

Original Research Article

Effectiveness of combined use of sodium bicarbonate sitz bath prescription and vaginal nystatin suppository in the treatment of patients with fungal vaginitis

Zehong Tao, Aihua Ye*

Tianchang Hospital of Traditional Chinese Medicine, Tianchang, Anhui, China

*For correspondence: **Email:** huateqk306665@163.com

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Abstract

Purpose: To investigate the clinical effect of a combination of sodium bicarbonate sitz bath prescription and vaginal nystatin suppository in the treatment of patients with fungal vaginitis.

Methods: Ninety patients with mycotic vaginitis admitted to Tianchang Hospital of Traditional Chinese Medicine from April 2018 to April 2019 were selected and divided into control group (vaginal sitz bath with 5 % sodium bicarbonate solution, $n = 45$) and study group (vaginal nystatin suppository in addition to vaginal sitz bath with 5 % sodium bicarbonate solution, $n = 45$) based on the order of admission. The therapeutic effectiveness of the two treatments was compared with respect to time of relief of various clinical indicators, incidence of adverse reactions, rate of recurrence after 3 and 6 months of drug withdrawal, and vaginal pH.

Results: The time taken to relieve itching was longer in the control group (5.21 ± 2.12 days) than in the study group (3.74 ± 2.03 days; $p < 0.05$). There was a higher recurrence rate of itching in the control group after drug withdrawal for 3 and 6 months than in the study group ($p < 0.05$). Total treatment effectiveness was significantly higher in the study group than in the control group ($p < 0.05$). However, the incidence of adverse reactions was comparable in the two groups ($p > 0.05$). Vaginal pH significantly improved (less acidic) in the study group, when compared to the control group ($p < 0.05$).

Conclusion: Application of a combination of vaginal sitz bath using 5 % sodium bicarbonate solution and vaginal nystatin suppository is effective in the treatment of fungal vaginitis. The combination produces a favorable vaginal pH environment and low recurrence of infection. However, the combined treatment should be subjected to further clinical trials prior to application in clinical practice.

Keywords: Sodium bicarbonate solution, Sitz bath, Nystatin suppository, Fungal vaginitis

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INTRODUCTION

Fungal vaginosis, also known as vulvovaginal candidiasis, is a common vulvovaginal inflammation caused by *Candida* [1,2]. Approximately 80 to 90 % of fungal vaginosis are

triggered by *Candida albicans* which thrives in the vaginal acidic environment as a result of its suitability for fungal growth [3]. When acidity increases in the vagina, there is rapid multiplication of *Candida albicans*, resulting in inflammation. Fungal vaginosis is a common

disease in gynecology, and it occurs predominantly in women of childbearing age. According to statistics, approximately 75 % of women experience the disease at least once throughout life, while 45 % of women experience it twice or more [4-6]. The rising prevalence of fungal vaginosis imposes detrimental impacts on the work, lives and physical and mental health of women.

In recent years, widespread application of antibiotics and corticosteroids has led to increased incidence of fungal vaginitis symptoms such as leucorrhea, itching and burning of the genitals, sleeplessness, and unbearable agony [7,8]. Yet, there are no ideal and effective treatment strategies for improving the prognosis of the disease [9,10]. Therefore, this trial was aimed at seeking a practical strategy for the prevention and treatment of fungal vaginitis by investigating the effectiveness of vaginal sitz bath using 5 % sodium bicarbonate solution in combination with vaginal nystatin suppository in the treatment of fungal vaginitis.

METHODS

Subjects

Ninety patients with fungal vaginitis who were treated in Tianchang Hospital of Traditional Chinese Medicine from April 2018 to April 2019 were found eligible as participants in the study. They were randomly and equally divided into control group (n = 45) and study group (n = 45), based on the order of admission. Patients in the control group were aged 20 - 51 years (mean age = 38.24 ± 5.12 years), with disease course of 1 - 8 weeks (mean duration of disease = 3.12 ± 2.01 weeks). Subjects in the study group were aged 21 - 51 years (mean age = 37.92 ± 5.04 years), with disease duration of 1 - 8 weeks (mean duration of disease = 3.24 ± 1.98 weeks). Baseline data were comparable in the two groups, as shown in Table 1.

