Clinical Trial/Experimental Study

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Effectiveness of *Bazhengsan* formula as an adjunctive therapy to ceftriaxone for female patients with uncomplicated gonorrhea

A pilot study

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Abstract

Background: This pilot study aimed to investigate the feasible effectiveness and safety of *Bazhengsan* formula (BZSF) as an adjunctive therapy to ceftriaxone for female patients with uncomplicated gonorrhea.

Methods: This pilot randomized controlled trial compared BZSF as an adjunctive therapy to ceftriaxone with ceftriaxone alone for Chinese female patients with uncomplicated gonorrhea. A total of 40 eligible patients were randomly allocated to a treatment group (received BZSF and ceftriaxone) or a control group (received ceftriaxone alone). All patients in both groups were treated for a total of 10 days. The primary outcome included bacteriological cure. It was assessed by the eradication of urogenital gonorrhea at any site cultured after taken the study medications. The secondary outcome was clinical response. For the safety assessment, adverse events were recorded during the study period.

Results: After treatment, patients in both groups achieved promising effectiveness. However, no significant differences in bacteriological cure ($P = .34$), clinical response ($P = .11$), and safety were found between 2 groups.

Conclusion: The findings of this study showed that BZSF as an adjunctive therapy to ceftriaxone may be not superior to the ceftriaxone alone for Chinese female patients with uncomplicated gonorrhea after 10 days treatment.

Abbreviations: BZSF = *Bazhengsan* formula.

Keywords: Bazhengsan formula, effectiveness, gonorrhea, safety

1. Introduction

Gonorrhea, caused by bacterium *Neisseria gonorrhoeae*, is a very common sexually transmitted disorder.[1–3] Previous studies have reported that about 78 million patients of gonorrhea were reported in 2012 globally.[4–5] Most infections occurred at genital, however, pharyngeal and anorectal can also be infected.[6–7] As for female patients, they are often infected by Neisseria without symptoms, except the most common symptoms as vaginal discharge.[8–9] If such condition can not be treated timely and effectively, it may cause pelvic inflammatory disease, chronic pelvic pain, and ectopic pregnancy in females.[10–13] In addition, it can also lead to conjunctivitis in newborns by mother-to-child transmission at birth.[14]

Prompt and effective antimicrobial therapy is one of the most efficacious ways to control and prevent gonorrhea.[15–19] Unfortunately, gonorrhea has progressively developed resistance to each medication, including sulfonamides, penicillins and so on.[15–16] Although cephalosporin antimicrobials, such as ceftriaxone was recommended by the Centers for Disease Control and Prevention as the only remaining agents to treat this disorder by 2007, their efficacy are still limited.[17–19] Thus, alternative therapeutic options for gonorrhea are still urgently needed.

Complementary and alternative medicine, especially traditional Chinese herbal medicine,[20–21] such as *Bazhengsan* formula (BZSF) is reported as an effective alternative therapy for patients with gonorrhea.[22–25] Although it is widely used to treat this disorder in China, and a variety of studies have reported it, the evidence for its effectiveness for uncomplicated gonorrhea is still limited. Therefore, the lacking evidence for BZSF in treating gonorrhea in female adult warrants strictly designed randomized clinical trials. Thus, in this pilot study, we hypothesized that for the treatment of uncomplicated gonorrhea in female patients, the feasible effectiveness of BZSF as an adjunctive therapy to ceftriaxone would be superior to ceftriaxone alone.

2. Methods and design

2.1. Ethical approval

The present study was approved by the ethics committee of Yan'an Hospital of Traditional Chinese Medicine. All included patients were required to provide the written informed consent.

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The authors have no conflicts of interest to disclose.

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2.2. Study design

This study was designed as a pilot randomized controlled trial with 2 parallel groups. The poster or advertise was made to recruit all eligible patients with trial information introduction. After screening, all included participants were randomly allocated to a treatment group or a control group at a ratio of 1:1. One week run-in period was included before the randomization. Patients in both groups were treated for a total of 10 days.

2.3. Patients

The inclusion criteria consisted of female participants aged between 18 and 65 years; infected with urethral or cervical gonorrhea; agreed to abstain from sexual intercourse or use condoms before the study completed; pregnancy tests were conducted before the study.

