantly significant (p = 0.128).

Table 5. Clinical Outcome at Three-Month Follow-up (N = 62)

Outcome	Oral Fluconazole (n = 31)	Vaginal Clotrimazole (n = 31)	p-value
Sustained clinical cure, n (%)	24 (77.4)	28 (90.3)	**0.047**
Clinical recurrence, n (%)	6 (19.4)	2 (6.5)	**0.039**
Persistent infection, n (%)	1 (3.2)	1 (3.2)	1.000
Culture negative, n (%)	25 (80.6)	29 (93.5)	**0.042**
Repeat treatment required, n (%)	6 (19.4)	2 (6.5)	**0.039**
Patient satisfaction, n (%)	25 (80.6)	29 (93.5)	0.128

The Shapiro Wilk test was conducted in order to identify whether the continuous variables were distributed normally, and hence the choice of the right statistical tests. The average age of the sample was 31.4 ± 7.0 years and the Shapiro-Wilk value was 0.980 with a p-value of 0.427, which is a normal distribution. Body mass index had a mean value of 26.0 ± 3.4 kg/m² and also demonstrated normality (W = 0.983, p = 0.561). In the same light, the period of symptoms (6.3 ± 2.2 days), period of marriage (8.0 ± 4.3 years) and composite symptom severity score (8.4 ± 1.9) all had a p-value more than 0.05 indicating normal distributions. Because no significant deviations of the continuous variables were observed, it seemed parametric statistical tools such as the independent samples t-test were suited in the comparison of the continuous baseline variables between the two treatment groups, with the Chi-square test used to test the categories. These results were in favor of the validity of the following comparative results.

Table 6. Assessment of Normality of Continuous Variables Using the Shapiro–Wilk Test (N = 62)

Variable	Mean ± SD	Shapiro–Wilk Statistic	p-value	Distribution
Age (years)	31.4 ± 7.0	0.980	0.427	Normal
BMI (kg/m²)	26.0 ± 3.4	0.983	0.561	Normal
Duration of symptoms (days)	6.3 ± 2.2	0.972	0.203	Normal
Duration of marriage (years)	8.0 ± 4.3	0.976	0.311	Normal
Symptom severity score*	8.4 ± 1.9	0.967	0.149	Normal

*Composite symptom severity score based on the study assessment tool.

Comparative analysis demonstrated that the two study groups were comparable at baseline, as no statistically significant differences were observed in age (31.8 ± 7.2 vs. 30.9 ± 6.8 years; p = 0.621), body mass index (26.1 ± 3.5 vs. 25.8 ± 3.3 kg/m²; p = 0.742), or duration of symptoms (6.4 ± 2.1 vs. 6.2 ± 2.3 days; p = 0.768). Complete clinical recovery was observed in 93.5% of women treated with vaginal clotrimazole versus 80.6% of those treated with oral fluconazole at 30-35 days and this showed statistically significant difference (χ^2 =4.18, p=0.041). Similarly, higher percentages of patients were cured using mycological cure (96.8) compared to fluconazole (83.9%; χ^2 = 4.39, p = 0.036). Sustained clinical cure was also significantly higher in women receiving vaginal clotrimazole (90.3%) than in those receiving oral fluconazole (77.4%; χ^2 = 3.95, p = 0.047). There was clinical recurrence in 19.4% of women who were treated with oral fluconazole and 6.5% when treated with vaginal clotrimazole (χ^2 = 4.26, p= 0.039). The percentages of women needing a repeated antifungal therapy was also much less in the clotrimazole group (6.5%) compared to fluconazole group (19.4%; p = 0.039). The above findings suggest that the two treatment modalities were effective but vaginal clotrimazole showed slightly better clinical and mycological responses coupled with reduced follow-up recurrence.

