The efficacy and safety of clotrimazole vaginal tablet vs. oral fluconazole in treating severe vulvovaginal candidiasis

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Summary

To compare the efficacy and safety of two doses of clotrimazole vaginal tablet 500 mg with two doses of oral fluconazole 150 mg in treating severe vulvovaginal candidiasis (SVVC), 240 consecutive patients with SVVC were studied at the Department of Obstetrics and Gynaecology of Peking University Shenzhen Hospital between June 2014 and September 2015. Patients were randomly assigned in a 1 : 1 ratio to receive treatment with either two doses of clotrimazole vaginal tablet or two doses of oral fluconazole. The clinical cure rates in the clotrimazole group and the fluconazole group at days 7–14 follow-up were 88.7% (102/115) and 89.1% (98/110) respectively; the clinical cure rates at days 30–35 in the two groups were 71.9% (82/114) and 78.0% (85/109) respectively. The mycological cure rates at days 7–14 follow-up in the two groups were 78.3% (90/115) and 73.6% (81/110) respectively. The mycological cure rates of the patients at days 30–35 in the two groups were 54.4% (62/114) and 56.0% (61/109) respectively (P > 0.05). The adverse events of clotrimazole were mainly local. This study demonstrated that two doses of clotrimazole vaginal tablet 500 mg were as effective as two doses of oral fluconazole 150 mg in the treatment of patients with SVVC and could be an appropriate treatment for this disorder.

Key words: Vulvovaginal candidiasis, clotrimazole, fluconazole, antifungal susceptibility.

Introduction

Vulvovaginal candidiasis (VVC) is symptomatic vaginitis, which affects up to 75% of child-bearing age women at least once in their lifetime. VVC can be classified as either uncomplicated or complicated, which includes severe VVC (SVVC) and recurrent VCC (RVVC).1 The USA Center for Disease Control and Prevention (CDC) recommended two doses of oral fluconazole 150 mg for the treatment of SVVC.1 Several other guidelines recommend using clotrimazole vaginal tablet 500 mg for treating VVC and RVVC.2–5 Few studies and guidelines recommend the use of clotrimazole vaginal tablet 500 mg for the treatment of SVVC. Accordingly, we performed a prospective, randomised study in patients with SVVC to determine whether two doses of clotrimazole vaginal tablet 500 mg was as effective as two doses of oral fluconazole 150 mg.
NCT02180828). The protocol and informed consent material were reviewed and approved by the hospital review board. Written informed consent was obtained from each patient. The patients with SVVC were equally randomised to either two doses of clotrimazole vaginal tablet 500 mg (clotrimazole group) or two doses of oral fluconazole 150 mg (fluconazole group). The Case definition, VVC classification, vaginal samples, identification methods and antifungal susceptibility testing were performed as previous study. All strains were identified using the API Candida (bioMérieux, Marcy l’Etoile, France). The VVC was classified based on the CDC criteria.

Vaginal microflora of Gram-stained vaginal smears collected from patients with SVVC at entry and two follow-up visits were evaluated based on the Nugent score and Lactobacillar grades (LBG). The criteria of LBG were (I) numerous pleomorphic lactobacilli, no other bacteria; (IIa) mixed flora, but predominantly lactobacilli; (IIb) mixed flora but the proportion of lactobacilli severely decreased due to increased number of other bacteria; and (III) lactobacilli severely depressed or absent because of overgrowth of other bacteria.

Admission criteria and treatment regimens

Eligible patients were 18–50 years old, generally healthy women with SVVC. Uncomplicated VVC and RVVC were excluded from the study. Enrolled patients agreed to abstain from sexual intercourse during the treatment period or use condoms for the remainder of the study period. During the study, they also agreed to abstain from using any other vaginal product. Patients were excluded from entry if they (i) had any other sexually transmitted disease or gynaecological abnormality requiring treatment; (ii) had a disease known to predispose them to candidiasis such as diabetes mellitus, or were receiving antibiotics or corticosteroids; (iii) were pregnant; (iv) had used antifungal medication during the week before entry; (v) were expected to menstruate within 7 days of the start of treatment; or (vi) were infected with more than one Candida species. Patients who met the study inclusion criteria received either clotrimazole vaginal tablet (LOT BXGJS62 Bayer HealthCare, Shanghai, China) or oral fluconazole 150 mg (LOT 1392010 Pfizer Pharmaceuticals Ltd, Shanghai, China) at day 1 and day 4.