Patients were excluded if they having a history of epilepsy, kidney or liver insufficiency, and gastrointestinal, hematologic, or cardiovascular disease or immunodeficiency; or allergy to quinolone antibiotics; or disseminated gonococcal infection; or current use any systemic antibiotic 72 hours before entered the study; or participated any other trials within 30 days; or clinically diagnosed as abdominal pain related to pelvic inflammatory disease; or diagnosed with bacterial vaginosis at enrollment, but agreed to defer its treatment after the study; or having pregnant or breastfeeding.

2.4. Randomization and blinding

Stratified randomization was performed by a computerized generation random number list, which was generated using SAS 9.1 package (SAS Institute Inc, Cary, NC). Patients who met all criteria were assigned random numbers in a 1:1 ratio by using sequentially numbered, opaque, sealed envelopes. Attending investigators, outcome assessors and data analysts were masked to the treatment allocation information.

2.5. Intervention

All patients in both groups were administrated ceftriaxone 250 mg intramuscularly once daily for a total of 10 days. In addition, patients in the treatment group received BZSF as an adjunctive therapy to ceftriaxone for female patients with uncomplicated gonorrhea.[22–25] The BZSF consists of *Dianthus superbus* 12 g, common knotgrass herb 12 g, anemone clematis stem 10 g, *Plantago asiatica* 15 g, talcum powder 20 g, raw cape Jasmine fruit 10 g, raw rhubarb 10 g, licorice tip 9 g, glabrous greenbrier rhizome 20 g, honeysuckle flower 30 g, houttuynia 20 g, and sevenlobed yam rhizome foochow yam 15 g.[22] It was administrated as decoction, one dose per day for a total of 10 days.[22] The remaining herbal dregs were added to 500 mL of water, and were fried until 350 mL, then were added to the bathtub. The patients were required to sit in bathtub 30 min daily for a total of 10 days.

2.6. Outcome measurements

The primary outcome was bacteriological cure. It is defined as eradication of urogenital gonorrhea at any site cultured 10 days after taken the study medications.

The secondary outcome included clinical response. The clinical response was categorized as cure (all signs and symptoms were disappeared), improvement (partial signs and symptoms were relieved), or failure (no apparent signs and symptoms were relieved or even became worse).

2.7. Safety evaluation

We checked and recorded for any adverse events at each visit, and then we documented its date of onset and cease, intensity, and also the association to this trial. We also took appropriate way to minimize the effectiveness of adverse reactions.

2.8. Statistical analysis

All data was analyzed by SAS 9.1 package (SAS Institute Inc, Cary, NC) using intent-to-treat principle. The t test or Mann–Whitney rank sum test was used to analyze the continuous data. Fisher's exact test was utilized to analyze the categorical data. A value of $P < .05$ was defined as statistically significant.

2.9. Sample size

This pilot study assessed the feasible effectiveness of BZSF as an adjunctive therapy to ceftriaxone for female patients with uncomplicated gonorrhea, as well as the feasibility of a large clinical trial. The desired sample size for this pilot study is 40 patients, with 20 subjects each group, and an assumed dropout rate of 20%.[26] It is the minimum required sample size to assess the feasible effectiveness of this therapy.

3. Results

A total of 55 eligible patients entered the study for the initial evaluation (Fig. 1). After selection, 15 subjects were excluded because they did not meet the inclusion criteria or declined to participate this study. Thus, a total of 40 patients were included and were randomly allocated to the treatment group or control group equally, each group 20 patients. After 10 days treatment, no patients in either group withdraw from the study, and all of them entered into the final data analysis.

The comparison of all characteristics between 2 groups is listed in Table 1. No significant differences regarding all the characteristic values were detected between 2 groups. These characteristics mainly consisted of age, race, married status, history of sexually transmitted disease, and human immunodeficiency virus, as well as the symptoms.

After 10 days treatment, patients in both groups achieved promising effectiveness (Tables 2 and 3). However, patients in the treatment group did not show better effectiveness in both acteriological cure ($P = .34$, Table 2), and clinical response ($P = .11$, Table 3).

Both groups had similar safety profile (Table 4). No severe adverse events, and death related to the treatment were recorded in either group in this pilot study.

