

Comparison of Boric Acid with Clotrimazole in the Treatment of Recurrent or Resistant Vulvovaginitis Caused by Non-Albicans Species of *Candida*

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Abstract

Background: Vulvovaginal candidiasis is one of the most common infections in gynecologic field, and non-albicans *Candida* species are emerging causative microorganisms. This species shows resistance to routine treatments. One of the suggested treatments is administration of vaginal suppositories of boric acid. The aim of the present study was to compare boric acid with clotrimazole in the treatment of recurrent or resistant vulvovaginitis.

Methods: In a double-blind, randomized clinical trial, 90 non-pregnant women were enrolled. The patients were divided into two groups to receive; boric acid (300 mg twice a day for 2 weeks) or clotrimazole (100 mg once a day for 2 weeks) intravaginally. Treatment responses were monitored by laboratory and clinical data.

Results: Treatment responses were significantly different in laboratory results for boric acid and clotrimazole groups (86.7% v 60%, P= 0.004). Clinical responses (improved signs and symptoms) showed no significant differences (8.2. v 6.5, P= 0.02). Drug side effects were not different in boric acid and clotrimazole groups (13.3% v 11.1%, P= 0.75).

Conclusion: Intra-vaginal administration of boric acid is more effective than clotrimazole in vaginal candidiasis caused by non-albicans species.

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Keywords • Clotrimazole • boric acid • candida glabrata • candida tropicalis • Treatment

Introduction

Genitourinary infections are one of the most common disorders for which the patients visit a gynecologist.¹ It is estimated that 75% of women experience at least one period of vulvovaginal candidiasis throughout their lives,² and approximately 45% of women will be infected twice or more.³

Candida albicans is the responsible germ in 85-90% of vaginal fungal infections. Other species of *Candida* (non-albicans *Candida*) such as *Candida glabrata*, *Candida tropicalis*, and *Candida cruzi* can also cause vulvovaginal signs.¹

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These organisms are usually resistant to the conventional treatment. The prevalence of non-albicans species of *Candida* as the cause of fungal vaginitis is increasing. The infection rates were 9.9% in 1995 and 17.2% in 1998.¹

Recurrent infection may be caused by the resistance of non-albicans species to the anti-fungal drugs. Experimental and clinical studies show that imidazoles such as miconazole and clotrimazole are not so effective on non-albicans *Candida*.⁴

Candida tropicalis and *Candida glabrata* are ten times less sensitive to miconazole than *Candida albicans*.⁴ A study performed on 250 patients with *Candida glabrata* infection showed that the organism was resistant to ketoconazole, itraconazole, and clotrimazole.⁵

In the study by Sobel et al. on 92 patients with fungal infections who were resistant to azole derivatives, treatment with boric acid resulted in 98% improvement.⁶

In another study by Sobel and Chaim on 60 symptomatic patients with *Candida glabrata* infection, clinical improvement was seen in 81% of patients with boric acid and in less than 50% with systemic and topical azole derivatives.⁷

Recently, most studies indicated that treatment failure with azole drugs can be managed by vaginal boric acid and approximately in 2/3 of single attacks treatment response has been observed with minimal side effects.^{8,9} In addition to conventional treatments, there are supplemental and substitution treatment for persistent vulvovaginal candidiasis. Efficacy and safety of these treatments should be assessed in randomized clinical trials.¹⁰ A study performed by Cuaschip and coworkers confirmed the efficacy of boric acid in non-albicans vulvovaginal candidiasis.¹¹

A study performed by Ray et al. concluded that diabetic women with *Candida glabrata* vulvovaginitis showed higher cure with vaginal suppositories of boric acid compared with oral single dose of fluconazole.¹²

However, azole derivatives are used in the treatment of *Candida* vulvovaginitis regardless of its type. Most women with chronic vaginal signs do not accept the conventional antifungal treatment because of the treatment failure with azole derivatives. They prefer alternative treatments. In one study 73% of patients with chronic vaginitis paid \$ US 2 to 1000 for these kinds of treatments in a 2-year period with self over treatment. Of these patients, 42% used alternative treatments such as vaginal douche, boric acid, tea tree oil, and garlic.¹³

The increasing prevalence of non-albicans species of *Candida* as the cause of resistant and recurrent vaginitis necessitates studies on

different drugs.

Our main goal in the present study was to compare boric acid with clotrimazole in the treatment of fungal vulvovaginitis caused by non-albicans species of *Candida*.