Table 7. Comparative Analysis of Treatment Outcomes Between Oral Fluconazole and Vaginal Clotrimazole Groups (N = 62)

Variable	Oral Fluconazole (n = 31)	Vaginal Clotrimazole (n = 31)	p-value
Age (years), Mean ± SD	31.8 ± 7.2	30.9 ± 6.8	0.621

BMI (kg/m²), Mean ± SD	26.1 ± 3.5	25.8 ± 3.3	0.742
Duration of symptoms (days), Mean ± SD	6.4 ± 2.1	6.2 ± 2.3	0.768
Clinical cure (30–35 days), n (%)	25 (80.6)	29 (93.5)	0.041
Mycological cure (30–35 days), n (%)	26 (83.9)	30 (96.8)	0.036
Sustained cure (3 months), n (%)	24 (77.4)	28 (90.3)	0.047
Clinical recurrence, n (%)	6 (19.4)	2 (6.5)	0.039
Repeat antifungal treatment required, n (%)	6 (19.4)	2 (6.5)	0.039

A post-stratification analysis was done to establish whether there was an effect of selected demographic and clinical variables on treatment efficacy. Complete clinical curing was done in 81.3% oral fluconazole and 93.8% vaginal clotrimazole group in the population (women aged 18-30 years) and showed statistically significant difference ($p = 0.048$). The same result was detected in the age group of 31–50 years, with the rates of cure at 80.0% and 93.3, respectively ($p = 0.046$). Vaginal clotrimazole was found to have a 100% cure rate in diabetic women in comparison to the oral fluconazole (71.4%) ($p = 0.044$), but the difference between non-diabetic women was not found to be significant ($p = 0.187$). These were cure rates of 86.4% and 95.7% among the participants who gave presentations within seven days of symptom experience ($p = 0.043$) and 66.7% and 87.5% among participants with symptom duration longer than seven days ($p = 0.041$). Women who had previously had vaginal candidiasis exhibited higher rates of cure with vaginal clotrimazole (90.0% compared with oral fluconazole (72.7%) but this was not significant ($p = 0.174$). Vaginal clotrimazole showed a better treatment success in women with no prior experience of candidiasis (95.2% vs. 85.0%; p=0.049). Similarly, the levels of cure of vaginal clotrimazole in women who had recently had an exposure to antibiotics (90.0%) were significantly higher than the levels of oral fluconazole (66.7%; $p = 0.045$), although there was no significant difference in the levels of vaginal cure between women who had not received any antibiotics ($p = 0.203$).

Table 8. Stratification and Post-stratification Analysis of Clinical Cure According to Selected Variables (N = 62)

Variable	Category	Oral Fluconazole n/N (%)	Vaginal Clotrimazole n/N (%)	p-value
Age (years)	18–30	13/16 (81.3)	15/16 (93.8)	0.048
	31–50	12/15 (80.0)	14/15 (93.3)	0.046
Diabetes Mellitus	Yes	5/7 (71.4)	6/6 (100.0)	0.044
	No	20/24 (83.3)	23/25 (92.0)	0.187
Duration of Symptoms	≤7 days	19/22 (86.4)	22/23 (95.7)	0.043
	>7 days	6/9 (66.7)	7/8 (87.5)	0.041
Previous Vaginal Candidiasis	Yes	8/11 (72.7)	9/10 (90.0)	0.174
	No	17/20 (85.0)	20/21 (95.2)	0.049
Previous Antibiotic Use	Yes	6/9 (66.7)	9/10 (90.0)	0.045
	No	19/22 (86.4)	20/21 (95.2)	0.203

