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Comparison of the effect of miconazole and clotrimazole in the treatment of vulvovaginal candidiasis among women seen in a tertiary medical center from 2016 to 2020

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Abstract:

BACKGROUND: Vulvovaginal Candidiasis (VVC) is one of the frequent infections of the female genital tract and is the second most common cause of vaginal infections after bacterial vaginosis. According to the Centers for Disease Control and Prevention, azoles are the first-line treatment for VVC. Among the azoles available in the Philippines, only miconazole and clotrimazole are recommended for both pregnant and non-pregnant women.

OBJECTIVE: Compare the effect of miconazole versus clotrimazole in the treatment of vulvovaginal candidiasis among patients seen at the out-patient department in a tertiary hospital

MATERIALS AND METHODS: This involved review of the records of patients diagnosed with VVC in a tertiary medical center from 2016 to 2020. All records of women, pregnant and non-pregnant, wherein single-dose 1200 mg miconazole or 6-day 100 mg clotrimazole given vaginally were included.

RESULTS: Eleven out of the 316 records (3.46%) remained symptomatic after treatment, about 18.1% (2/161) from those who used miconazole and 81.8% (9/155) from those treated with clotrimazole (p 0.027). In terms of failure rate, for miconazole it was 1.2% (2/161), whereas for clotrimazole it was 5.8% (9/155). None of the charts were found to have recorded adverse reaction to the given treatment.

CONCLUSION: Single-dose miconazole intravaginal regimen has a higher clinical cure rate than the 6-day clotrimazole intravaginal treatment. Thereby, single-dose intravaginal miconazole has the potential to improve patient compliance and treatment outcome at a lower cost.

Keywords:

Azole antifungals, clotrimazole, miconazole, vaginitis, vulvovaginal candidiasis

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Introduction

Vaginitis is one of the most common reasons why women seek consult from obstetricians and gynecologists. Vulvovaginal candidiasis (VVC) is one of the frequent infections of the female genital tract and is the second most common cause of vaginal infections after bacterial vaginosis. More than 90% of cases are caused by *Candida albicans*.[1] It affects 75% of women at least once in their lifetime, with 50% developing a second episode. About 5% of women will have recurrent vulvovaginal candidiasis, defined as four or more episodes of such infection within a year.[2]

VVC is usually diagnosed based on clinical signs and symptoms or microscopic examination or a combination of both. With regard to treatment of VVC, based on

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the Centers for Disease Control and Prevention (CDC) recommendation, azoles are considered as the first-line drug class. It is further categorized as uncomplicated VVC, which involves a short course of azole antifungals and complicated VVC, wherein azoles are given for a longer duration [Appendix A]. However, due to poor compliance, increasing recurrence rates, and emergence of drug-resistant *Candida* strains worldwide, further studies are being done to determine which among the recommended drugs is the ideal regimen.

The azoles that are available in the Philippines include clotrimazole, miconazole, and fluconazole. Those that are recommended for both pregnant and nonpregnant women are miconazole and clotrimazole. However, it is only miconazole that can be given as a single dose. Hence, in terms of management, single-dosing regimen may translate to better compliance than multiple dosing regimen. This study, therefore, would like to compare the effect of the 6-day 100 mg clotrimazole suppository versus the single-dose 1200 mg miconazole suppository in the treatment of VVC.

Review of related literature

The CDC classifies vuvlvovaginal candidiasis into two: uncomplicated and complicated VVC.[3] Uncomplicated VVC includes infections caused by *C. albicans*, periodic VVC, mild-to-moderate VVC, and those affecting a nonimmunocompromised host. On the other hand, complicated VVC encompasses infections caused by non-*C. albicans*, recurrent vuvlvovaginal candidiasis, severe vuvlvovaginal candidiasis, or those affecting immunocompromised hosts.

Signs and symptoms include the presence of a thick, white vaginal discharge in association with vulvar itching, burning with or without dysuria. Most women with signs and symptoms of VVC can be diagnosed with the use of saline wet mount, 10% potassium hydroxide (KOH) test, or Gram stain of vaginal discharge. In cases with VVC, the smear demonstrates hyphae or pseudohyphae of *Candida* species, or a vaginal culture test shows a *Candida* species.[4]

Age appears to be an important risk factor in the overall incidence of VVC because episodes occur mostly during the reproductive years.[4] Other factors such as pregnancy, diabetes mellitus, immunosuppression, use of artificial contraceptives (pills, intrauterine devices, and diaphragms), poor perineal hygiene, and vaginal douching are also contributory for the development of VVC. Moreover, compliance to treatment may also be a contributing factor for recurrence. Hence, if treatment will be given as single course with associated improvement in symptomatology and eradication of the organism, issues on compliance with the institution of appropriate treatment will be addressed accordingly.

