Oral versus topical antifungal treatment for recurrent vulvovaginal candidiasis

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Objective
To evaluate the effect of using oral versus topical antimycotic preparations in treatment of recurrent vulvovaginal candidiasis.

Background
Vaginal candidiasis is a common disease in women during their lifetime. Although several antifungal drugs are routinely used for treatment, recurrent vaginal candidiasis is a challenge for patients and gynecologists.

Patients and methods
This was a randomized control trial that included 88 cases complaining of recurrent vaginal candidiasis, with occurrence ranging from 4 to 8 episodes/year, with confirmed clinical and mycological diagnosis of vaginal candidiasis. Patients were divided into two groups by randomized number sequence: group A received oral fluconazole and group B received local clotrimazole vaginal tablets. This trial was conducted at the Department of Obstetrics and Gynecology, Zawyet Aal-Naoora Hospital, in Menoufia from March 2017 to June 2018.

Results
This study revealed a total clinical cure rate of 81% for fluconazole group and 76.1% for clotrimazole group. Total mycological cure rate was 80.5% for group A and 77.3% for group B. There was no statistically significant difference regarding clinical or mycological cure rates in all visits between the two groups. The most frequent adverse effect in group A was nausea and for group B was vaginal burning sensation.

Conclusion
Response to treatment of recurrent vulvovaginal candidiasis was similar among fluconazole and long-term use of clotrimazole vaginal tablets.

Keywords:
candidiasis, oral, recurrent, topical, vulvovaginal

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Introduction

Vulvovaginitis is the inflammation of the vagina and the vulva. Candidal vaginal infections are predominantly caused by strains of *Candida albicans* (>90%) [1].

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, the Candida multiplies, and symptoms of candidiasis like nonspecific vulvovaginal pruritus, soreness, thick vaginal discharge, vulvar pain, and dyspareunia appear [2].

Recurrent Vulvovaginal candidiasis (VVC) is defined as four or more episodes of VVC in 1 year and affects ~ 5% of women. Although it affects only a minority of patients, it accounts for a large proportion of clinic time. This is because of management difficulties related to a higher incidence of resistant atypical Candida species. Candida species are a part of the commensal flora in 10–20% of asymptomatic healthy women and cause no long-term sequelae [3].

Recurrent VVC may have severe physical and psychological effects on women and their partners [4].

For recurrent symptoms, a high vaginal swab for yeast culture should be sent to confirm the diagnosis, and underlying host problems excluded. However, it is important to remember that owing to the proportion of asymptomatic women who are colonized with Candida, positive culture alone does not indicate that it is the identified yeasts causing vaginal symptoms. An alternative diagnosis as lichen sclerosis or seborrheic dermatitis should always be considered in women whose symptoms fail to improve with antifungals [5].

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Most patients with recurrent candidal infections require long-term treatment with suppressive therapy. Both topical and oral preparations are available, with oral regimens perhaps being more acceptable with regard to ease of administration and avoidance of potentially messy creams and suppositories. Several regimens have achieved success in reducing the number of symptomatic episodes of vaginitis [6].

So, this study aimed to assess the effect of oral versus topical antimycotic preparations in treatment of recurrent vulvovaginal candidiasis.

Patients and methods

This randomized control trial was conducted at the Department of Obstetrics and Gynecology, Zawyet Aal-Naoora Hospital in Menoufia from March 2017 to June 2018. The approval of Menoufia Faculty of Medicine and Zawyet Aal-Naoora Hospital institutional review boards was obtained before the study. The study participants were women attending outpatient clinic with a diagnosis of recurrent vulvovaginal candidiasis (four or more episodes of vulvovaginal candidiasis per year).

The sample size was calculated according to the study by Witt *et al.* [7]; with a study power of 80% at alpha error of 5%, the required total sample size is 88 women. The participants were divided into two groups by random number sequence: group A included 42 cases that received oral fluconazole and group B included 46 cases that received local clotrimazole vaginal tablet.

The study protocol was explained to the patients, and all patients provided an informed consent. Criteria of selected cases were all women who had at least four episodes of Candida vaginitis in the year before study inclusion and complained of symptoms of acute candida vaginitis, women between 18 and 50 years old, and abstaining from using any other vaginal products. However, patients excluded from the study were women with liver or endocrinal impairment, pregnant women, women who had used antifungal medication in the week before enrollment, and immunocompromised patients (patients who are on corticosteroid or chemotherapy or are known to have chronic debilitating diseases like chronic liver failure, diabetes mellitus, or HIV infection).

