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Clinicians' use of Intravaginal Boric Acid Maintenance Therapy for Recurrent Vulvovaginal Candidiasis and Bacterial Vaginosis

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Abstract

A retrospective chart review characterized clinicians' use of maintenance intravaginal boric acid (BA) for women with recurrent vulvovaginal candidiasis or bacterial vaginosis. Average length of use was 13 months with high patient satisfaction and few adverse events. Prospective studies are needed to evaluate the efficacy of maintenance BA for these conditions.

Short Summary:

We characterized clinician's use of maintenance boric acid for women with recurrent VVC or BV. Average length of use was 13 months with high patient satisfaction and few adverse events.

Keywords

Vulvovaginal candidiasis; Bacterial Vaginosis; Boric Acid

INTRODUCTION

Despite considerable patient morbidity, options for the treatment of recurrent bacterial vaginosis (rBV) (1) and recurrent vulvovaginal candidiasis (rVVC) (particularly in the setting of azole resistance) (2) are limited. Boric acid (BA) is an inorganic acid which has been used for decades to treat vulvovaginal and otic infections.(3–6) Short courses of BA are recommended or are under investigation as part of treatment of BV and VVC. Intravaginal BA for 10–14 days has been shown to be effective for VVC(3, 7) and has become a first line alternative to azoles in the context of resistance.(2) An oral nitroimidazole followed by intravaginal BA 600mg daily for 21 days with subsequent suppressive intravaginal

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metronidazole gel twice weekly improved outcomes in women with rBV and is recommended by the CDC.(8, 9) While unpublished data suggest that intravaginal BA alone may be inadequate for achieving a satisfactory response in acute BV,(1) a protocol for a randomized controlled trial of 10 days of 600mg intravaginal BA versus intravaginal metronidazole gel and placebo to treat acute BV has been described.(10) A novel BA and EDTA containing intravaginal agent (TOL-463) used for 7 days in Phase 2 trials shows efficacy in treating VVC (clinical cure rate of 92% for the insert and 81% for the gel form) with lower efficacy in treating BV (59% for insert and 50% for gel) though reported symptom resolution was high in both groups (69–93%).(11)

The use of BA maintenance therapy in women with azole resistant rVVC is often advised by clinical experts, however optimal administration frequency is undetermined and long-term safety data are not available.(2) The literature on maintenance BA therapy is limited. For VVC, case reports have described the successful use of longer term (over months) maintenance BA, however regimens varied.(3, 12) One study of intermittent therapy treated 92 women with refractory VVC with 600mg BA for 14 days, followed by once daily BA during menstruation for 4 months in 38 of the patients.(13) A second small trial treated 11 patients with rVVC with intermittent oral itraconazole and 11 patients with intermittent BA (300mg daily in vaginal ovules for 14 days followed by 300mg daily for 5 days during menses for 5 months, with similar efficacy to itraconazole and few side-effects in the BA group.(14) There are no published data on the use of BA maintenance therapy in patients with rBV.

Despite the lack of published data, anecdotally clinicians use long term maintenance intravaginal BA to treat women with rVVC, rBV, or both. Understanding use of these regimens may improve our understanding of clinical practice, provide reassurance regarding the tolerability of chronic BA use, and provide preliminary data to design larger, prospective trials to evaluate the effectiveness of these regimens. Therefore, in this study, we performed a retrospective chart review to characterize clinicians' use of maintenance BA regimens to treat rVVC and rBV in a large network of university-affiliated outpatient gynecology clinics.

MATERIALS AND METHODS

We searched for the phrase "boric acid" in all clinic notes within the Johns Hopkins affiliated outpatient GYN clinic system (which has over 100,000 patient visits per year) from 4/2013–5/2018. Initially we obtained a total of 1306 clinic visits from 647 patients. We then narrowed this to patients who had ≥2 clinic visits in which BA was discussed, yielding 931 visits from 272 patients. Charts from these 272 patients were reviewed. Patients in whom it could not be determined if BA was ever used, in those for whom BA was not used specifically for a diagnosis of rVVC or rBV, or forwhom the dosage of the BA regimen prescribed was unclear, those who were not prescribed a maintenance regimen of BA planned to be longer than a month (e.g. patients with rBV prescribed BA for 21 days and then transitioned to long term maintenance metronidazole intravaginal gel), and those for whom no information was available on length of use or satisfaction with use were excluded from analysis. Patients' satisfaction was characterized as "not satisfied", "satisfied" or "partially satisfied" based on clinician documentation and assessment. In a few patients in

whom satisfaction was poorly documented, continued refill requests were used as a proxy for satisfaction. Length of use was estimated from clinician documentation and refill requests. BA was typically obtained through compounding pharmacies.