Follow-up visits

The patients were followed up at 14 (7–14) days and 35 (30–35) days following the second dosing. During these visits, the patient was questioned about any adverse events or concomitant medications. Symptoms, signs and adverse events were scored and recorded. Clinical cure was defined as the resolution of symptoms present at baseline with a total severity score of ≤2. Improvement was defined as considerable reduction in the severity of baseline signs and symptoms with a decrease in the total score by ≥50%. Patients not clinically cured or showing improvement were considered clinical failures.

Statistical methods

We calculated the sample size assuming that fluconazole therapy would have a clinical success rate of 85%, and it was estimated that 240 patients (allowing for a drop-out rate of 10%) would be required in each treatment group to detect a treatment difference of 10%, with 90% power and a two-sided alpha level of 0.05. Therapy outcomes were analysed using a chi-squared test to compare the results of treatment at the short- and long-term visits. A Student’s t test was used to compare the difference between the mean ages of the patients. Statistical significance was set at P < 0.05. Statistical analysis of the data was performed using spss 10.0 (SPSS Inc, Chicago, IL, USA).

Results

Clinical characteristics and yeast species

A total of 240 patients with SVVC were enrolled in the study. The average ages of participants were 29.35 ± 6.323 and 29.89 ± 6.457 years old in the clotrimazole group and fluconazole group respectively (F = 0.432, P = 0.512). Fifty-one patients had a history of VVC episodes (27 in the clotrimazole group and 24 in the fluconazole group). Seven patients had a history of antibiotic therapy prior to the development of VVC (six vs. one in the clotrimazole group and fluconazole group respectively). Three patients had a history of allergy to drugs or food or an allergic disease (two in the clotrimazole group and one in the fluconazole group). No patients were infected with HIV. The demographic characteristics and vaginal fungal culture analysis of the baseline vaginal isolates from the patients are shown in Table 1. Of those isolates, 90.0% (216/240) of cases were caused by C. albicans. Non-albicans Candida included C. glabrata (5.4%, 13/240), C. parapsilosis (2.9%, 7/240), C. inconspicua
(0.8%, 2/240), *C. tropicalis* (0.4%, 1/240) and *C. Krusei* (0.4%, 1/240).

Eight patients (four in the clotrimazole group and four in the fluconazole group) withdrew from the study after enrolment because they were not willing to continue. Three patients (all in the fluconazole group) were eliminated from the study because of drug side effects or pregnancy. Six patients (two in the clotrimazole group and four in the fluconazole group, including two at the second follow-up visit) were lost to follow-up (Fig. 1).

Efficacy and antifungal susceptibility

Efficacy analyses were performed on both the intention to treat (ITT) and per-protocol set (PPS). However, because the results in the ITT group were similar to those of the PPS, only the results based on PPS are assessed for eligibility ($n = 335$)

- Excluded ($n = 95$)
  - Declined to participate ($n = 38$)
  - Pregnant ($n = 6$)
  - No sexual intercourse history ($n = 5$)
  - Near menstruation ($n = 6$)
  - Mixed infections ($n = 4$)

Randomised ($n = 240$)

- Allocated to clotrimazole group ($n = 120$)
  - Received allocated intervention ($n = 116$)
  - Did not receive allocated intervention (Withdraw $n = 4$)

- Allocated to fluconazole group ($n = 120$)
  - Received allocated intervention ($n = 116$)
  - Did not receive allocated intervention (Withdraw $n = 4$)