Subjects and Methods

This study was designed as a double-blind, randomized clinical trial comparing two groups of women. One group received vaginal suppositories of clotrimazole while the other group received vaginal suppositories of boric acid. In the present study, we investigated the effect of clotrimazole and boric acid on vaginitis caused by non-albicans *Candida*.

This study was approved by the Ethical Committee of Mashhad University of Medical Sciences.

Of the 120 patients referred to the gynecology clinic of Imam Reza Hospital, Mashhad, Iran from February 2004 to January 2005 with recurrent or resistant vulvovaginal signs, 90 patients who fulfilled the inclusion criteria were recruited.

Included patients were those who accepted to participate in the study and were married, aged between 18 to 44 years, educated, non-pregnant, and did not have intrauterine devices. The patients with the history of cardiac disease, immune system defects, diabetes, coagulopathies, kidney or other organ transplant, and with recent anemia were excluded from the study. The patients did not have any serious physical or mental problems and were able to answer the questions. They did not have pelvic inflammatory disease, and cervicitis. Also, they did not have an abnormal pap smear during the last year. The overall score for signs and symptoms of vaginal infection was at least 3. The wet smears were negative for *trichomonas* and *hemophilus vaginalis*. Vaginal discharge cultures were positive for non-albicans *Candida* species and were negative for gonococci and *hemophilus vaginalis*. The patient did not use any other antifungal drugs.

Vaginal suppositories of boric acid were manufactured in the laboratory of pharmacy school with a fixed ratio of boric acid (300mg), glycerin and gelatin.

The study population was 90 women with signs and symptoms of vaginal fungal infections who were resistant to conventional treatment and also patients with recurrent vaginitis. After the completion of a questionnaire about the parity, age, and education level of the patients and performing physical examination, vaginal discharges were cultured for non-albicans species. The patients who were positive for non-albicans *Candida* and were

negative for trichomonas or bacterial vaginosis entered the study. They were randomly divided into two groups. Group one received vaginal suppositories of boric acid (300 mg twice a day for 2 weeks) and the other group received vaginal suppositories of clotrimazole (100mg a day for 2 weeks).

After 2 weeks, the patients were visited and their vaginal discharges were sent to the laboratory for culture. The patients in the two groups were compared for the treatment response (clinical signs and symptoms and discharge culture results), adverse reactions, compliance, and satisfaction.

The data were analyzed by SPSS software version 11.5. Student *t* test for quantitative parameters and Chi square for qualitative parameters were used.

Results

A total of 90 patients (45 in each group) received vaginal clotrimazole or boric acid. The demographic characteristics of the patients were similar (table 1).

Regarding the economic status of the patients' families, 73.3% in the clotrimazole group and 82.2% in the boric acid group had a

moderate income (P=0.61).

Of the patients in boric acid group, 31.1% were employed but this rate was 8.1% in clotrimazole group (P=0.008).

The two groups were different considering hygienic recommendations during the treatment period (p=0.008). In the clotrimazole group, 91.1% of the patients followed all hygienic recommendations and in the boric acid group 68.9% followed the recommendations.

In both groups, 40% of the patients had itching and 60% had no itching (p=1).

In boric acid group 24.4% and in clotrimazole group 17.8% of the patients had forgotten at least one dose of their drugs (P=0.001).

In the boric acid group 35.6% and in clotrimazole group 15.6% of the patients had a history of recurrent infection during the last year (P=0.03).

Treatment success rates were evaluated based on the results of vaginal discharge cultures 2 weeks after starting the treatment. The success rate was 86.7% in boric acid group and 60% in clotrimazole group (P=0.004, figure 1).

Figure 2 shows clinical response to anti-fungal treatment in the two groups.

11.1% of the patients in clotrimazole group and 13.3% of patients in boric acid group

Table 1: Demographic characteristics of the patients with vulvovaginal non-albicans candidiasis

Characteristics	Clotrimazole (n= 45)	Boric Acid (n=45)	P
Age (year)	29.31±5.07	30.54±5.78	0.61
Body mass index (Kg/m ²)	25.21±4.22	24.72±2.91	0.73
Regular menstrual cycle (%)	68.91	68.92	1
Breast feeding history (%)	15.61	4.43	0.08
Stressful accidents in the treatment period (%)	13.31	8.92	0.5
Using antibiotics during the treatment and 2 weeks afterwards (%)	15.61	17.82	0.77
Using oral contraceptive pills during the treatment period (%)	13.31	4.42	0.14