Ethical considerations

This trial was reviewed and approved by the ethic committee of Tianchang Hospital of Traditional Chinese Medicine (approval no. TC20298). In addition, this trial was conducted as per the protocol of Helsinki Declaration [9].

Inclusion and exclusion criteria

Patients were considered eligible if they had visible symptoms of vulvar and vaginal itching, dysuria, frequent urination, dyspareunia, and cheese-like leucorrhea or bean dreg-like leucorrhea. In contrast, patients who were pregnant or intending to get pregnant, and those who had vulvar and vaginal ulcers or diabetes, were considered ineligible.

Treatments

The control group was given vaginal sitz bath with 5 % sodium bicarbonate solution, once daily for 14 consecutive days, while the study group was given vaginal nystatin suppository (500,000 U) in addition to vaginal sitz bath with 5 % sodium bicarbonate solution, once a day, for 14 consecutive days. Treatment effectiveness and disease recurrence 3 and 6 months after drug withdrawal were determined and compared between the two groups.

Evaluation of parameters/outcomes

Primary outcomes

Total treatment effectiveness

The clinical symptoms of patients were evaluated 14 days after treatment, and the symptoms were rated under four grades: Cured, markedly effective, effective and ineffective. A patient was considered cured if the clinical symptoms disappeared, and microscopic examination showed no mold in the vaginal secretion.

Table 1: Comparison of general data of the two groups of patients {n (%)}

Parameter	Control group	Study group	t or χ^2	P-value
Age (years)	38.24 ± 5.12	37.92 ± 5.04	0.299	0.766
Course of disease (weeks)	3.12 ± 2.01	3.24 ± 1.98	-0.285	0.776
Marital status				0.655
Married	31	29		
Single	14	16		
Educational background			0.271	0.602
Junior high school and below	18	16		
High school	15	15		
University and above	12	14		

Treatment was considered markedly effective if vulva and vaginal itching were significantly mitigated, symptoms of urinary tract irritation and vaginal swelling and bleeding were basically absent, and vaginal secretion showed no mold under microscopic examination. If vulvar and vaginal itching were reduced, and symptoms of urinary tract irritation were relieved in the presence of slight vaginal redness and bleeding, with microscopic evidence of mold in vaginal secretions, the treatment was regarded as effective. However, treatment was deemed ineffective if the various symptoms were not mitigated, or if they became exacerbated.

Recurrence after drug withdrawal

Recurrence was deemed to have occurred if after treatment, the clinical symptoms and signs disappeared, and microscopic examination showed no mold in vaginal secretions, but the symptoms re-appeared after 3 or 6 months.

Time taken for relief of various clinical indicators

It includes the times taken for the disappearances of symptoms of abnormal leucorrhea, genital itching, waist and abdominal pain, and burning pain during urination).

Secondary outcomes

Occurrence of adverse reactions (nausea, burning sensation in vagina, vaginal dryness, dizziness, and headache), time taken for remission of itching symptoms after treatment, and vaginal pH values. In the determination of vaginal pH, after rinsing the vagina, samples of vaginal secretions were collected before and after treatment. The pH of each sample was measured with pH test paper.

Statistical analysis

Data analysis was done using SPSS version 22.0 software. Measurement data are expressed as mean \pm standard deviation (SD), while two-group comparison was carried out with Student's *t*-test. Count data are presented as numbers (n), and comparison between the two groups was done using chi-square (χ^2) test. Significant difference was fixed at $p < 0.05$.

RESULTS

Remission times of various clinical indicators

In the control group, the times taken for disappearance of symptoms of abnormal leucorrhea, genital itching, waist and abdominal pain, and burning pain during urination, as well as the time taken for recovery from disease were longer than the corresponding times in the study group (2.61 \pm 0.52 days vs. 1.50 \pm 0.22 days, 4.11 \pm 0.45 days vs. 2.32 \pm 0.47 days, 5.70 \pm 0.31 days vs. 3.21 \pm 0.62 days, 4.26 \pm 0.44 days vs. 2.15 \pm 0.34 days, and 7.62 \pm 0.47 days vs. 5.36 \pm 0.23 days, respectively; $p < 0.05$). These results are shown in Table 2.