Before the treatment, each patient underwent an evaluation that included a standardized history: vaginal discharge, personal and family history, and detailed present history including vaginal discharge, its character, amount, and duration. Moreover, symptoms in their partners, contraceptive methods, together with previous treatments were evaluated too.

All patients underwent pelvic examination, direct microscopic examination of the discharge, and vaginal culture at their pretreatment assessment visit.

In direct microscopic examination, 10% KOH was added to the vaginal discharge then checked by microscopy to demonstrate blastoconidia and pseudohyphae. Then high vaginal swab for yeast culture was sent to confirm the diagnosis and underlying host problems excluded.

After establishing the diagnosis, the patients were randomly divided into two groups according to random number sequence generated from a random number table in a statistical textbook. The random number sequence was distributed into sequenced opaque enclosed envelopes, where each envelope contained a single assignment for either group A or group B.

Patients in group A (contained 42 cases) received initial oral fluconazole (Flucoral 150 mg; SEDICO pharmaceutical Co. found in 6 October city, Egypt, (every third day for a total of three doses: days 1, 3, and 7), and then a maintenance dose of 150 mg fluconazole every week was given for 6 weeks and then every 2 weeks for the remaining period of 3 months.

Patients in group B (contained 46 cases) received 100 mg clotrimazole vaginal tablets (Canesten V6; Bayer Pharmaceuticals Pvt Ltd, Bayer zydus pharma pvt.Ltd, Hiranandani Estate, thane (west)-400607) once daily at night for 14 days followed by twice weekly 100 mg of clotrimazole vaginal tablets for 3 months.

It should be mentioned that during the second visit, one patient of fluconazole group was excluded because of irregular visits. On the contrary, in clotrimazole group, two patients were excluded in the second visit: one of them because of irregular visits and the other because of local hypersensitivity to the drug.

After initial treatment, they were seen in the clinic fortnightly and then every month till end of maintenance treatment. An additional clinic visit was done 1 week after the end of maintenance treatment to check for relapsed cases of recurrent vulvovaginal candidiasis. In each clinic visit, specific symptoms and signs of vaginal candidiasis were assessed separately. Microscopic examination and culture of vaginal swabs were done at the end of maintenance treatment.

Statistical analysis

Data were collected, tabulated, and statistically analyzed using an IBM personal computer with Statistical Package of Social Science (SPSS), version 20 (2011; IBM Corporations, Armonk, New York, USA) and

Epi Info 2000 programs, where the following statistics were applied.

(1) Descriptive statistics: in which quantitative data were presented in the form of mean, SD, and range, and qualitative data were presented in the form numbers and percentages.
(2) Analytical statistics:
(a) χ^2 test was used to study the association between two qualitative variables, whereas Fisher's exact test for 2 × 2 tables when expected cell count of more than 25% of cases was less than 5
(b) Student's *t* test is a test used for comparison between two groups having quantitative parametric variables, whereas Mann–Whitney test is a test of significance used for comparison between two groups not normally distributed having quantitative variables
(c) Kaplan–Meier estimator curve is a nonparametric statistic used to estimate the survival function from lifetime data (Fig. 1).

Statistical significance was set as follows:

P value of more than 0.05 was considered not statistically significant. *P* value of less than or equal to 0.05 was considered statistically significant. *P* value of less than or equal to 0.001 was considered statistically highly significant.

Results

Mean age in group A was 32.5 ± 6.8 years and for group B was 30.5 ± 6.9 years (*P* = 0.18, >0.05). The mean parity was 2.5 ± 0.83 in group A and 2.3 ± 0.93 for group B and *P* = 0.14 (>0.05). There was no statistically significant difference between the two groups regarding age or parity. Fisher's exact test for education was 1.9 and *P* value was 0.36 (>0.05), and Fisher's exact test was 0.87 for contraception and *P* value was 0.89 (>0.05), with no statistically significant difference (Table 1).

Regarding mycological cure rate, group A showed a mycological cure rate of 80.5 and 77.3% in group B (*P* = 0.72, >0.05), so no statistically significance difference between the two groups was found (Table 2).