Azole antifungals such as miconazole and clotrimazole work by inhibiting the cytochrome P450-dependent enzyme lanosterol 14-alpha-demethylase that is necessary for the conversion of lanosterol to ergosterol, which is a vital component of the cellular membrane of *Candida* species. Their effectiveness in treating VVC has long been a topic in researches.

A computer-based literature search was done to find relevant articles for the study. The search terms vulvovaginal candidiasis, miconazole, and clotrimazole, according to rank, were used. Union and intersection of the search terms were done. Combination of search terms using vulvovaginal candidiasis, miconazole, and clotrimazole yielded 71 articles; among the 71 articles, 10 were relevant to the study. Addition of pregnancy to the combination of search terms yielded 12 articles, 6 of which are relevant to our study. Hand search was also done thru the Philippine Obstetrical and Gynecological Society database, which yielded no article.

The single-dose miconazole vaginal suppository consists of 1200 mg of miconazole nitrate along with other inactive ingredients. According to Barnhart, it is proven to exhibit fungistatic and fungicidal activity against *Candida* species. In the same year, the author also conducted a multicenter randomized controlled trial involving 573 women with VVC. Patients were given a single-dose 1200 mg miconazole vaginal ovules either in daytime or bedtime.[5] Clinical cure rates were 74.5% and 73.6% in the daytime and bedtime groups, respectively. The study concluded that the efficacy of daytime and bedtime administration of single-dose miconazole was the same.

In a prospective randomized case–control study conducted by Fan *et al.*, a total of 577 cases of VVC were treated with either 1200 mg miconazole vaginal suppository or 150 mg fluconazole tablet and were followed up after treatment.[6] After 7 days of treatment with miconazole, the clinical cure rate was 75.9%, whereas the mycological cure rate was 84%. The study concluded that therapy with intravaginal miconazole is as effective as fluconazole in treating VVC.

Two randomized, single-blind, multicenter, controlled trials involving 558 patients with VVC were conducted by Upmalis *et al*. in 2000.[7] They tried to determine the efficacy of single-dose 1200 mg miconazole vaginal ovule versus seven consecutive doses of miconazole 2% vaginal cream. In both the studies, patients were assigned to two treatment groups and were followed up 14–18 days after the initiation of treatment. For the first study, clinical cure rate was 93% for the miconazole ovule and 97% for the miconazole cream. Whereas, for the second study,

clinical cure rate was 88% for the miconazole ovule and 84% for the miconazole cream. They concluded that single-dose miconazole ovule is as efficacious as 7-day miconazole cream in the treatment of VVC.

Clotrimazole is a broad-spectrum antimycotic drug that is also widely used in treating VVC. The intravaginal forms are either 100, 200, or 500 mg, given daily for 6, 3, or 1 day (s), respectively.[8]

In an open, parallel randomized study conducted by Zhou *et al*., there were 240 women with VVC who were either given two doses of 500 mg clotrimazole intravaginally or two doses of 150 mg fluconazole orally.[9] After 7–14 days, the clinical cure rate in the clotrimazole group was 88.7%, whereas it was 89.1% in the fluconazole group. The researchers concluded that two doses of 500 mg clotrimazole given intravaginally were as effective as two doses of 150 mg oral fluconazole in treating VVC.

Sekhavat *et al*. conducted a prospective study by involving 142 patients with acute VVC.[10] Participants were either given oral single-dose fluconazole tablet or 200 mg clotrimazole intravaginal tablet for 6 days. Patients were followed up 7 days and 1 month posttreatment. After 7 days, 61 (84.7%) patients were cured clinically and 58 (80.5%) patients mycologically in the fluconazole group and 60 (83.3%) patients were cured clinically and 49 (70%) patients mycologically in the clotrimazole group. The authors concluded that both the treatment regimens have comparable clinical efficacy.