4. Discussion

Gonorrhea is one of the most venereal diseases, which often greatly reduces quality of life in patients with such disorder. The management of antimicrobial therapy is commonly used to relieve the signs and symptoms for patients with this condition. However, it has progressively developed resistance to a variety of medication and thus has limited efficacy. Therefore, alternative therapies are very important to be investigated for the treatment of this disorder.

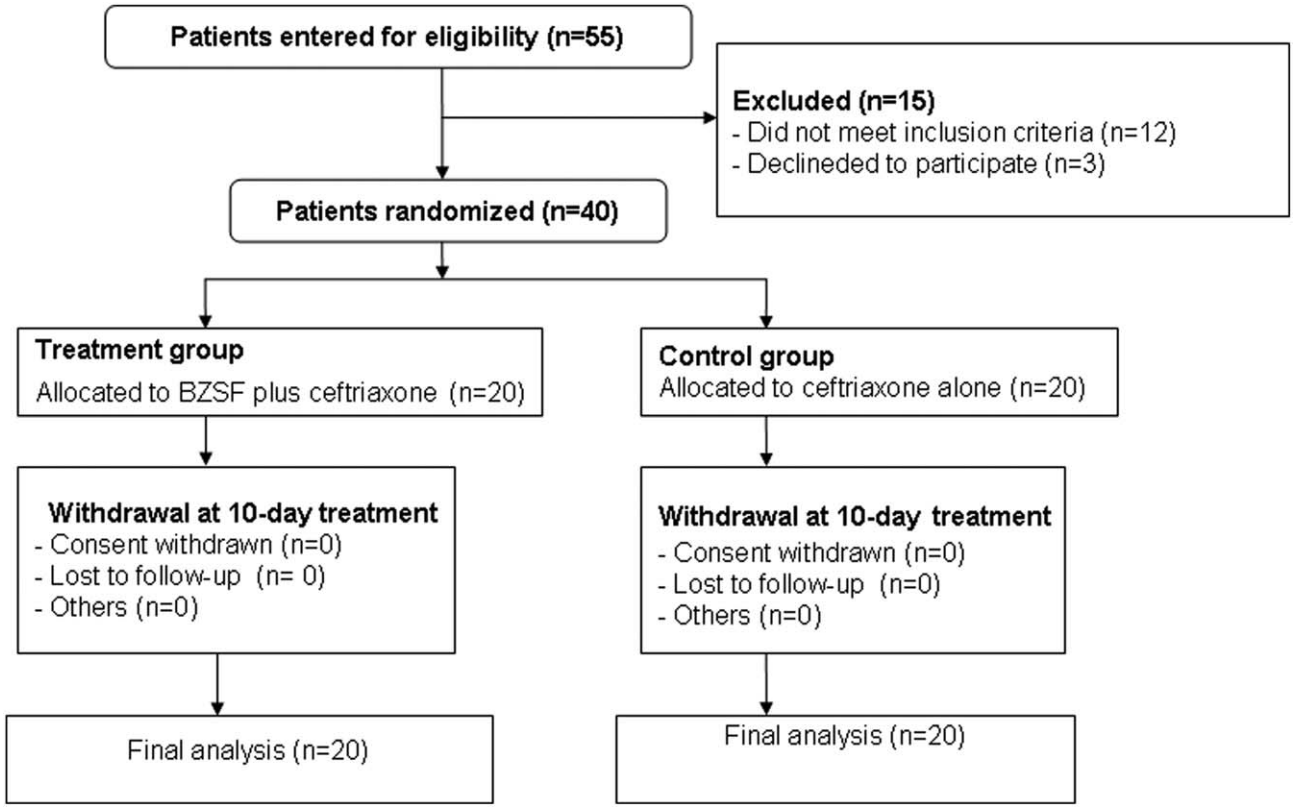

Figure 1. Study design flowchart.

Traditional Chinese medicine, such as BZSF has been reported to treat gonorrhea with promising effectiveness.[20–25] However, no study reported BZSF as an adjunctive therapy to other treatments for this condition. To our best knowledge, this pilot study is the 1st randomized controlled trial to explore the feasible effectiveness of BZSF as an adjunctive therapy to ceftriaxone for the treatment of Chinese female patients with uncomplicated gonorrhea.