Per protocol population (114)

- Discontinued study ($n = 0$)
- Drop out at first follow-up ($n = 1$)
- Drop out at second follow-up ($n = 1$)

Per protocol population (109)

- Discontinued study ($n = 3$)
- Drop out at first follow-up ($n = 3$)
- Drop out at second follow-up ($n = 1$)

Analysed safety population ($n = 115$)

- Excluded from analysis (Withdraw $n = 4$, dropout $n = 1$)
- Efficacy-valid population ($n = 114$)
  - Withdraw ($n = 4$)
  - Discontinued study ($n = 0$)
  - Drop out at first follow-up ($n = 1$)
  - Drop out at second follow-up ($n = 1$)
  - Vaginal microflora population ($n = 114$)
    - Withdraw ($n = 4$)

Analysed efficacy-valid population ($n = 109$)

- Excluded from analysis (Withdraw $n = 4$, dropout $n = 3$)
- Efficacy-valid population ($n = 109$)
  - Withdraw ($n = 4$)
  - Discontinued study ($n = 3$)
  - Drop out at first follow-up ($n = 3$)
  - Drop out at second follow-up ($n = 1$)
  - Vaginal microflora population ($n = 109$)
    - Withdraw ($n = 4$)

Figure 1 Flow diagram of patients through trial.
presented. The clinical cure rates in the clotrimazole group and fluconazole group at days 7–14 follow-up were 88.7% (102/115) and 89.1% (98/110) respectively; the clinical cure rates at days 30–35 in the two groups were 71.9% (82/114) and 78.0% (85/109) respectively. The mycological cure rates at day 7–14 follow-up in the two groups were 78.3% (90/115) and 73.6% (81/110) respectively. The mycological cure rates of the patients at days 30–35 in the two groups were 54.4% (62/114) and 56.0% (61/109) respectively (Table 2). A higher percentage of patients in the clotrimazole group experienced relief of symptoms such as itching, burning, discharge and erythema at the first 12 h time point compared to the fluconazole group (Table 3). Of the 24 patients infected with non-\textit{Candida albicans} species, 21 patients had follow-up results. The clinical cure rates at days 7–14 and days 30–35 follow-up in the clotrimazole group and the fluconazole group were 9/11 and 9/10 respectively; the mycological cure rates of the patients at days 7–14 follow-up in the clotrimazole group and the fluconazole group were 3/11 and 3/10 respectively; the mycological cure rates of the patients at days 30–35 follow-up in the clotrimazole group and the fluconazole group were 2/11 and 1/10 respectively. Only one of the 13 patients with SVVC caused by \textit{C. glabrata} had a mycological cure. At days 7–14 follow-up, five of the seven patients infected with \textit{C. parapsilosis} had a mycological cure (three in the clotrimazole group and two in the fluconazole group); the two mycological failure patients were in the fluconazole group. At days 30–35 follow-up, only two of the seven patients with SVVC caused by \textit{C. parapsilosis} had a mycological cure (in the clotrimazole group). Two patients infected with \textit{C. inconspicua}, one with \textit{C. krusei} and one with \textit{C. tropicalis} were all classified as mycological failure at the two follow-up visits.

\textit{In vitro} susceptibilities of 240 yeast isolates to seven azoles according to the NCCLS M27-A broth

**Table 1** Characteristics and \textit{Candida} species of patients with severe vulvovaginal candidiasis in the clotrimazole group and fluconazole group (ITT).