Attempts to compare the efficacy of miconazole and clotrimazole can be traced back in the 1970s. Eliot *et al*. conducted a multicenter randomized controlled trial comparing the efficacy of nystatin, clotrimazole, and miconazole in the treatment of 166 women with VVC.[11] Patients were given 100,000 units nystatin pessaries nightly for 14 days, 100 mg clotrimazole vaginal tablets nightly for 6 nights, 100 mg miconazole pessaries nightly for 14 days, or 100 mg miconazole pessaries in the morning and in the evening for 7 nights. Mycological cure rate 4 weeks posttreatment was 93% for nystatin, 88% for clotrimazole, 91% for 14-day miconazole, and 86% for the 7-day miconazole group. The trial concluded that cure rates were comparable for the four treatment groups. However, the relapse rate was higher for those in the clotrimazole and nystatin groups at 50% and 28.3%, respectively, compared with the 14-day miconazole (2.4%) and 7-day miconazole groups (3.4%).

Balsdon conducted a randomized controlled trial comparing the use of twice daily 100 mg miconazole-coated tampons for 5 days and 6-day course of clotrimazole intravaginal tablets once a day in the treatment of VVC in 100 women.[12] Patients were followed up 7 days after treatment, where clinical cure is found out to be 98% for the clotrimazole and 99% for the miconazole group. The study concluded that both the treatment regimens were equally effective in treating VVC. However, the miconazole-coated tampons were more acceptable to patients because of the lesser duration of treatment and ease of use, as there was no leakage of medications from the vagina.

Common adverse reactions with the use of azole antifungals include vomiting, loose stools, abdominal pain, paresthesia, headache, dizziness, fever, chills, vaginal burning, stinging, itching, and irritation.[3] More of these systemic adverse effects are likely to be reported with oral compared with intravaginal antifungal administration.[4] In the same study by Fan *et al*. mentioned earlier, adverse effect rate of miconazole was found to be at 0.9%.[6] The adverse effects reported were vulvar burning, pain, edema, and itching. Moreover, reports on the adverse effects of clotrimazole were mainly local and similar to that of miconazole. In the previously mentioned study of Zhou *et al*., 16 out of 115 patients who received vaginal clotrimazole experienced adverse events, most of which include vulvovaginal pruritus, burning, irritation, and bleeding.[9]

Topical antifungals such as miconazole and clotrimazole are classified as Pregnancy Category C [Appendix B]. They have minimal absorption, hence can be given at any time during pregnancy.[13] A retrospective cohort study by Rotem *et al*. involving 2306 pregnancies evaluated the risk for major malformations following first‐trimester exposure to vaginal azoles (clotrimazole and miconazole).[14] Crude and adjusted relative risks for major congenital malformations and for specific malformations according to organ systems were calculated using a multivariate negative binomial regression. They found no significant association between first-trimester exposure to clotrimazole nor miconazole vaginal tablets and total major malformations or specific malformations according to organ systems.

Daniel *et al*. also conducted a historical cohort study involving 3246 pregnancies with exposure to vaginal antimycotics before 20 weeks age of gestation for the treatment of vulvovaginal candidiasis.[15] Clotrimazole was administered to 2712 women, whereas 633 women received miconazole. A computerized database of medication dispensation was linked with 2 computerized databases containing information on births and spontaneous abortions. Time-varying Cox regression models were constructed adjusting for mother's age, diabetes mellitus, hypothyroidism, obesity, hypercoagulable or inflammatory conditions, recurrent miscarriages, intrauterine contraceptive device, ethnicity,

tobacco use, and the year of admission. They concluded that exposure to vaginal antimycotics such as miconazole and clotrimazole was not associated with spontaneous abortion (adjusted hazard ratio = 1.34; 95% confidence interval: 0.99–1.8).

Based on the evidence available, both miconazole and clotrimazole are efficacious in the treatment of VVC. However, in terms of studies comparing the efficacy of these two antifungals, they were found to be outdated (1979–1981). Even so, there are still no studies based on computerized literature search comparing the effect of the single-dose miconazole regimen with azoles that can be given regardless of pregnancy status like clotrimazole. A meta-analysis conducted by Qin *et al*. reviewed 41 randomized controlled trials on the efficacy of the different antifungal drugs used in the treatment of VVC.[16] None of them compared the use of single-dose miconazole with clotrimazole. Hence, in our study, we would like to assess the effect of the single-dose 1200 mg miconazole compared with 6-day 100 mg clotrimazole regimen in treating VVC.