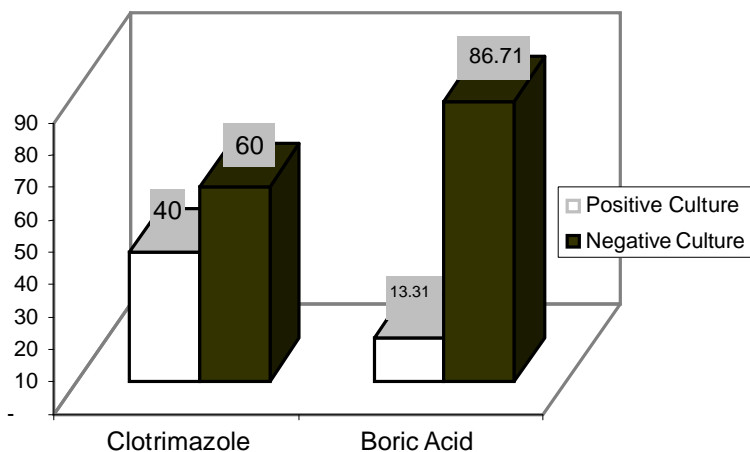


Figure 1: Comparison of the treatment response in the two groups of patients with vulvovaginal non-albicans candidiasis (P=0.004).

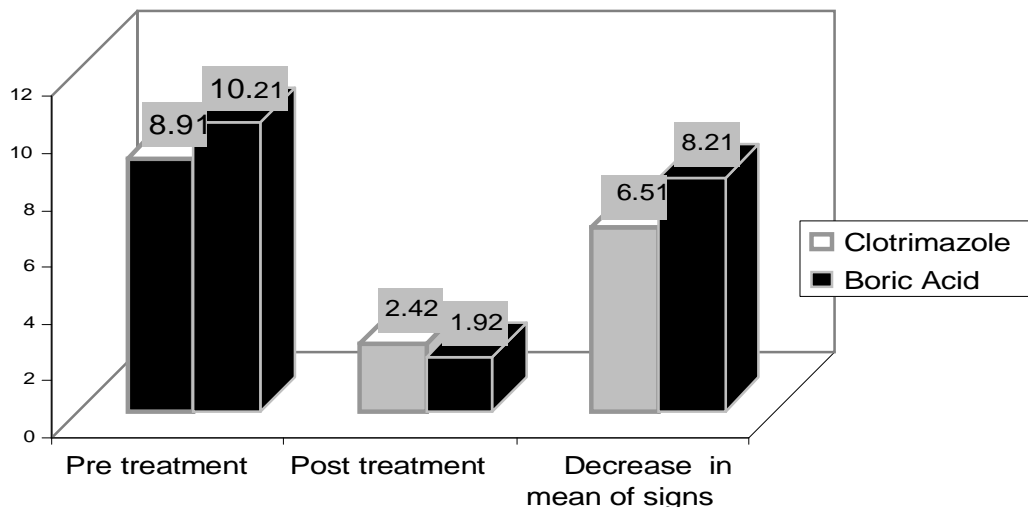


Figure 2: Comparison of the mean signs in the two groups of patients with vulvovaginal non-albicans candidiasis (P=0.09, P=0.32, P=0.02 respectively).

complained from the drugs' side effects. There was no statistically significant difference between the two groups. (P=0.75)

One patient in boric acid group discontinued her medication due to skin irritation.

In clotrimazole group, 71.1% of the patients and in boric acid group, 68.9% of the patients were completely satisfied with their treatment regimen. In clotrimazole group, 24.4% of the patients and in boric acid group, 26.7% of the patients were partially satisfied with their treatment regimen. Two patients in each group were not satisfied with the treatments.

Discussion

The results of the present study showed that the success rate of treatment was significantly higher in boric acid group compared with the clotrimazole. Walter Sobel conducted a study in vaginitis clinic of Vienna University on 102 symptomatic patients with vaginitis caused by *Candida glabrata*. They administered boric acid vaginal suppositories with clinical and para clinical response of 64%. In their study population, 40 patients had a history of treatment failure with azole derivatives.¹³

In another study by Jovani et al. on 92 patients with vaginal fungal infection resistant to conventional antifungal treatments and violet de gensen, vaginal suppositories of boric acid improved the condition in 98% of patients.⁶