| Characteristics and Candida species | Clotrimazole group (n, %) | Fluconazole group (n, %) | F value or $\chi^2$ value | P value |
|------------------------------------|--------------------------|--------------------------|---------------------------|---------|
| Ages                               | 29.35 ± 6.232            | 29.89 ± 6.457            | 0.422                     | 0.512   |
| VVC scores at baseline             | 7.5246 ± 0.74093         | 7.5339 ± 0.71231         | 0.010                     | 0.921   |
| Candida species                    |                          |                          |                           |         |
| \textit{C. albicans}               | 108                      | 108                      | 2.418                     | 0.789   |
| \textit{C. glabrata}               | 7                        | 6                        |                           |         |
| \textit{C. parapsilosis}           | 3                        | 4                        |                           |         |
| \textit{C. tropicalis}             | 1                        | 0                        |                           |         |
| \textit{C. krusei}                 | 0                        | 1                        |                           |         |
| \textit{C. inconspicua}            | 1                        | 1                        |                           |         |
| Total                              | 120                      | 120                      |                           |         |

**Table 2** Comparison of the therapeutic efficacy of clotrimazole and fluconazole (PPS)*.

| Therapeutic efficacy | Clotrimazole group (n, %) | Fluconazole group (n, %) | $\chi^2$ | P value | OR  | 95% CI   |
|----------------------|--------------------------|--------------------------|----------|---------|-----|---------|
| Day 7–14             |                          |                          |          |         |     |         |
| Clinical             | 115                      | 110                      |          |         |     |         |
| Cure                 | 102, 88.7                | 98, 89.1                 | 0.009    | 0.925   | 1.041 | 0.453–2.392 |
| Improvement          | 1, 0.9                   | 2, 1.8                   | 0.374    | 0.487   | 2.111 | 0.189–23.619 |
| Failure              | 12, 10.4                 | 10, 9.1                  | 0.115    | 0.734   | 0.777 | 0.326–1.852 |
| Mycological cure     | 90, 78.3                 | 81, 73.6                 | 0.659    | 0.147   | 1.289 | 0.698–2.380 |
| Day 28–35            |                          |                          |          |         |     |         |
| Clinical             | 114                      | 109                      |          |         |     |         |
| Cure                 | 82, 71.9                 | 85, 78.0                 | 1.085    | 0.298   | 1.382 | 0.751–2.544 |
| Improvement          | 5, 4.4                   | 5, 4.6                   | 0.005    | 0.942   | 1.048 | 0.295–3.726 |
| Failure              | 27, 23.7                 | 19, 17.3                 | 1.331    | 0.249   | 1.231 | 0.847–1.789 |
| Mycological cure     | 62, 54.4                 | 61, 56.0                 | 0.056    | 0.813   | 1.033 | 0.788–1.355 |

*The patients with a positive Candida culture at first follow-up will continue to calculate clinical and mycological outcome at second follow-up based on their first follow-up.
The MIC90 values of seven azoles to *C. albicans*, *C. glabrata* and non-*Candida albicans* other than *C. glabrata* species were 0.25–4.00, 0.25–4.00 and 0.13–4.00 μg/ml respectively. The resistance rates of *C. albicans*, *C. glabrata* and non-*Candida albicans* other than *C. glabrata* species for azoles were 0–6.5%, 0–46.2% and 0–9.1% respectively. The six strains of fluconazole resistant Candida strains (*C. albicans*, five strains, *C. krusei*, one strain) were treated with fluconazole (three cases) or clotrimazole (three cases). The therapeutic failure occurred on the patient infected with *C. krusei*. Four of the other five patients infected with fluconazole resistant Candida infection got a mycological cure.

**Vaginal microflora**

The normal vaginal microflora based on the Nugent score of Gram stained vaginal smears collected from patients with SVVC at entry in the clotrimazole group and the fluconazole group were 30.8% (37/120) and 28.3% (34/120) respectively. At the first follow-up, the normal vaginal microflora in the clotrimazole group and the fluconazole group were 83.5% (96/115) and 72.7% (80/110) respectively; at the second follow-up, the normal vaginal microflora in the clotrimazole group and the fluconazole group were 79.8% (71/89) and 80.0% (64/80) respectively (*P* > 0.05). The Nugent scores in the clotrimazole group at entry, first and second follow-up were 4.69 (SD 2.144), 1.56 (SD 1.523) and 1.69 (SD 2.156), *t* = 14.036, *P* = 0.00. The Nugent scores in the fluconazole group at entry, first and second follow-up were 4.76 (SD 2.089), 1.90 (SD 1.968) and 1.78 (SD 2.030), *t* = 12.130, *P* = 0.00 (Table 5). Vaginal microflora of Gram stained vaginal smears collected from patients with SVVC treated with clotrimazole (case 206) or fluconazole (case 230) at entry and two follow up visits were shown on figure 2.