Significance of the study

More and more women, especially those who are pregnant, are troubled by the high prevalence and recurrence rates of VVC. In our institution, the most commonly prescribed azole is clotrimazole followed by miconazole. Although azoles are efficacious in providing complete cure for VVC, only miconazole can be given as a single dose for the treatment of this infection. The findings in this study will primarily have implications for ensuring compliance of patients. The advantage of single-dose regimen is that treatment is more convenient, hence subsequently improving compliance. Thereby, the primary implication of the findings in this study is toward ensuring compliance of patients. This can be contributory in promoting appropriate treatment that will consequently lower the incidence and associated health-care cost in the management of VVC. Ultimately, this will translate to improved health outcomes among women with VVC regardless of pregnancy status.

Objective

General objective

To compare the effect of miconazole versus clotrimazole in the treatment of VVC among patients seen at the outpatient department in a tertiary hospital.

Specific objectives

To compare the effect on the rates of the following parameters between miconazole and clotrimazole:

a. Clinical cure (primary outcome)
b. Adverse event (secondary outcome)
c. Treatment failure (secondary outcome).

Definition of variables and operational terms

Independent variable refers to the treatment evaluated in this study which was encoded and entered as:

1. Miconazole
2. Clotrimazole.

Dependent variable refers to the outcome of the study.

Clinical cure rate

Refers to the proportion of participants who had absence or resolution of any of the following sign and symptoms after completion of treatment:

- Curd-like discharge
- Pruritus
- Dyspareunia
- Vulvar erythema.
- The following are the signs and symptoms of VVC which were observed and recorded in this study:

Curd-like vaginal discharge: The presence of a thick, white, highly viscous discharge upon history taking or on speculum examination. This was later be categorized, encoded, and entered as:

1. Without curd-like vaginal discharge
2. With curd-like vaginal discharge.

Vulvar pruritus: The presence of vulvar itching upon history taking. This was later be categorized, encoded, and entered as:

1. Without vulvar pruritus
2. With vulvar pruritus.

Dyspareunia: The presence of painful intercourse upon history taking. This was later be categorized, encoded, and entered as:

1. Without dyspareunia
2. With dyspareunia.

Vulvar erythema: The presence of vulvar redness upon history taking or physical examination. This was later be categorized, encoded, and entered as:

1. Without vulvar erythema
2. With vulvar erythema.

Overall, these was categorized, encoded, and entered as:

1. Absent
2. Present refers to the occurrence/persistence of any one of the signs/symptoms of VVC.

Adverse effects

Refers to the signs and symptoms due to the side effects that the participants experienced during or after treatment with miconazole or clotrimazole. The actual side effects were recorded as well as categorized, encoded, and entered as:

1. Absent
2. Present.

Treatment failure

Defined as persistence of any of the signs and symptoms, enumerated, and defined above, after 7 days from the initiation of treatment.

Methodology

Study design

This was a retrospective cohort study.

Setting and target population

This study entailed review records of patients at the obstetrics and gynecology outpatient department of a tertiary private medical center from January 2016 to March 2020. This study included women regardless of pregnancy status who were given either intravaginal miconazole or clotrimazole as treatment for VVC.

Inclusion criteria

All women fulfilling the following criteria were included in this study:

1. Age 18 years to 35 years old
2. Those with any one of the following signs and symptoms of VVC:
    - Curd-like vaginal discharge
    - Vulvar pruritus
    - Dyspareunia
    - Vulvar erythema.
3. Those with pseudohyphal or hyphal elements seen on Gram stain, Wet smear, or KOH
4. Those who completed the treatment and had follow-up evaluation recorded in the chart.

Exclusion criteria

Those women with the following conditions were excluded:

1. Current infection or infection within 2 weeks from recruitment involving other types or causes of vaginitis such as bacterial vaginosis and trichomoniasis as well as those with pelvic inflammatory disease and pyelonephritis
2. Complicated VVC (four or more episodes of candidiasis per year (recurrent vulvovaginal candidiasis or severe symptoms or findings (severe VVC), or non-*C. albicans* infection, or abnormal host (e.g. uncontrolled diabetes, debilitation, or immunosuppression).