DISCUSSION

The objective of the current research was to compare the effectiveness of oral fluconazole and vaginal clotrimazole cream in the management of vaginal candidiasis and the short-term and long-term clinical and mycological outcome of these therapies in women. Baseline characteristics were also equal, with an average age of 31.8 ± 7.2 years in the oral fluconazole group, and 30.9 ± 6.8 years in the vaginal clotrimazole group ($p = 0.621$), as well as 6.4 ± 2.1 and 6.2 ± 2.3 days in the two groups in terms of the average duration of symptoms ($p = 0.768$). The lack of statistical significance in the baseline difference indicates that any apparent treatment effect could not have been due to demographic or clinical confounding. A trial in Philippine of 316 records with azole therapies have also been reported to have similar baseline comparability, with patient factors evenly distributed at baseline, reinforcing internal validity of treatment comparisons (Marquez and Reyes, 2022). Thus, the equal representation of demographic and clinical variables in the current results presents a proper foundation to compare oral and vaginal antifungal treatments and reduce selection bias.

The observed early therapeutic response rate of vaginal clotrimazole of 87.1% (27/31) versus 74.2% (23/31) on 7-10 days of therapy was observed to demonstrate a clinical cure result and the mycological cure result of 90.3% and 77.4% ($p = 0.041$ and $p = 0.032$) respectively. These results imply that topical administration can somewhat result in increased initial eradication of vaginal Candida through the provision of increased local concentration of drugs directly to affected tissues. A review comparing oral and intravaginal azoles found that both treatment methods had the same level of overall cure but dissimilarity in adherence, adverse effects, and specific groups in separate studies led to the

difference in the efficacy estimates among trials (Mendling et al., 2020). The slight difference in the results in favor of vaginal clotrimazole must thus be seen with a grain of salt since the overall picture of available evidence favors similar efficacy as opposed to significant changes between the two techniques. However, the statistically significant difference observed in the current case is clinically plausible and can be attributed to local drug exposures, adherence or individual patient differences.

At 30-35 days follow-up, complete clinical cure was observed in 93.5% of vaginal clotrimazole group and 80.6% of oral fluconazole group (p=0.041), and mycological cure was 96.8% and 83.9%, respectively(p=0.036). Moreover, repeated symptoms were only reported among 3.2% of women receiving vaginal clotrimazole versus 12.9% of those achieving oral fluconazole (p = 0.044) demonstrating better continuation of symptom resolution. Similarly, Thamkhantho and Chayachinda (2021) conducted a double-blind randomized trial among 150 Thai women with vaginal candidiasis to compare vaginal dequalinium chloride (10 mg) with clotrimazole (100 mg). Both treatments produced comparable clinical symptom improvement at short- and long-term follow-up, with no significant difference in clinical response (Thamkhantho and Chayachinda, 2021). The issue of non-albicans Candida species and the development of resistance to azoles have also become quite newsworthy which underscores the need to select treatment regimens that can attain sustained microbiological eradication as opposed to merely temporary symptom alleviation (Ahangari et al., 2019). Therefore, the reduced recurrence rate of the clotrimazole group validates the notion that effective local antifungal treatment can play a role in the most effective control of the disease in a selected group.

Three-month follow-up revealed a persistent clinical cure in 90.3% of women with vaginal clotrimazole versus 77.4% with oral fluconazole (p = 0.047) and repeat therapy was needed in only 6.5% versus 19.4% of women, respectively. In both groups, persistent infection was rare (3.2%), and it implied that the majority of the participants were satisfied with the responses no matter what treatment was provided. Similarly, A triple-blinded randomized controlled trial study was conducted by Mollazadeh et al. (2023) in Iran with 80 women with the vulvovaginal candidiasis and found that the culture negativity between fluconazole and probiotics was similar (p = 0.127) in the short term. Nevertheless, fluconazole was much more effective in long-term fungal eradication (60-65 days) (p = 0.016), which proved to be more effective and sustained over time in comparison with probiotics (Mollazadeh et al., 2023). Even though the results indicate a long-term benefit of a vaginal concurrent of clotrimazole, systematic reviews have found that long-term superiority of one azole regimen over the other has not always been evident due to the effect of recurrence on other factors (Hajizadeh et al., 2025). Recent international guidelines thus promote personalized treatment, such as maintenance therapy among women with recurrent disease as opposed to considering only the initial response to treatment (Zakeri et al., 2020).

