The importance of diagnostic work-up in the management of candidal vulvovaginitis. A prospective study

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Summary

Objective: To assess the accuracy of the diagnostic work-up in identifying vaginal candidal infection, and to determine the safety, efficacy and speed of action of clotrimazole vaginal tablets.

Participants: Two hundred and twenty-three patients with symptoms and signs of candidal infection, a presence of vaginal pH ≤ 4.5 and positive 10% KOH examination.

Methods: After vaginal culture was taken, the eligible patients were treated with clotrimazole 200 mg vaginal tabs (manufactured by Teva or Agis).

Results: Cultures grew *Candida albicans* in 189 cases (85%), and *Candida non-albicans* in five (2.2%); 29 patients (13%) did not have any candidal infection. Of the 189 *C. albicans*-positive patients, 174 were reassessed for effects of clotrimazole treatment by self-reports and objective measures. Ninety-four percent of the patients reported improvement after treatment, rated moderate to high by 87%. The physician evaluation was similar: some improvement in 96%, and moderate or high improvement in 91%. At the second examination, 7.5% of the treated patients still had a positive culture for *Candida albicans*, and they remained positive on KOH microscopic examination, although vaginal pH was significantly higher. Maximal improvement was recorded three to four days after starting treatment.

Conclusion: It is important that the diagnostic work-up for suspected candidal infections consist of at least vaginal pH measurement and microscopy study with KOH. We encourage the use of vaginal cultures, especially in recurrent cases. Clotrimazole is a safe and effective treatment.

Key words: Clotrimazole; Candida; Vulvovaginitis; Diagnosis, Treatment.

Introduction

Symptomless colonization by *Candida* may be found in 20% of healthy asymptomatic women during the reproductive premenopausal years[1]. Candidal vulvovaginitis (CVV), occasionally an evolution of asymptomatic vaginal candidiasis, occurs in 72-75% of all women in their lifetime [1, 2]. About 50% of affected women have a second event [3,4], and 5% have recurrent CVV [5]. CVV is a leading cause of colpitis [1], second after bacterial vaginosis [6].

Probably because of its high prevalence, CVV is routinely diagnosed without the aid of microscopy or culture, or even self-diagnosed. However, studies have shown that as many as half these diagnoses may be false [7, 8], as the clinical signs and symptoms of CVV, namely, pruritus, irritation, soreness, dyspareunia, burning on micturition, and whitish, cheesy vaginal discharge are not specific enough. As a result, Sobel *et al.* [7] proposed a diagnostic work-up that includes vaginal pH and direct microscopy with saline and 10% KOH. The combination of positive microscopy findings combined with a vaginal pH of ≤ 4.5 and without an excess of white blood cells (WBC) is sufficient for the initiation of antifungal treatment. Positive findings with pH > 4.5 and excess of WBC indicate a possible mixed infection that should also be treated with an antifungal agent. If microscopy is negative, a culture should be done.

Among the 150 *Candida* species, *Candida albicans* is by far the most common, being responsible for 80-90% of all cases of CVV [1, 7]. The most common non-albicans species are *Candida glabrata*, found in 5-15% of cases, and *Candida tropicalis,* found in 5% [1, 7]. More recent studies have reported a significant increase in these rates, particularly in recurrences, of up to 20-30% [9].

The treatment of an uncomplicated acute episode of CVV usually includes topical imidazole agents or oral agents such as fluconazole. A single oral dose of fluconazole (150 mg) has been found to be as safe and effective as seven days of intravaginal clotrimazole therapy, with respective success rates of 94% and 97% [10]. Nevertheless, clotrimazole remains a popular agent for the treatment of CVV among both patients and physicians.

The aim of the present study was to evaluate the accuracy of the diagnostic work-up in identifying vaginal candidal infection, and to determine the safety, efficacy, and speed of action of clotrimazole vaginal tabs.