Data were abstracted from relevant charts. Demographics, BA prescribed regimens, and satisfaction were compared in women prescribed BA for rVVC and rBV. Two sample t-tests were used to compare continuous outcomes and chi^2 to compare categorical outcomes. All analyses were conducted using STATA v.15. This study was granted approval by the Johns Hopkins IRB (IRB00164072).

RESULTS

After exclusions (the majority due to lack of documentation of initiation or duration of use), data from 78 patients (35 prescribed BA for rVVC, 33 for rBV and 10 for both rVVC and rBV) based on notes from 47 different providers were available for analysis (see Table 1). Most (74.4%) of women were prescribed an “induction” regimen of daily BA to be used for 7–14 days prior to initiating the maintenance regimen. An additional 2 women (2.6%) were given a 21 day BA induction regimen. For maintenance, women were generally prescribed either 300mg or 600mg of intravaginal BA to be used 2–3 times per week. All women who were prescribed a 300mg induction regimen were transitioned to a 300mg maintenance regimen; similarly all women who were prescribed a 600mg induction regimen were transitioned to a 600mg maintenance regimen.

34.6% of women were additionally prescribed an induction antifungal or antibacterial regimen to be taken before or concomitant with the BA induction regimen. For women with rVVC, prescribed medications included either fluconazole or topical azoles. For women with rBV or mixed rBV and rVVC, these included antibacterials (oral metronidazole 500mg po BID X 7 days, or metronidazole intravaginal 0.75% gel once daily for 5 days, oral or topical clindamycin or oral tinidazole). Some women with rBV or rBV and rVVC were also prescribed antifungals (e.g. oral fluconazole 150mg po X 1 after finishing induction metronidazole, presumably to stave off VVC). A larger proportion (45.5%) of women with rBV were given a prescription for non-BA induction therapy as compared to those with rVVC (17.1%), $p<0.01$.

The average length of BA use was estimated at 13.3 months. However, 37.2% of patients used maintenance BA for a year or more. A few patients used BA for an extended period of time, including 9 who used it for >=3 years. Side-effects were uncommonly reported. One patient complained of BA leaking out the day after use. One patient who was using 600mg reported irritation and decreased her dose to 300mg BA with good results. Three others reported some moderate vaginal irritation.

Satisfaction with the BA regimen was high (76.9% overall). Unsatisfied women reported that vaginal symptoms continued unabated or worsened. Although there were no statistically significant differences between proportions of patients who reported satisfaction with their regimen based on receipt of BA induction, BA dose, or antifungal/antibacterial induction,

the only patients with rBV who were not satisfied with their regimen did not receive antibacterial induction therapy.

DISCUSSION

We found that clinicians are using BA maintenance regimens to treat rVVC, rBV, or both, often preceded by a daily BA and antifungal or antibacterial “induction” regimen. BA is rapidly absorbed by mouth and oral ingestion can lead to death, although vaginal absorption appears to be minimal.(5) Importantly, in our study intravaginal BA appeared to be well tolerated even when used over several years, and reported satisfaction with these regimens was high. The mechanism by which boric acid may be alleviating symptoms in women with rVVC and rBV is unclear, though BA has been reported to inhibit *in vitro* growth of yeast, gram positive and gram negative bacteria, and the formation of biofilms.(15, 16) It is also possible that BA improves symptoms by modulating metabolites produced by yeast or bacteria, or the host’s immune response to these organisms.

There were a number of limitations. This was a retrospective study based on clinical charts. Since documentation was often sparse (the full Amsel’s criteria were rarely documented) and Nugent scores were not done, (17) it was not possible to establish clear clinical or microbiologic endpoints to measure treatment efficacy. Clinicians were not always systematic in assessing and documenting patient satisfaction. It is possible that we could have inadvertently excluded some women who discontinued BA use early due to bothersome side effects. Also, given the limited number of women in our study we might not have detected uncommon side effects. Importantly, no comparison with other regimens for rVVC (e.g. suppressive weekly fluconazole) or rBV (e.g. suppressive twice weekly metronidazole intravaginal gel) was possible.

Despite these limitations, our study does provide some reassurance regarding the long-term tolerability of intravaginal boric acid maintenance therapy. It also suggests that BA maintenance regimens of 300–600mg used twice weekly, particularly after induction BA and perhaps antifungal or antibacterial therapy may hold promise in the treatment of rVVC and rBV. However, larger, prospective studies are needed before these regimens can be recommended for routine clinical use.

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Table 1.