The results of this study showed that BZSF as an adjunctive therapy to ceftriaxone did not show better effectiveness neither in acteriological cure ($P=.34$), nor in clinical response ($P=.11$) in patients with uncomplicated gonorrhea, compared with

Table 1

Comparison of characteristics at baseline.

Characteristics	Treatment group (n=20)	Control group (n=20)	*P value*
Age, y: mean (±SD)	28.9 (12.4)	31.1 (11.7)	.56
Race, Asian (Chinese), n (%)			
Han ethnicity	20 (100.0)	20 (100.0)	–
Married status			
Married, n (%)	16 (80.0)	15 (75.0)	.71
Divorced	3 (15.0)	2 (10.0)	.63
Single, n (%)	1 (5.0)	3 (15.0)	.31
Previous STD (self-report)			
Gonorrhea, n (%)	8 (40.0)	6 (30.0)	.51
Chlamydia, n (%)	5 (25.0)	7 (35.0)	.49
HIV infection (self-report)			
Positive, n (%)	2 (10.0)	1 (5.0)	.56
Negative, n (%)	15 (75.0)	14 (70.0)	.72
Unknown, n (%)	3 (15.0)	5 (25.0)	.43
Symptoms			
Vaginal discharge, n (%)	13 (65.0)	11 (55.0)	.52
Vaginal area burning or itching, n (%)	6 (30.0)	8 (40.0)	.51
Frequent painful urination, n (%)	7 (35.0)	6 (30.0)	.74
Genitals redness and swelling, n (%)	5 (25.0)	7 (35.0)	.49
Sore throat, n (%)	3 (15.0)	5 (25.0)	.43

HIV = human immunodeficiency virus, SD = standard deviation, STD = sexually transmitted disease.

Table 2

Comparison of eradication rate by source at 10 days treatment.

Eradication rate	Treatment group (n=20)	Control group (n=20)	*P value*
Cervix	16/17 (95.0)	15/18 (85.0)	.34
Urethra	0/0 (0)	1/1 (100.0)	–
Pharynx	3/3 (100.0)	2/2 (100.0)	–
Rectum	4/4 (100.0)	5/5 (100.0)	–

Data are present as number (%); PADQLQ = Paediatric Allergic Disease Quality of Life Questionnaire scores.

Table 3

Comparison of clinical response after 10 days treatment.

Clinical response	Treatment group (n=20)	Control group (n=20)	*P value*
Cure	19 (95.0)	16 (80.0)	–
Improvement	1 (5.0)	2 (10.0)	–
Failure	0 (0)	2 (10.0)	–
Success	20 (100.0)	16 (80.0)	.11

Data are present as number (%).

Table 4

Adverse events.

Adverse events	Treatment group (n = 20)	Control group (n = 20)	*P* value
Eosinophilia	2 (10.0)	3 (15.0)	.63
Thrombocytosis	1 (5.0)	2 (10.)	.56
Leucopenia	1 (5.0)	0 (0)	.49
Diarrhea	2 (10.0)	1 (5.0)	.56
Nausea	1 (5.0)	0 (0)	.49

Data are present as mean ± standard deviation.

ceftriaxone alone. In addition, no significant differences of all adverse events were found between 2 groups.

This study had several limitations. First, it is a pilot study, and it aimed to assess the feasible effectiveness and safety of BZSF as an adjunctive therapy to ceftriaxone in Chinese female patients with uncomplicated gonorrhea. Thus, the sample size in this study is pretty small. Second, patients were not masked to this study, because they were told to receive additional BZSF or not before the study, which may result in high risk bias of patient selection.

5. Conclusion

The results of this study demonstrated that the effectiveness of BZSF as an adjunctive therapy to ceftriaxone may be not superior to the ceftriaxone alone for the treatment of Chinese female patients with uncomplicated gonorrhea.

Author contributions

Conceptualization: Ning Li, Li Li.
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Formal analysis: Li Li.
Investigation: Ning Li.
Methodology: Li Li.
Resources: Ning Li, Li Li.
Software: Li Li.
Supervision: Ning Li.
Validation: Ning Li, Li Li.
Visualization: Ning Li, Li Li.
Writing – original draft: Ning Li, Li Li.
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