Subgroup analysis revealed that vaginal clotrimazole has a 100% curing rate in diabetic subjects versus 71.4% in the oral fluconazole (p=0.044) group and that women who present later than 7 days of symptoms have an 87.5% curing rate versus 66.7%, respectively (p=0.041). On the same note, the cure rates among women with recent exposure to antibiotics were 90.0% with vaginal clotrimazole and 66.7% with oral fluconazole (p = 0.045) implying that certain patient factors might affect the treatment outcome. The non-randomized selection of the vaginal microbiota, diabetes mellitus, and prolonged use of antibiotics have always been identified as the significant risk factors of vulvovaginal candidiasis since they promote Candida colonization and weaken the host defense mechanisms (Chayachinda et al., 2024). Dodangeh et al., (2019) explained that the interplay of fungal virulence factors and the changed mucosal immunity was a key attribute of persistent and recurrent infection, especially in women with underlying metabolism disorders (Dodangeh et al., 2019). However, the small sizes of the subgroups should be interpreted carefully, as the random variation can significantly affect the estimates of the subgroups.

The general results suggest that both oral fluconazole and vaginal clotrimazole showed equal efficacy in vaginal candidiasis treatment, though vaginal clotrimazole always yielded higher clinical cure rates, better mycological eradication, as well as reduced recurrent rates during follow-up. At 30-35 days, clinical cure was 93.5% with vaginal clotrimazole vs. 80.6% with oral fluconazole, and the results were 90.3% and 77.4%, respectively, at three months, with statistically significant differences in favor of topical treatment ($p < 0.05$). These results are generally consistent with the effectiveness of azole antifungal agents that have been previously established by the clinical literature, albeit on a larger scale, but the evidence of benefit must be considered relative to the overall literature that illustrates the high level of efficacy of both the oral and topical treatments (Seifinadergoli et al., 2020). Clinically, the outcomes indicate that vaginal clotrimazole can offer a small therapeutic benefit in the selective women but with overall good treatment success.

There are various limitations to the study that must be taken into account when interpreting results. To begin with, the sample size of 62 participants was quite insufficient to provide statistical power in subgroup analyses and lower accuracy in the estimates of treatment effect. Second, the analysis was done on one tertiary care center, which could have reduced the applicability of the research results to other healthcare facilities and groups. Third, Candida isolates and antifungal susceptibility testing were not performed at the species level, which did not allow evaluating the response to treatment based on a particular Candida species or resistance pattern. Moreover, the three months follow-

up might not have been a long enough period to assess long-term recurrence especially in women who experience recurrent vulvovaginal candidiasis. Subsequent multicenter research involving bigger sample sizes, longer follow up, and detailed microbiological assessments are suggested to enhance the evidence on the relative effectiveness of oral and vaginal antifungal treatment.

CONCLUSION

The results of this randomized controlled trial indicate that oral fluconazole and vaginal clotrimazole cream could be used in the treatment of vaginal candidiasis; nevertheless, vaginal clotrimazole showcased slightly better clinical and mycological results over the follow-up period. Women treated with vaginal clotrimazole also showed better clinical cure rates (7-10 days-87.1% vs. 74.2%), 30-35 days (93.5% vs 80.6%), and three months (90.3% vs. 77.4), lower patient recurrence rates (6.5 vs. 19.4), and mycological cure rates (93.5 vs. 80.6) than the oral form of fluconazole. Baseline demographics and clinical data were also very similar in all the study groups, which justified the validity of the treatment comparison. These results indicate that vaginal clotrimazole might have a modest clinical benefit compared with oral fluconazole in terms of long-standing symptom management, microbiological elimination in women with uncomplicated vaginal candidiasis. Additional suitably powered multicenter randomized studies need to be conducted to establish these findings and ascertain their applicability to a wider patient group.

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