Patients and Methods

Two hundred and twenty-three patients attending community women's health clinics in Israel from June to December 2001 were recruited for the study. Inclusion criteria were as follows: otherwise healthy; aged ≥ 18 years; presence of one or more clinical symptoms and signs of CVV: pruritus, irritation, sore-

Revised manuscript accepted for publication September 6, 2003

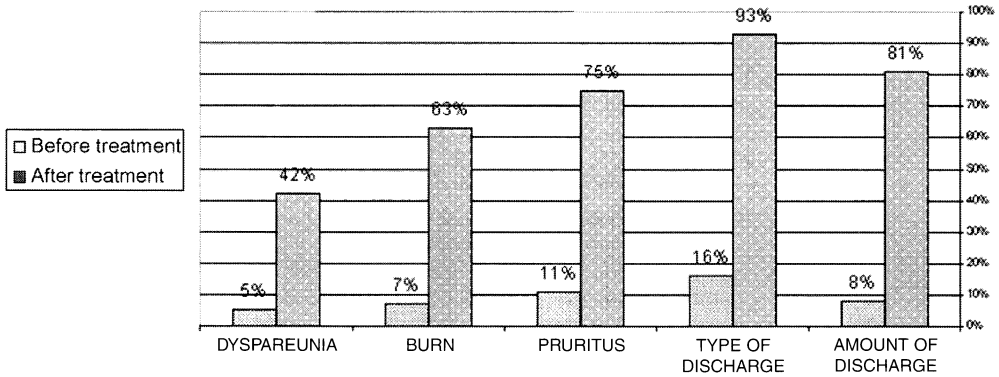

Figure 1. — Severe to moderate patient complaints before and after treatment. All differences are statistically significant ($p < 0.001$).

ness, dyspareunia or painful examination, and whitish, cheesy vaginal discharge; vaginal pH ≤ 4.5; positive 10% KOH microscopic examination. After vaginal culture was taken, the eligible patients were treated with 200 mg vaginal tabs of clotrimazole (manufactured by Teva or Agis), once daily at night, for three days.

The patients were all asked not to wash the vagina, swim, take a bath, or perform other activities that could affect the vaginal agent during treatment, and to abstain from sexual activity or to use condoms for an additional week thereafter. None of the women were menstruating during treatment, and all were using effective contraception. The women were given a targeted daily diary for recording quantity and type of secretion, pruritus, burning sensation and pain level, and were scheduled for a follow-up examination 7-11 days after treatment. At follow-up, a history and physical examination were performed, along with a vaginal pH and microscopy examination with 10% KOH, and culture for *Candida*, and the diary was reviewed.

Table 1. — *Patients' subjective complaints before and after treatment.*

	First examination (n = 174)	Second examination (n = 174)
Vaginal discharge		
None	2 (1.1%)	72 (41.3%)
Mild	28 (16.0%)	88 (50.5%)
Moderate	101 (58.0%)	12 (6.9%)
Severe	43 (24.7%)	2 (1.1%)
Type of discharge		
Transparent	2 (1.1%)	91 (52.3%)
Watery	8 (4.6%)	55 (31.6%)
White	101 (58.0%)	25 (14.4%)
Cheesy	63 (36.2%)	3 (1.7%)
Pruritus		
None	9 (5.2%)	119 (68.4%)
Mild	34 (19.6%)	35 (20.1%)
Moderate	74 (42.5%)	15 (8.6%)
Severe	57 (32.8%)	5 (2.8%)
Burning		
None	19 (10.9%)	118 (67.8%)
Mild	43 (24.7%)	43 (24.7%)
Moderate	62 (35.6%)	8 (4.6%)
Severe	50 (28.7%)	5 (2.8%)
Dyspareunia		
None	42 (24.1%)	133 (76.5%)
Mild	31 (17.8%)	32 (18.4%)
Moderate	59 (33.9%)	5 (2.8%)
Severe	42 (24.1%)	4 (2.3%)

A significant improvement occurred from the first to the second examination, for each complaint ($p < 0.05$).