Methodology proper

This study involved review of charts for a period of 4 years from 2016 to 2020. The records were gathered from the medical records section of the tertiary hospital after consent from the chief information and data privacy officer was secured. The eligible records underwent data extraction by the primary investigator. The data that were gathered were encoded in a standard data collection sheet. The patient characteristics that were extracted from the charts included the age, gravidity and parity. In addition, presence of any signs and symptoms such as curd-like vaginal discharge, vulvar pruritus, dyspareunia, and vulvar erythema were also recorded. Presence of signs and symptoms on initial consult, its persistence or resolution on follow-up were recorded as well. The presence of pseudohyphal, hyphal, or fungal elements seen on gram stain and wet smear or KOH as well as the antifungal agent used, it's route of administration, and adverse effects were also extracted from the charts.

Sample size calculation

The sample size was computed based on the formula of comparison of proportions from two independent samples. These proportions were based on two studies: (1) Fan *et al*. reported that 75.9% of their participants given single-dose miconazole for VVC were noted to have clinical cure[6] and (2) Zhou *et al*. found that the clinical cure rate among women with VVC given clotrimazole was 88.7%.[9]

With a proportion of 0.76 (P1) and 0.89 (P2), a total of 308 charts of women seen at the outpatient department were retrieved. This sample size gives a probability of 80% of rejecting the null hypothesis of equal proportions if the alternative holds. The test of equality of proportions was carried out at 0.05 level of significance.

Data management and analysis

Microsoft Excel was used for data entry and encoding. For data analysis, Stata version 9.0 was used. Univariate analysis such as mean and range was used to describe continuous variables such as age, gravidity, and parity. Frequency distribution was used to describe the categorical variables, which include the proportion of participants with presence or absence of symptoms as well as the pseudohyphal or hyphal elements on microbiologic examination. With regard to the presence or absence of side effects, this was also described using frequency distribution. Chi-square was used to analyze the comparison of the proportion of the participants with the above categorical variables, whereas *t*-test was used to compare the continuous variables between the two treatment groups.

Ethical consideration

The study proposal before its implementation underwent review and was approved by the technical and ethics review board of the research center for development. Permission to retrieve and review the records was obtained from the office of the chief medical officer, data privacy officer, and the medical records section.

This study complied with the Data Privacy Act of 2012. Pertinent information such as name and address were

not included nor mentioned in this study. Each patient was assigned a specific number code to represent their case on the data collection tool. No identifiable information pertaining to the participant appeared on the data collection sheet. These ensured anonymity of the participants in this study as well as maintained confidentiality.

A waiver of informed consent was obtained from the board of ethics. There was no direct risk involved since this only entailed review of chart records of the eligible participants. The personal data taken from patient charts were not included, so that no identifiable information pertaining to the patient will appear in any part of the paper. There were no conflicts of interest involved in this study. The authors have no affiliations with or involvement in any organization or entity with any financial or nonfinancial interest in the subject matter or material discussed in this manuscript.

Results

A total of 316 charts were eligible to be included in this study. Among women whose chart records were included, there were 161 (50.94%) who used miconazole, whereas 155 (49.05%) took clotrimazole. The age range of women whose charts were included was 18–35 years old with a mean age of 28. Among the chart records, 16% (53/316) were pregnant and 82% (263/316) were nonpregnant. The range of gravidity was from 0 to 5 with a mean gravidity of 1, while the range of parity was 0–3 with a mean parity of 1. However, when the baseline characteristics of women were compared, the record showed that those women in the miconazole group were significantly older with greater parity as compared to those given clotrimazole [Table 1].

All of the 316 records of women included in the study presented with signs and symptoms of VVC. The most common of which is curd-like vaginal discharge (86.7%), followed by vulvar pruritus (80.7%) and vulvar erythema (50.6%), and the least occurring is dyspareunia (0.94%). When the signs and symptoms were individually compared between the two treatment arms, no statistically significant differences were noted. The detailed comparison on the different signs and symptoms between the two treatment arms is shown in Table 2.

During the chart review, women diagnosed with VVC were either given single-dose 1200 mg miconazole or 6-day 100 mg clotrimazole and were asked to follow-up after 7 days from initiation of treatment. Upon follow-up, 11 out of 316 (3.46%) were still symptomatic, which was noted in 2 (18.1%) from the miconazole group and 9 (81.8%) from the clotrimazole group [Table 3]. The difference for these outcomes between the treatment groups was statistically significant. With regard to treatment failure rate, for miconazole, it was 1.2% (2/161), whereas for clotrimazole, it was 5.8% (9/155).