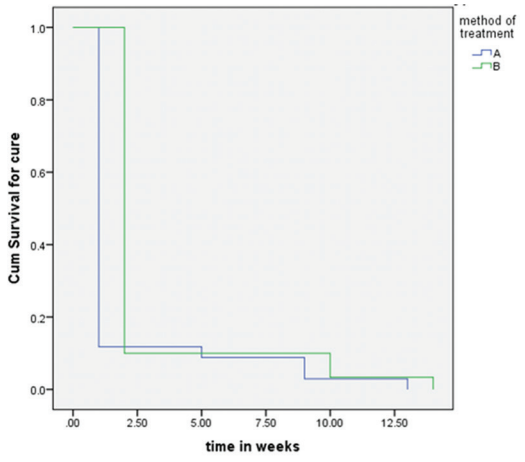
Regarding follow-up visits, for the first visit, the clinical cure rate in group A was 71.4% and in group B was 69.6%, with *P* value of 0.40 (>0.05). In the second visit, clinical cure rate was 73.8% in group A and 71.7% in group B, with *P* value of 0.99 (>0.05). In the third visit, cure rate was 78.6% in group A and 76.1% in group B, with *P* value of 0.72 (>0.05). In the fourth visit, the cure rate was 81% in group A and 76.1% in group B, with *P* value of 0.72 (>0.05). The fifth visit was for detection of relapse. There was no statistically significant difference in all visits between the two groups (Table 3).

Regarding adverse effects of two medication groups, nausea was observed in 7.1% of participant of group A versus 0% in group B. In addition, dizziness was seen in 2.4% in group A versus 0% in group B. Vaginal burning sensation was not observed in group A, whereas it resembled 10.9% in participants of group B (Table 4).

Regarding total clinical and mycological cure in the two treatment medications at the end of treatment course, clinical cure rate was 81% in group A and 76.1% in group B. Improvement rate was 11.9% in group A and 15.2% in group B. Failure rate was 7.1% in group A and 8.7% in group B. Mycological cure rate was 80.5% in group A and 77.3% in group B. The *P* value was 0.72(>0.05), so there is no statistically significance difference between the two groups (Table 5).

It is of value to mention that there was no statistically significant correlation between the type of contraception and the prevalence of vaginal candidal infection.

Figure 1



Survival function for cure in relation to treatment type/week. The figure shows two survival curves for the study of two medication regimens (a, oral), (b, local) which shows the cumulative cure rate along time by using Kaplan–Meier test. There was a statistically significance difference between the two curves. 95% confidence interval=1.703–3.110. P value=0.000.

Discussion

This study assessed the effect of fluconazole as a systemic antimycotic versus clotrimazole as a topical antimycotic for treatment of recurrent vaginal candidiasis, and it was

Table 1 Demographics of studied groups

Items	A (*n*=42) [*n* (%)]	B (*n*=46) [*n* (%)]	Test of significance (*P*)
Age			
Mean±SD	32.5±6.8	30.5±6.9	*t* test=1.3
Minimum-maximum	20-44	20-45	*P*=0.18 (>0.05)
Parity			
Mean±SD	2.5±0.83	2.3±0.93	Mann-Whitney=1.5
Minimum-maximum	1-4	1-4	*P*=0.14 (>0.05)
Education			
Illiterate	2 (4.8)	2 (4.3)	Fisher's exact=1.9
Middle education	30 (71.4)	27 (58.7)	*P*=0.36
Graduated	10 (23.8)	17 (37)	
Contraception type			
COC	19 (45.2)	23 (50)	Fisher's exact=0.87
Injection	14 (33.3)	12 (26.1)	
IUD	8 (19)	9 (19.6)	*P*=0.89
POP	1 (2.5)	2 (4.3)	

COC, combined oral contraceptive piles; IUD, intrauterine contraceptive devise; POP, progesterone only piles.