**Safety**

The adverse events of clotrimazole vaginal tablet were mainly local and mild. Most of the adverse events of fluconazole were systemic (Table 6). Two patients in the fluconazole group had severe skin allergy and discontinued the study (Fig. 3). The two patients
studied 398 patients with complicated VVC, of which 197 were randomised to single-dose fluconazole and 201 received two sequential doses. They found that women with SVVC achieved superior clinical and mycological eradication with a two-dose fluconazole regimen. The two-dose oral fluconazole regimen is currently a standard regimen for the treatment of complicated VVC, mainly SVVC. In this study, based on the patient’s self-assessment, a higher percentage of patients treated with clotrimazole experienced relief of symptoms at the first 12 h time point compared to those treated with fluconazole; however, improvements in the symptoms in general were similar at day three and later in the two treatment groups. The mycological cure rates at days 7–14 follow-up in the two groups were 78.3% and 73.6% respectively. The mycological cure rates of the patients at days 30–35 in the two groups were 54.4% and 56.0% respectively (P > 0.05). The mycological cure rates of the patients with SVVC in fluconazole group at this study was similar as our recent published clinical trial which showed a mycological cure rates of 71.2% and 53.0% in fluconazole group at days 7–14 follow-up and days 30–35 follow-up. In our more early studies, the mycological cure rates in fluconazole group was 84.0–86.4% and 69.7–75.4% at days 7–14 follow-up and days 30–35 follow-up. The decreased mycological cure rates of the patients with SVVC in fluconazole group may related with distinction of the patients such as the Candida or the previous episode times of the diseases. The clinical cure rates at days 7–14 follow-up in the clotrimazole group and the fluconazole group were 88.7% and 89.1% respectively; the clinical cure rates at days 30–35 in the two groups were 71.9% and 78.0% respectively. The clinical cure rates in fluconazole group were higher than that in our previous publication which showed a clinical cure rate of 75.8% and 56.1% in fluconazole group at days 7–14 follow-up and days 30–35 follow-up. The decreased mycological cure rates of the patients with SVVC in fluconazole group may related with distinction of the patients such as the Candida or the previous episode times of the diseases. The clinical cure rates at days 7–14 follow-up in the clotrimazole group and the fluconazole group were 88.7% and 89.1% respectively; the clinical cure rates at days 30–35 in the two groups were 71.9% and 78.0% respectively. The clinical cure rates in fluconazole group were higher than that in our previous publication which showed a clinical cure rate of 75.8% and 56.1% in fluconazole group at days 7–14 follow-up and days 30–35 follow-up. We rechecked the two original data and found that the follow-up discharge score was higher in previous study than in this study. It was that the improper discharge score caused the low clinical cure rates at previous study.

VVC caused by non-albicans Candida is increasing. Eradication of non-albicans Candida infections may be more difficult because of antimicrobial resistance to commonly used agents. In this study, only one of the 13 patients with SVVC caused by C. glabrata had a mycological cure. The VVC caused by other non-albicans Candida including C. glabrataand C. parapsilosis had a high mycological failure rate, which will require further study.