Table 1: Comparison of baseline characteristics as to age, gravidity, parity and pregnancy status between miconazole and clotrimazole

Baseline Characteristics	Antifungal agent, mean±SD		*P*
	Miconazole	Clotrimazole	
Age	29.78 (3.49)	28.04 (4.04)	0.001
Gravidity	1.15 (0.96)	0.95 (0.84)	0.05
Parity	0.84 (0.82)	0.63 (0.95)	0.01
Pregnancy status, *n* (%)			
Pregnant	23 (14)	30 (19)	0.33
Nonpregnant	138 (55)	125 (80)	

SD: Standard deviation

Table 2: Comparison of baseline signs and symptoms between miconazole and clotrimazole

Baseline signs and symptoms	Antifungal agent		*P*
	Miconazole, *n* (%)	Clotrimazole, *n* (%)	
Curd-like vaginal discharge	135 (83)	139 (89)	0.13
Pruritus	127 (78)	128 (82)	0.40
Dyspareunia	0	3 (1)	0.08
Erythema	82 (50)	78 (50)	0.91

Table 3: Comparison of the resolution of signs and symptoms with treatment between miconazole and clotrimazole

Signs and symptoms of vulvovaginal candidiasis	Antifungal agent		*P*
	Miconazole (*n*=161), *n* (%)	Clotrimazole (*n*=155), *n* (%)	
Absent	159 (52.4)	146 (47.5)	0.027
Present	2 (18.1)	9 (81.8)	

In this study, adverse effects of intravaginal antifungal treatment such as vulvar burning, pain, edema, and itching were also reviewed. However, none of the charts of these women had recorded adverse reaction to the given treatment.

Discussion

VVC remains one of the most common reasons for women to seek consult to the clinics. But according to Al Quaiz (2000), only around 12% of women presenting with signs and symptoms of VVC usually consults in the clinic.[17] In our institution, out of 1134 women complaining of vaginal discharge from 2016 to 2020, approximately 37% were diagnosed with VVC.

Among all the antifungal agents used in treating vulvovaginal candidiasis, only miconazole and clotrimazole are proven safe for pregnant and nonpregnant women alike. The intravaginal forms of

these antifungals allow effective treatment of the disease with the least side effects possible. Clotrimazole is given as a 6-day regimen, but only miconazole can be given as a single-dose treatment.

In our study, we compared the effect of miconazole versus clotrimazole in the treatment of VVC among patients seen at the outpatient department in a tertiary hospital from 2016 to 2020. The result of the comparison between the two types of antifungal agents revealed that single-dose 1200 mg miconazole is more efficacious than the 6-day 100 mg clotrimazole regimen in the promoting clinical cure of VVC. The clinical cure rate for miconazole was 98%, whereas for clotrimazole, it was 94%. Thereby, treatment failure rate as expected was lower among those in the miconazole group (1.2%) as compared to those in the clotrimazole group (5.8%).

In contrast to our study, there were two trials that showed comparable cure rates between miconazole and clotrimazole in the treatment of vulvovaginal candidiasis. The first study was that of Eliot *et al*. in 1971, wherein the cure rate of the 6-day 100 mg clotrimazole was 88%, for 7-day 100 mg miconazole given twice daily, it is 86% and for 14-day 100 mg miconazole, it was noted to be at 91%.[11] For the second study, which was a randomized controlled trial conducted by Balsdon in 1981, twice daily 100 mg miconazole tampons given for 5 days had a clinical cure rate of 99%, whereas a 6-day course of 100 mg clotrimazole intravaginal tablets yielded a clinical cure rate of 98%.[12] Azole antifungals such as miconazole and clotrimazole inhibit the cytochrome P450-dependent enzyme lanosterol 14-alpha-demethylase that is necessary for the synthesis of ergosterol, a vital component of the cellular membrane of *Candida* species.[9] Several literature have found that such enzyme inhibition is dependent on the dose of azoles, with higher concentrations achieving greater fungistatic activity.[18,19] This is most likely the reason why in this study, the single-dose 1200 mg miconazole regimen yielded a higher clinical cure rate than the 6-day 100 mg clotrimazole regimen. Another reason may be due to lesser product misuse since the single-dose miconazole regimen only entails one-time application. Finally, the shorter treatment duration with the single-dose miconazole regimen may have contributed to patient compliance during the treatment.