Adverse reactions

In the control group, there was 1 case of nausea, 1 case of vaginal burning, no vaginal dryness, and 1 case of dizziness and headache. In the study group, there was 1 case of nausea, no vaginal burning sensation, and 1 case of vaginal dryness, but there were 2 cases of dizziness and headache. The safety profiles in the two groups were similar {3 (7 %) vs. 4 (9 %)}. These data are shown in Table 3.

Table 2: Comparison of the remission time of various clinical indicators between the two groups of patients (days, mean \pm SD, n = 45)

Group	Time taken for disappearance of leucorrhea symptoms	Time taken for disappearance of genital itching symptoms	Time taken for disappearance of abdominal pain symptoms	Time taken for disappearance of burning pain during urination	Time taken for recovery
Control	2.61 \pm 0.52	4.11 \pm 0.45	5.70 \pm 0.31	4.26 \pm 0.44	7.62 \pm 0.47
Study	1.50 \pm 0.22	2.32 \pm 0.47	3.21 \pm 0.62	2.15 \pm 0.34	5.36 \pm 0.23
t	13.188	18.454	24.097	25.455	28.973
P-value	<0.001	<0.001	<0.001	<0.001	<0.001

Table 3: Comparison of adverse reactions in the two groups of patients (n (%))

Reaction type	Control group (n=45)	Study group (n=45)	χ^2	P-value
Nausea	1	1	-	-
Vaginal burning	1	0	-	-
Vaginal dryness	0	1	-	-
Dizziness and headache	1	2	-	-
Total	3 (7%)	4 (9%)	0.155	0.694

Vaginal pH

Vaginal pH values were similar in the two groups before treatment (4.41 ± 0.33 vs. 4.36 ± 0.37). However, after treatment, the study group had markedly less favorable vaginal pH for fungal growth than the control group (4.81 ± 0.25 vs. 5.44 ± 0.16 ; $p < 0.05$). These results are shown in Table 4.

Table 4: Comparison of vaginal pH between the two groups of patients (mean \pm SD, n = 45)

Group	Vaginal pH	
	Before treatment	After treatment
Control	4.41 ± 0.33	4.81 ± 0.25
Study	4.36 ± 0.37	5.44 ± 0.16
t	0.505	3.192
p	0.615	<0.01

Disease recurrence rate at 3 and 6 months after drug withdrawal

After 3 months of drug withdrawal, there were 14 cases of recurrence in the control group (31 % recurrence), and 3 cases of recurrence in the study group (7 % recurrence). After 6 months of drug withdrawal, recurrence occurred in 17 patients in the control group (38 % recurrence), while 5 patients (11 %) had recurrence in the study group. The control group had higher % recurrence in patients after drug withdrawal for 3 and 6 months, than the study group ($p < 0.05$). These results are shown in Table 5.

Total treatment effectiveness

There was significantly higher total treatment effectiveness in the study group than in the control group ($p < 0.05$; Table 6).

DISCUSSION

Fungal vaginitis, a common genital tract infection

in obstetrics and gynecology, is caused by *Candida albicans* infection. Due to its unique anatomy, the vagina is open to the outside, a feature which predisposes it to infection and fungal vaginitis. There are many contributing factors to fungal vaginitis. Some of these factors comprise contact infections from polluted public toilets, bathtubs and towels, as well as the use of unclean toilet paper. Moreover, some patients use antibiotics and estrogens, while some frequently use medicinal lotions to lavage the vagina: these practices destroy the normal vaginal acid-base environment in the long run, thereby enhancing the proliferation of vaginal *Candida* [11].