Table 4 In vitro susceptibilities of 240 yeast isolates to seven azoles according to the NCCLS M27-A broth microdilution method.

| Yeast species and antifungal agents | Range | Geometric mean | MIC (50, 90) | Resistant % |
|-----------------------------------|-------|----------------|--------------|-------------|
| C. albicans (n = 216)             |       |                |              |             |
| Buconazole                        | 0.03–16.00 | 0.4314        | 0.25, 2.00   |             |
| Clotrimazole                      | 0.03–4.00  | 0.0456         | <0.03, 0.25  |             |
| Fluconazole                       | 0.13–64.00 | 1.3871         | 0.50, 4.00   | 5, 2.3      |
| Itraconazole                      | 0.03–16.00 | 0.1529         | 0.06, 0.50   | 14, 6.5     |
| Miconazole                        | 0.03–16.00 | 0.5337         | 0.50, 4.00   |             |
| Terconazole                       | 0.03–16.00 | 0.3939         | 0.25, 2.00   |             |
| Voriconazole                      | 0.03–16.00 | 0.1746         | 0.06, 0.25   | 0           |
| C. glabrata (n = 13)              |       |                |              |             |
| Buconazole                        | 0.03–16.00 | 0.7915         | 0.50, 4.00   |             |
| Clotrimazole                      | 0.03–2.00  | 0.2466         | 0.25, 1.00   |             |
| Fluconazole                       | 0.13–8.00  | 3.3250         | 2.00, 4.00   | 0           |
| Itraconazole                      | 0.03–16.00 | 0.6853         | 0.25, 4.00   | 6, 46.2     |
| Miconazole                        | 0.03–2.00  | 0.4537         | 0.25, 1.00   |             |
| Terconazole                       | 0.03–2.00  | 0.3589         | 0.25, 1.00   |             |
| Voriconazole                      | 0.03–1.00  | 0.1353         | 0.06, 0.25   | 0           |
| Non-C. albicans other than C. glabrata species (n = 11) | | | | |
| Buconazole                        | 0.03–16.00 | 1.6732         | 2.00, 4.00   |             |
| Clotrimazole                      | 0.03–2.00  | 0.1117         | 0.03, 0.25   |             |
| Fluconazole                       | 0.13–64.00 | 2.3784         | 1.00, 8.00   | 1, 9.1      |
| Itraconazole                      | 0.03–8.00  | 0.1117         | 0.06, 0.25   | 1, 9.1      |
| Miconazole                        | 0.06–16.00 | 1.4070         | 2.00, 4.00   |             |
| Terconazole                       | 0.03–8.00  | 0.2049         | 0.03, 2.00   |             |
| Voriconazole                      | 0.03–4.00  | 0.0862         | 0.03, 0.13   | 0           |

recovered after anti-allergic agent therapy. One of the two patients was treated with intravenous infusion of dexamethasone for 4 days and diphenhydramine for 7 days (Fig. 3). Two patients in the fluconazole group were pregnant; one of them had a spontaneous abortion, and the other had an induced abortion.

Discussion

Efficacy

Clotrimazole is a broad-spectrum antimycotic drug that is in widespread use for the treatment of Candida and other fungal infections. The primary mechanism of action of clotrimazole against yeast is based on the inhibition of the enzymatic conversion of lanosterol to ergosterol, the latter being the essential membrane component of the fungus membrane. In the treatment of VVC, the normal dosage forms are either 100, 200 or 500 mg, which are administered daily for 6, 3 or 1 day(s) respectively. Sobel et al. [10] studied 398 patients with complicated VVC, of which...
In vitro antifungal susceptibility

Richter et al. [15] found that 3.6% and 16.2% of vaginal isolates of *C. albicans* were resistant to fluconazole and itraconazole respectively. Consistent with previous data, our study showed that azoles had comparable activity against *C. albicans* isolates (resistant rates to fluconazole and itraconazole were 2.3% and 6.5% respectively). In this study, the antifungal activity of the azole agents was lower against *C. glabrata* than *C. albicans* (the geometric means of fluconazole for *C. glabrata* and *C. albicans* were 3.32 and 1.38 respectively; those for itraconazole for *C. glabrata* and *C. albicans* were 0.68 and 0.15 respectively). The MIC90 of clotrimazole for all yeast isolates from the patients with SVVC was the lowest of the drugs tested, except for voriconazole, which is currently not used for treating VVC. The high antifungal activity and high local