Characteristics of patients prescribed Boric Acid

	Total N=78	**Prescribed BA for rVVC N=35**	**Prescribed BA for rBV N=33**	**Prescribed BA for both rVVC and rBV N=10**	**P value comparing rVVC vs. rBV patients***
Age mean (SD)	39.7(10.6)	41.3(12.6)	38.2(9.1)	38.7(7.2)	0.26
Race					
Black	36(46.2)	3(8.6)	25(75.8)	8(80.0)	<0.01
White	37(47.4)	29(82.9)	6(18.2)	2(20.0)	
Other	5(6.4)	3(8.6)	2(6.1)	0	
Parity ** mean(SD)	1.4(1.4)	1.0 (1.4)	1.7(1.5)	1.2 (1.1)	0.05
Hormonal Contraception	24(30.8)	11(31.4)	10(30.3)	3(30.0)	0.92
Topical or systemic hormone replacement	6(7.7)	3(8.6)	2(6.1)	1(10.0)	0.69
History of BV	48(61.5)	5(14.3)	33(100.0)	10 (100.0)	<0.01
History of VVC	57(73.1)	35(100.0)	12(36.4)	10 (100.0)	<0.01
Other concomitant chronic vaginal conditions					
Chronic pelvic pain/ pelvic floor dysfunction	3(3.9)	2(5.7)	1(3.0)	0(0.0)	<0.01
Vulvodynia	13(16.7)	10(28.6)	2(6.1)	1(10.0)	
Vaginal atrophy	2(2.6)	2(5.7)	0(0.0)	0(0.0)	
Vulvodynia/atrophy	1(1.3)	1(2.9)	0(0.0)	0(0.0)	
Lichen sclerosus/simplex	4(5.1)	4(11.4)	0(0.0)	0(0.0)	
BA induction prescribed					
300mg daily X 7–14 days	28(35.9)	10(28.6)	15(45.5)	3(30.0)	0.09
600mg daily X 7–14 days	30(38.5)	16(45.7)	7(21.2)	7(70.0)	
600mg daily X21 days	2(2.6)	0(0.0)	2(6.1)	0(0.0)	
None	18(23.1)	9(25.7)	9(27.3)	0(0.0)	
BA maintenance prescribed					
300mg 2–3X per week†	42(53.9)	17(48.6)	22(66.7)	3(30.0)	0.06
600mg 2–3X per week‡	34(43.6)	18(51.4)	9(27.3)	7(70.0)	
Other (sporadic)††	2(2.6)	0(0.0)	2(6.1)	0(0.0)	
Use of antifungal (for rVVC) or antibacterial (for rBV) induction when starting BA	27(34.6)	6(17.1)***	15(45.5)	6(60.0)	0.01
Average length of BA use (mos)**	13.3(16.5)	10.3(12.7)	17.2(20.6)	11.3(10.0)	0.10
Length of BA use (mos)					
<1mo	2(2.6)	0(0.0)	1(3.0)	1(10.0)	0.39
1–5mos	25(32.1)	14(40.0)	9(27.3)	2(20.0)	
6–11mos	22(28.2)	10(28.6)	9(27.3)	3(30.0)	

	Total N=78	Prescribed BA for rVVC N=35	Prescribed BA for rBV N=33	Prescribed BA for both rVVC and rBV N=10	P value comparing rVVC vs. rBV patients*
12–23 mos	13(16.7)	6(17.1)	4(12.1)	3(30.0)	
>=24mos	16(20.5)	5(14.3)	10(30.3)	1(10.0)	
Satisfaction with BA use					
No	13(16.7)	7(20.0)	4(12.1)	2(20.0)	0.27
Yes	60(76.9)	27(77.1)	25(75.8)	8(80.0)	
Partial	5(6.4)	1(2.9)	4(12.1)	0(0.0)	

There are concerns that BA may be teratogenic. Importantly, no patients were known to be pregnant at the time that BA was first prescribed.(5)

*Patients prescribed BA for both rVVC and rBV excluded due to small numbers (N=10). T-test for continuous and chi2 for categorical values.

**missing data on one patient.

***one patient was prescribed clindamycin due to an episode of BV though the primary indication for BA use was rVVC.

****those with months of use <1 mo were replaced with 0.5.

†6 patients were prescribed 1–2 times per week, one was prescribed 3–4 times per week. One patient transitioned from 300mg 2 times per week to 600mg 2 times per week.

ƒOne patient was prescribed 1–2 times per week. Another patient started out using 600mg 2 times per week and transitioned to 300mg 2 times per week.

††One patient was prescribed 600mg 2–3 times per week and then transitioned to using it sporadically as needed with symptoms, another patient was prescribed 600mg to use after menses and sporadically with symptoms.