Table 2. — *Findings on examination before and after treatment.*

	First examination (n = 174)	Second examination (n = 174)
Vaginal discharge		
Mild	16 (9.2%)	55 (31.6%)
Moderate	112 (64.4%)	112 (64.3%)
Severe	46 (26.4%)	7 (4.0%)
Type of discharge		
Transparent	0	90 (51.7%)
Watery	3 (1.7%)	46 (26.4%)
White	87 (50.0%)	32 (18.4%)
Cheesy	84 (48.2%)	6 (3.5%)
Erythema		
None	13 (7.5%)	126 (72.4%)
Mild	44 (25.3%)	45 (25.9%)
Moderate	83 (47.7%)	1 (0.6%)
Severe	34 (19.5%)	2 (1.1%)
White plaque		
None	23 (13.2%)	145 (83.3%)
Mild	40 (22.9%)	26 (15.0%)
Moderate	77 (44.2%)	3 (1.7%)
Severe	34 (19.5%)	0
Painful examination		
None	42 (24.1%)	145 (83.3%)
Mild	63 (36.2%)	25 (14.3%)
Moderate	47 (27.0%)	3 (1.8%)
Severe	22 (12.6%)	1 (0.6%)

A significant improvement occurred from the first to the second examination, for each finding ($p < 0.05$).

Statistical analysis was performed using SAS software. Results are expressed in mean ± SD or rate. The Student's t-test was used to compare continuous data and chi-square and Fisher's exact tests for categorical data. A p value of < 0.05 was considered significant.

Results

Cultures were positive for *Candida albicans* in 189 cases (85%), and for non-albicans *Candida* in five (2.2%); 29 patients (13%) did not have a candidal infection. Of the 189 patients who were positive for Candida albicans, 174 were available for follow-up (mean age 33.3 ± 9.9 years). Overall, by history, 76 patients (43.6%) had recurrent CVV. The interval between the two examinations was 10.2 ± 1.7 days.

Table 1 presents the patients' subjective complaints before and after treatment. A significant improvement in

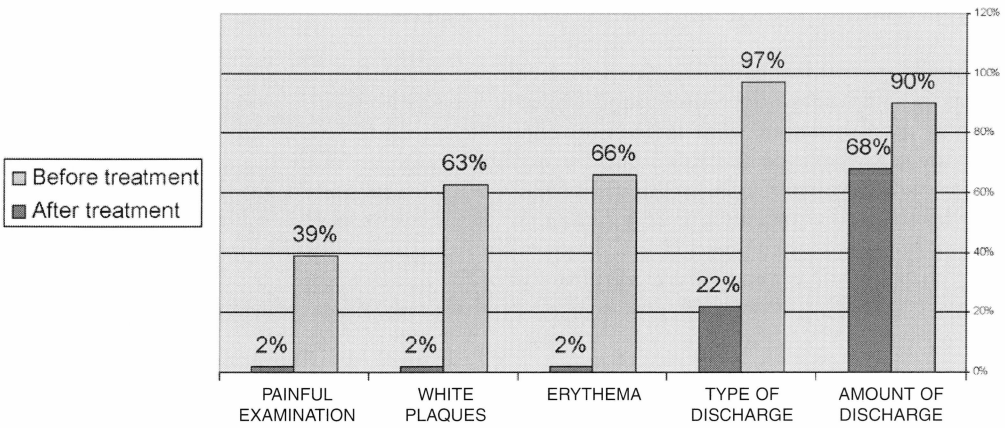

Figure 2. — Severe to moderate findings on examination before and after treatment. All differences are statistically significant ($p < 0.001$).

Table 3. — *Laboratory findings before and after treatment.*

	First examination (n = 174)	Second examination (n = 174)
Positive 10% KOH smear	174 (100%)	10 (5.8%)
Positive vaginal culture	174 (100%)	13 (7.5%)
Vaginal pH	3.76 ± 0.52	5.16 ± 1.07

A significant improvement occurred from the first to the second examination ($p < 0.05$).

Table 4. — *Patient and physician evaluation of treatment effectiveness.*

	n = 174
Patient evaluation	
Worse	2 (1.1%)
No change	9 (5.1%)
Mild improvement	12 (6.9%)
Moderate improvement	25 (14.4%)
High improvement	126 (72.4%)
Physician evaluation	
No change	6 (3.4%)
Mild improvement	8 (4.5%)
Moderate improvement	31 (17.8%)
High improvement	129 (74.1%)

each of the symptoms occurred from the first to the second examination ($p < 0.05$). Figure 1 shows the change in the severe and moderate complaints. All differences were statistically significant ($p < 0.001$).