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**Table 5** Clotrimazole or fluconazole treatment on vaginal microflora*.

| Nugent score characteristic | Clotrimazole group (n, %) | Fluconazole group (n, %) | Pearson $X^2$ | $P$ value | $R$ | 95% CI |
|-----------------------------|---------------------------|--------------------------|---------------|-----------|-----|---------|
| Baseline $N = 240$          |                           |                          |               |           |     |         |
| 0–3                         | 37, 30.8                  | 34, 28.3                 | 0.180         | 0.389     | 0.887 | 0.509–1.544 |
| 4–6                         | 56, 46.7                  | 63, 52.5                 | 0.817         | 0.366     | 1.263 | 0.761–2.097 |
| ≥7                          | 27, 22.5                  | 23, 19.2                 | 0.404         | 0.317     | 0.817 | 0.437–1.525 |
| First follow-up $N = 225$   |                           |                          |               |           |     |         |
| 0–3                         | 96, 83.5                  | 80, 72.7                 | 3.815         | 0.051     | 0.512 | 0.276–1.008 |
| 4–6                         | 19, 16.4                  | 27, 24.1                 | 2.113         | 0.099     | 1.622 | 0.853–3.168 |
| ≥7                          | 0, 0                      | 3, 2.7                   | 3.179         | 0.075     | 0.483 | 0.421–0.552 |
| Second follow-up $N = 169$  |                           |                          |               |           |     |         |
| 0–3                         | 71, 79.8                  | 64, 80.0                 | 0.001         | 0.971     | 1.014 | 0.477–2.154 |
| 4–6                         | 14, 15.7                  | 14, 17.5                 | 0.095         | 0.757     | 0.936 | 0.621–1.411 |
| ≥7                          | 4, 4.4                    | 2, 2.5                   | 0.489         | 0.484     | 0.545 | 0.097–3.058 |

*The patients with a positive Candida culture at first follow-up will not evaluate vaginal microflora at Second follow-up.

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**Table 6** Comparison of the adverse events in the clotrimazole group and fluconazole group (mITT).

| Characteristic                          | Clotrimazole group (n = 115) | Fluconazole group (n = 113) | $X^2$ | $P$ value | OR 95% CI |
|----------------------------------------|------------------------------|-----------------------------|-------|-----------|-----------|
| Systemic: weak, palpitation, tachycardia, migraine, headache, dizzy, rhinorrhea, numb, dizziness, fatigue. | 1 | 9 | 6.678 | 0.010 | 9.649 | 1.203–77.395 |
| Vulvovaginal pruritus, burning, irritation, and bleeding | 12 | 1 | 9.841 | 0.002 | 0.767 | 0.010–0.591 |
| Gastrointestinal tract: abdominal pain, diarrhoea, nausea. | 3 | 3 | 0 | 0.658 | 1.000 | 0.198–5.057 |
| Skin sensitivity, urticaria rash, erythematous rash, irritation, | 0 | 3 | 3.038 | 0.123 | 0.494 | 0.434–0.562 |
| Total (cases) | 16 | 12 | 0.647 | 0.274 | 0.722 | 0.326–1.600 |

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concentrations of clotrimazole vaginal tablet could account for its better efficacy.\textsuperscript{15,16} Non-albicans Candida species have increasingly been identified as the cause of vulvovaginitis.\textsuperscript{14} Elevated fluconazole MICs (>16 \textmu g/ml) were observed in C. glabrata [15.2\% resistant (R), 51.8\% susceptible-dose dependent (S-DD)].\textsuperscript{15} Azole agents are less likely to be effective against non-albicans species, especially C. glabrata, and these infections with these species should be treated with non-azoles.\textsuperscript{15} In our current study, the clinical and mycological cure rates of SVVC caused by non-albicans species were low. This result supports the use of non-azoles for treating this subgroup of patients.