The adverse effects associated with azoles administered intravaginally include vulvar burning, pain, edema, and itching.[4] Such adverse effects are reported by patients given with either miconazole or clotrimazole vaginal suppositories as treatment for VVC.[6,9] However, according to literature, the adverse effects of these agents are well tolerated.[9] This is probably the reason why in this study, there were no recorded or reported adverse effects during the time of azole treatment. In the study of Fan *et al*., there may be reports of adverse effects, but they were only noted in 2 out of 290 patients who were given intravaginal miconazole.[6] Similarly, in the study of Zhou *et al*., only 16 out of 115 patients developed adverse reactions after administration of intravaginal clotrimazole.[9] None of them discontinued the treatment because of the said adverse effects. This shows that side effects associated with local antifungal agents remain negligible.

When it comes to cost, the average price of miconazole 1200 mg intravaginal tablet given as a single dose is Php 552.67. In comparison with clotrimazole 100 mg intravaginal tablet, the average cost is Php 106.50 per suppository usually inserted once a day for 6 days. With this, the total cost for clotrimazole is Php 639.00. Therefore, aside from a shorter treatment duration, the single-dose miconazole is better in terms of affordability with cost savings of Php 86.33 per treatment course. This may translate to better patient compliance that may eventually improve the outcome of treatment.

The main limitation of our study is its retrospective nature. Because of this, the cases that we gathered per arm were unequal. The eligible charts that were gathered did not include complicated and recurrent VVC since the recorded follow-up was mostly done once, and that is, immediately after treatment. It may also be useful if such information from patients having these conditions were included. Furthermore, microbiologic cure was not assessed in this study since most of the eligible cases did not have a repeat Gram stain, wet smear, nor KOH smear of their vaginal discharge posttreatment.

Conclusion

In our institution, clotrimazole and miconazole are both widely used in the management of VVC. As seen in our study, the single-dose miconazole regimen has a significantly higher clinical cure rate than the 6-day clotrimazole, with adverse effects being uncommon for both agents. Since these agents appear to be comparable in providing relief of symptoms with negligible adverse effects, the single-dose miconazole regimen has the potential to improve patient compliance and improve treatment outcome at a lower cost.

Recommendation

For a more accurate comparison between miconazole and clotrimazole, a prospective randomized controlled study with equal participants per arm is therefore recommended. Future studies may include patients with complicated VVC such as those with comorbidities.

Finally, a more profound investigation may be achieved by assessing the complete cure rate, which includes both microbiologic and clinical cure rates between the two treatment arms. It is also worthwhile to determine the recurrence rate of VVC between the two treatment arms. Hence, it is recommended to conduct the trial with a longer follow-up.

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Conflicts of interest
There are no conflicts of interest.

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Appendixes

Appendix A: Centers for Disease Control and Prevention (2015) recommended treatment for uncomplicated vulvovaginal candidiasis

Drug	Dose	Duration
Clotrimazole	1% cream 5 g intravaginally daily	7-14 days
Clotrimazole	2% cream 5 g intravaginally daily	3 days
Clotrimazole	100 mg vaginal suppository	6 days
Miconazole	2% cream 5 g intravaginally	7 days
Miconazole	4% cream 5 g intravaginally	3 days
Miconazole	100 mg vaginal suppository, one suppository daily	7 days
Miconazole	200 mg vaginal suppository, one suppository daily	3 days
Miconazole	1200 mg vaginal suppository, one suppository	1 day
Tioconazole	6.5% ointment 5 g intravaginally in a single application	
Butoconazole	5 g intravaginally in a single application	
Terconazole	0.4% cream 5 g intravaginally daily	7 days
Terconazole	0.8% cream 5 g intravaginally daily	7 days
Terconazole	0.8% cream 5 g intravaginally daily	3 days
Terconazole	80 mg vaginal suppository, one suppository daily	3 days
Fluconazole	150 mg orally in a single dose	

Appendix B: Food and drug administration pregnancy categories

Category A

Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

Category B

Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Category C

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category D

There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category X

Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.