Similar results were found for the findings on physical examination before and after treatment (Table 2). Changes in the severe and moderate findings are shown in Figure 2. All differences were statistically significant ($p < 0.001$).

Table 3 presents the laboratory findings before and after treatment. A significant improvement was noted from the first to the second examination ($p < 0.05$). Only three patients reported any side-effects of the drug.

Patient and physician evaluations of treatment effectiveness (Table 4) showed that 163 (94%) women noted an improvement after treatment, with 151 (87%) reporting moderate to high improvement. The physician evaluations were similar, with some improvement reported in

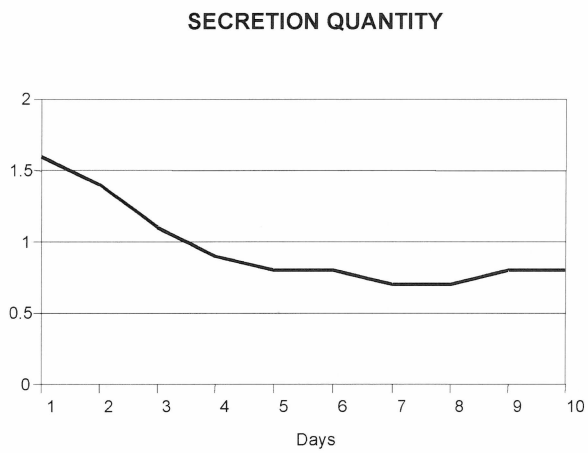

Figure 3. — Mean change in quantity of secretion by time after treatment and study group. Similar results were found in all other symptoms, which were recorded by the patients, such as type of secretion, pruritus, burning and pain.

168 women (96%) and moderate to high improvement in 160 (91%).

Maximal improvement in quantity and type of secretions, pruritus, burning and pain level, according to the patients' daily diaries, was recorded three to four days after starting treatment (one example is presented in Figure 3).

It is noteworthy that the two forms of clotrimazole used here (Teva and Agis) were distributed randomly to 90 and 84 of the women, respectively. No differences were found in safety, efficacy, and time to clinical improvement of symptoms, or in findings on microscopy and physical examination between these two groups (Ben-Haroush *et al.*, unpublished data).

Discussion

Recurrent CVV, a common and disturbing problem, was found in 43.6% of our patients. Of the 223 patients with symptoms and signs of CVV, vaginal pH ≤ 4.5, and positive findings on 10% KOH microscopy examination,

only 189 (85%) had positive cultures for *Candida albicans*, and 29 (13%) did not have a candidal infection at all. Hence, clinical impression alone would probably yield higher rates of false diagnosis; indeed, others have reported false diagnoses in almost half their cases [8]. Furthermore, although vaginal pH and KOH microscopy examination have been described as being sensitive and specific enough for the diagnosis of CVV, and sufficient for the initiation of antifungal treatment [7], according to our work-up, 15% of the patients were not infected by *Candida albicans*. This finding stresses the importance of cultures in the diagnosis of CVV, particularly in recurrent cases.

Regarding treatment, our results show that clotrimazole is highly effective, both subjectively (Table 1) and objectively (Table 2) in treating proven CVV. It is noteworthy, however, that 7.5% of the treated patients still had a positive *Candida* culture at the second examination (Table 3) in addition to a positive 10% KOH microscopy examination, although the vaginal pH was significantly higher.

Before treatment, the moderate to severe complaints included type (93%) and quantity (81%) of discharge, pruritus (75%), burning (63%), and dyspareunia (42%). All significantly improved after treatment (Figure 1). Ninety-four percent of the whole sample noted at least some improvement in symptoms after treatment, with 87% reporting moderate to high improvement. Rates were similar for the physician evaluation. Maximal improvement was recorded three to four days after starting treatment.

In conclusion, as part of the diagnostic work-up of patients with suspected CVV, physicians need to perform at least vaginal pH measurement and KOH microscopic examination. This protocol led to a false diagnosis of CVV in only 13% of patients, a much lower rate than previously reported. Therefore, it is important to use vaginal cultures, especially in recurrent cases. Clotrimazole in both available forms is safe and effective in treating CVV. Maximal improvement can be expected within three to four days.

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