Effect of clotrimazole treatment on vaginal microflora

Ross \textit{et al.} \textsuperscript{17} studied the effects of \textit{C. albicans} infection and clotrimazole treatment on vaginal microflora \textit{in vitro}. After challenge with \textit{C. albicans}, the model developed abnormal microflora. Treatment of the model with clotrimazole resulted in a decrease in \textit{C. albicans} counts to 0 within 48 h. The treatment also altered other components of the vaginal microflora, which did not return to normal. Addition of clotrimazole to the model in the absence of \textit{C. albicans} also resulted in an abnormal model by 24 h.

Boag \textit{et al.} \textsuperscript{18} studied the effect of clotrimazole 500 mg vaginal pessary and oral fluconazole 150 mg on the vaginal microbial flora. Quantitative microbiological examination was carried out on samples of vaginal secretions at intervals up to 10 days after treatment. No significant difference was found in the vaginal flora before or after therapy in individual patients or between the treatment groups.

In this study, we evaluated vaginal microflora using Nugent score and LBG of Gram stained vaginal smears collected from patients with SVVC at entry and two follow up visits was evaluated based on Nugent score and Lactobacillary grades (LBG): (a) Case 206 at entry, Nugent score 2, LBG IIa; (b) Case 206 at first follow up, Nugent score 0, LBG I; (c) Case 206 at second follow up, Nugent score 0, LBG I; (d) Case 230 at entry, Nugent score 2, LBG IIa; (e) Case 230 at first follow up, Nugent score 0, LBG I; (f) Case 230 at second follow up, Nugent score 0, LBG I.

Safety

Ritter \textit{et al.} \textsuperscript{16} found that fungicidal concentrations of clotrimazole in vaginal fluid were detectable up to 3 days after application of one vaginal tablet containing
500 mg. In contrast, clotrimazole plasma levels being lower than 0.01 µg/ml showing that clotrimazole is safe and well tolerated. Topical forms of clotrimazole are available as over-the-counter medication and are safe and without serious side effects. There is no evidence of a risk to a developing foetus in pregnancy, and this drug is safe for use in breast-feeding mothers.\textsuperscript{11,19} In this study, the adverse drug reactions to clotrimazole were mainly local, and no patients discontinued their treatment because of severe adverse reactions.

\textbf{Figure 3} A patient with SVVC experienced allergic urticaria rash (a, b, c) and a patient with SVVC experienced erythematous rash (d, e, f) on the upper and lower extremities following oral administration of fluconazole 150 mg.
The administration of oral azoles, including fluconazole, during the first trimester is not recommended because reports have described a pattern of birth defects. Based on a study from Denmark, a significantly increased risk of tetralogy of Fallot was observed (seven cases in fluconazole-exposed pregnancies (prevalence, 0.10%) compared with 287 cases in unexposed pregnancies (prevalence, 0.03%); adjusted prevalence odds ratio, 3.16; 95% CI, 1.49 to 6.71). Other common treatment-related adverse events were diarrhoea, nausea, headache, rash and allergic reaction. In this study, two patients in the fluconazole group had severe skin allergy and discontinued the study. One patient in the fluconazole group was pregnant and had a miscarriage, although it is difficult to prove the exact reason for the miscarriage. These results suggest that clotrimazole vaginal tablets are safer than oral fluconazole for treating VVC in reproductive age women.

In summary, we found similar clinical and mycological response rates to treatment with either two doses of clotrimazole vaginal tablet 500 mg or two doses of oral fluconazole 150 mg in patients with SVVC. Clinical cure or improvement occurred in 90% of evaluated patients treated with either clotrimazole or fluconazole, and the mycological eradication rates were comparable. The use of clotrimazole vaginal tablet was safer than oral fluconazole. This study demonstrated that two doses of clotrimazole vaginal tablet 500 mg were as effective as two doses of oral fluconazole 150 mg for the treatment of patients with SVVC and could be a treatment for the disorder.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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