The vagina is an acidic environment, with pH range of 4.5 to 5.5. *Candida albicans* grows optimally in an environment with pH range of 4 to 4.7. Therefore, vaginal pH can be adjusted to inhibit the growth of vaginal *Candida albicans* [12]. In this study, the vaginal pH values of the two groups of patients were compared before and after treatment. The results showed that after treatment, the vaginal pH value of patients in the study group was significantly less acidic than that of the patients in the control group. These results suggest that the use of sodium bicarbonate sitz bath prescription in combination with vaginal nystatin suppository effectively improved the vaginal pH values of patients and reduced the growth of vaginal *Candida albicans* [13-15]. The mainstay of treatment for fungal vaginitis is to apply local or systemic antifungal drugs. Nystatin is a polyene antifungal drug with outstanding antibacterial effect against *Candida*. It binds to sterols on the fungal cell membrane, reduces the permeability of the cell membrane, and exerts an antifungal effect due to loss of cell contents [16]. The results obtained in this study indicate that the combined use of 5 % sodium bicarbonate solution for vaginal sitz bath and vaginal nystatin suppository yielded a promising outcome in terms of effectiveness, reduction of

Table 5: Comparison of recurrence rate 3 and 6 months after drug withdrawal between the two groups {(n (%))}

Group	N	3 months after drug withdrawal	Recurrence	6 months after drug withdrawal	Recurrence
Control	45	14	31%	17	38%
Study	45	3	7%	5	11%
χ^2	-	8.775	-	8.663	-
P-value	-	0.003	-	0.003	-

Table 6: Comparison of total treatment effectiveness between the two groups {(n (%))}

Group	N	Cured	Markedly effective	Effective	Ineffective	Total
Control	45	18 (40%)	9 (20%)	10 (22%)	8 (18%)	37 (82%)
Study	45	26 (58%)	11(24%)	6 (13%)	2 (4%)	43 (96%)
χ^2	-	-	-	-	-	4.05
P-value	-	-	-	-	-	0.044

recurrence, and shortening of time of relief of itching, as well as mitigation of abnormal leucorrhea, genital itching and burning pain during urination. These findings are consistent with reports in previous studies [17,18]. Therefore, there is need for good hygiene habits, prevention of mold growth, adoption of regular exercise habits, and reasonable intake of nutrients in order to boost immunity and enhance resistance to fungal infection. Interestingly, there was no significant difference in incidence of adverse reactions between the two groups. This indicates the good safety profiles of the two treatments.

CONCLUSION

The combined application of vaginal sitz bath using 5 % sodium bicarbonate solution and vaginal nystatin suppository is effective and safe in the treatment of fungal vaginitis. However, the combined treatment should be subjected to further clinical trials prior to application in clinical practice.

DECLARATIONS

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Ethical approval

This work was approved by the Ethic Committee of Tianchang Hospital of Traditional Chinese Medicine, China (approval no. TC20298).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Zehong Tao wrote the main manuscript text and prepared the

Figures and Tables. All authors reviewed, read and approved the manuscript.

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REFERENCES

1. Adrogué HJ, Awan AA, Madias NE. Sodium Fate after Sodium Bicarbonate Infusion: Influence of Altered Acid-Base Status. *Am J Nephrol* 2020; 51(3): 182-191.
2. Cabrera-Jaime S, Martínez C, Ferro-García T, Giner-Boya P, Icart-Isern T, Estrada-Masllorens JM, Fernández-Ortega P. Efficacy of Plantago major, chlorhexidine 0.12% and sodium bicarbonate 5% solution in the treatment of oral mucositis in cancer patients with solid tumour: A feasibility randomised triple-blind phase III clinical trial. *Eur J Oncol Nurs* 2018; 32: 40-47.
3. Collins A, Sahni R. Uses and misuses of sodium bicarbonate in the neonatal intensive care unit. *Semin Fetal Neonatal Med* 2017; 22(5): 336-341.
4. Ameye D, Honraet K, Loose D, Vermeersch H, Nelis H, Remon JP. Effect of a buccal bioadhesive nystatin tablet on the lifetime of a Provox silicone tracheoesophageal voice prosthesis. *Acta Otolaryngol* 2005; 125(3): 304-306.
5. de Aguiar MM, de Albuquerque RP, Marinho DS, Braga BR, Dornelas CB, Oliveira A, de Sousa VP, Torres SR, Alviano DS, Alviano CS, Cabral LM, Holandino C. Oral sustained release nystatin tablets for the treatment of oral candidiasis: formulation development and validation of UV spectrophotometric analytical methodology for content determination. *Drug Dev Ind Pharm* 2010; 36(5): 594-600.
6. Llabot JM, Manzo RH, Allemandi DA. Double-layered mucoadhesive tablets containing nystatin. *AAPS PharmSciTech*. 2002;3(3): E22. doi: 10.1208/pt030322. PMID: 12916937; PMCID: PMC2784051.
7. Bahadoran P, Rokni FK, Fahami F. Investigating the therapeutic effect of vaginal cream containing garlic and thyme compared to clotrimazole cream for the treatment of mycotic vaginitis. *Iran J Nurs Midwifery Res* 2010; 15(Suppl 1): 343-9.
8. Bruhat MA. Place d'une association antibiotique locale dans le traitement des vaginites mycosiques et vaginites mixtes [Use of a local antibiotic combination in the