In another study by Sobel and Chaim on 60 symptomatic patients with vaginal infection with *Candida glabrata* alone or comorbid with bacterial vaginosis, clinical improvement was seen in 81% and fungal eradication was seen

in 66% of the patients after treatment with boric acid. Clinical and para clinical improvement was less than 50% with systemic or topical azole derivatives.⁷

In another retrospective study by Sobel and Chaim on 141 women with *Candida glabrata* vaginitis, vaginal suppositories of boric acid resulted in clinical and para clinical improvements in 64 to 71% of the patients.¹³

In a double-blind randomized study on 108 patients with fungal vaginitis, improvement rate with boric acid was 92% and treatment success rate was 64% with nystatin.⁶ Our study results showed that one patient discontinued the treatment because of the side effects of boric acid but there was not such a case in clotrimazole group. In the study by Sobel et al. 10% of the patients in boric acid group sometimes experienced a burning sensation but none of them stopped their treatment as a cause of topical or systemic side effects of the drug.¹³

In an investigation by Sobel et al. the side effects were seen in four patients but it was not serious to result in treatment discontinuation.⁶

In a study by Watson et al. in 2002, the rate of side effects of clotrimazole was reported to be 12%.¹⁴

Conclusions

The treatment success rate of vaginal suppositories of boric acid was more than vaginal clotrimazole in women with vaginal candidiasis with non-albicans species. The adverse reactions profile was similar with the two drugs.

Conflict of Interest: None declared

References

- 1 Spoer DE. Genitourinary infections and Sexually transmitted disease in: Berek J.S. Novaks. 13th ed Gynecology Philadelphia lippincott Williams and wilkins; 2002. p. 453.
- 2 Hurley R, De Louvois J. Candida vaginitis. *Postgrad Med J* 1979; 55: 645-7.
- 3 Hurley R. Recurrent Candida infection. *Clin Obstet Gynaecol* 1981; 8: 209-14.
- 4 Rinydahl EN. Treatment of recurrent vulvovaginal candidiasis. *Am Fam Physician* 2000; 61: 3306-12.
- 5 White DJ, Johnson EM, Warnock DW. Management of persistent vulvo vaginal candidosis due to azole-resistant Candida glabrata. *Genitourin Med* 1993; 69: 112-4.
- 6 Sobel JD, Faro S, Force RW, et al. Vulvovaginal candidiasis: epidemiologic, diagnostic, and therapeutic considerations. *Am J Obstet Gynecol* 1998; 178: 203-11.
- 7 Sobel JD, Chaim W. Treatment of torulopsis glabrata vaginitis: retrospective review of boric acid therapy. *Clin Infect Dis* 1997; 24: 649-52.
- 8 Sobel JD, Brooker D, Stein GE, et al. Single oral dose fluconazole compared with conventional clotrimazole topical therapy of Candida vaginitis. Fluconazole Vaginitis Study Group. *Am J Obstet Gynecol* 1995; 172: 1263-8.
- 9 Shinohara YT, Tasker SA. Successful use of boric acid to control azole-refractory Candida vaginitis in a woman with AIDS. *J Acquir Immune Defic Syndr Hum Retroviro* 1997; 16: 219-20.
- 10 Van Kessel K, Assefi N, Marrazzo J, Eckert L. Common complementary and alternative therapies for yeast vaginitis and bacterial vaginosis: a systematic review. *Obstet Gynecol Surv* 2003; 58: 351-8.
- 11 Guaschino S, De Seta F, Sartore A, et al. Efficacy of maintenance therapy with topical boric acid in comparison with oral itraconazole in the treatment of recurrent vulvovaginal candidiasis. *Am J Obstet Gynecol* 2001; 184: 598-602.
- 12 Ray D, Goswami R, Banerjee U, et al. Prevalence of Candida glabrata and its response to boric acid vaginal suppositories in comparison with oral fluconazole in patients with diabetes and vulvovaginal candidiasis. *Diabetes Care* 2007; 30: 312-7.
- 13 Sobel JD, Chaim W, Nagappan V, Leaman D. Treatment of vaginitis caused by Candida glabrata: use of topical boric acid and flucytosine. *Am J Obstet Gynecol* 2003; 189: 1297-300.
- 14 Watson MC, Grimshaw JM, Bond CM, et al. Oral versus intra-vaginal imidazole and triazole anti-fungal agents for the treatment of uncomplicated vulvovaginal candidiasis (thrush): a systematic review. *BJOG* 2002; 109: 85-95.