Table 2 Mycological cure rate after treatment

Items	A (*n*=41) [*n* (%)]	B (*n*=44) [*n* (%)]	Test of significance (*P*)
Microscopic examination			
Positive	8 (19.5)	10 (22.7)	χ^2=0.13
Negative	33 (80.5)	34 (77.3)	*P*=0.72 (>0.05)
Culture			
Positive	8 (19.5)	10 (22.7)	χ^2=0.13
Negative	33 (80.5)	34 (77.3)	*P*=0.72 (>0.05)

Table 3 Follow-up data in studied groups

Items	A (*n*=42) [*n* (%)]	B (*n*=46) [*n* (%)]	Test of significance (*P*)
First visit			
Clinical cure	30 (71.4)	22 (69.6)	Fisher's exact=2.1
Improved	8 (19)	10 (21.7)	*P*=0.402 (>0.05)
No progress	4 (9.6)	4 (8.7)	
Second visit			
Clinical cure	31 (73.8)	33 (71.7)	Fisher's exact=0.17
Improved	8 (19)	9 (19.6)	*P*=0.99 (>0.05)
No progress	3 (7.2)	4 (8.7)	
Third visit			
Clinical cure	33 (78.6)	35 (76.1)	Fisher's exact=0.78
Improved	6 (14.3)	8 (17.4)	*P*=0.72 (>0.05)
No progress	3 (7.1)	3 (6.5)	
Fourth visit			
Clinical cure	34 (81)	35 (76.1)	Fisher's exact=0.66
Improved	5 (11.9)	7 (15.2)	*P*=0.72 (>0.05)
Failure	3 (7.1)	4 (8.7)	
Fifth visit (relapse)			
Positive[a]	1 (2.4)	3 (6.8)	Fisher's exact=0.91
Negative	40 (97.6)	41 (93.2)	*P*=0.62 (>0.05)

[a]Positive microscopic and culture.

Table 4 Adverse effects of two medication groups

Items	A (*n*=42) [*n* (%)]	B (*n*=46) [*n* (%)]	Test of significance (*P*)
Nausea	3 (7.1)	0	Fisher's exact=3.4 *P*=0.11 (>0.05)
Dizziness	1 (2.4)	0	Fisher's exact=1.1 *P*=0.48 (>0.05)
Vaginal burning	0	5 (10.9)	Fisher's exact=4.8 *P*=0.035* (>0.05)

*Statistically significant value.

found that there was no statistically significant difference in clinical and mycological cure rate between two drugs. Our study results agreed with the study by Zhou *et al.* [8], which demonstrated that clotrimazole vaginal

Table 5 Total clinical and mycological cure in the two treatment medications at the end of treatment course

Items	A (*n*=42) [*n* (%)]	B (*n*=46) [*n* (%)]	Test of significance (*P*)
Clinical cure	34 (81)	35 (76.1)	
Improved	5 (11.9)	7 (15.2)	FE=0.66
Failure	3 (7.1)	4 (8.7)	*P*=0.72 (>0.05)
Mycological cure	33 (80.5)	34 (77.3)	

tablets were as effective as oral fluconazole 150 mg in the treatment of patients with severe vulvovaginal candidiasis and could be an appropriate treatment for this disorder.

The results of the present study correlate with that of Lírio *et al.* [9], who found that the different antifungals have similar efficacies, and both routes promote appropriate treatment.

On the contrary, our results stood against Qin *et al.* [10], who performed a network meta-analysis (Bayesian approach) of the published studies on the effectiveness of antifungal drugs in the treatment of vulvovaginal candidiasis (up to April 2018), which were retrieved from PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov, and reported that among the antifungal drugs fluconazole appeared to have superiority, being the best drug for the treatment of vulvovaginal candidiasis.

Moreover, the results of our study do not correlate with that of Sekhavat *et al.* [11], which found that oral fluconazole is more effective than topical clotrimazole in treatment of vulvovaginal candidiasis and can be more effective in reduction of the relapse rate of the disease rather than clotrimazole.

In this study, no baseline characteristics (age, parity, education, and method of contraception) appeared to be significant predictors of vaginal candidiasis. This comes in agreement with Fardyazar *et al.* [12], who found these demographic characteristics of patients were of no significant difference between the studied groups. However, our results disagree with Yusuf *et al.* [13], who found that there was a significant relationship (P = 0.002) between the type of contraception used and the prevalence of vaginal infections by Candida species, with the highest prevalence of vaginal candidiasis found in oral contraceptive pill users followed by injectables and IUCD users. They explained such results claiming that contraceptions containing estrogen and progesterone increase glycogen in the vagina, which is converted into lactic acid by lactobacilli. Thus, overgrowth of Candida species occurs owing to decreased pH.

Conclusion

Our results show that oral fluconazole 150 mg was as effective as clotrimazole vaginal tablets in treatment of recurrent vaginal candidiasis.

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Conflicts of interest

There are no conflicts of interest.

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