- treatment of mycotic vaginitis and mixed vaginitis]. *Rev Fr Gynecol Obstet* 1992; 87(3): 161-8. French.
9. Associazione Medica Mondiale (AMM) dichiarazione di Helsinki. Principi etici per la ricerca medica che coinvolge soggetti umani [World Medical Association (AMM). Helsinki Declaration. Ethical principles for medical research involving human subjects]. *Assist Inferm Ric* 2001; 20(2): 104-7. Italian.
 10. Magalhães APSPA, Toma HK, do Carmo FA, Mansur CRE. Development of purified cashew gum mucoadhesive buccal tablets containing nystatin for treatment of oral candidiasis. *Drug Dev Ind Pharm* 2021; 47(5): 825-837.
 11. Sakeer K, Al-Zein H, Hassan I, Desai S, Nokhodchi A. Enhancement of dissolution of nystatin from buccoadhesive tablets containing various surfactants and a solid dispersion formulation. *Arch Pharm Res* 2010; 33(11): 1771-9.
 12. Gemzell-Danielsson K, Sitruk-Ware R, Creinin MD, Thomas M, Barnhart KT, Creasy G, Sussman H, Alami M, Burke AE, Weisberg E, Fraser I, Miranda MJ, Gilliam M, Liu J, Carr BR, Plagianos M, Roberts K, Blithe D. Segesterone acetate/ethinyl estradiol 12-month contraceptive vaginal system safety evaluation. *Contraception* 2019; 99(6): 323-328.
 13. Wang NM, Cui L, Ma CF, Wang HX. [Clinical observation on treatment of mycotic vaginitis with *Sophora gel* combined with Fluconazole capsules. *Zhongguo Zhong Yao Za Zhi* 2015; 40(5): 978-80. Chinese.
 14. Jaber S, Paugam C, Futier E, Lefrant JY, Lasocki S, Lescot T, Pottecher J, Demoule A, Ferrandi re M, Asehnoune K, et al; BICAR-ICU Study Group. Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial. *Lancet* 2018; 392(10141): 31-40.
 15. Jude B, Naorunroj T, Neto AS, Fujii T, Udy A, Bellomo R. Sodium bicarbonate in 5% dextrose: can clinicians tell the difference? *Crit Care Resusc* 2020; 22(1):80-82.
 16. Piroomchai P, Laohakittikul C, Khunnawongkrit S, Srirompotong S. Cerumenolytic Efficacy of 2.5% Sodium Bicarbonate Versus Docusate Sodium: A Randomized, Controlled Trial. *Otol Neurotol* 2020; 41(7): e842-e847.
 17. Škerk V, Kolumbić Lakoš A, Gašparić M, Matrapazovski Kukuruzović M, Magdić Blažević I. Effectiveness and Pharmacokinetic evaluation of Geonistin® (Oxytetracycline and Nystatin) Vaginal Tablets for Unspecific and Mixed Vulvovaginal Infections (GENIE Study). *Acta Dermatovenerol Croat* 2019; 27(4): 235-244.
 18. Hao MH, Zhang F, Liu XX, Zhang F, Wang LJ, Xu SJ, Zhang JH, Ji HL, Xu P. Qualitative and quantitative analysis of catechin and quercetin in flavonoids extracted from *Rosa roxburghii* Tratt. *Trop J Pharm Res* 2018; 17(1): 71-76.