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ORIGINAL ARTICLE

Safety and efficacy of levofloxacin *versus* ciprofloxacin for the treatment of chronic bacterial prostatitis in Chinese patients

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Levofloxacin is a synthetic fluoroquinolone that is usually used to treat chronic bacterial prostatitis. We investigated the safety and efficacy of levofloxacin compared with ciprofloxacin for the treatment of chronic bacterial prostatitis in Chinese patients. This was a multicenter, open-label, randomized controlled non-inferiority trial. Four hundred and seventy-one patients with clinical symptoms/signs were enrolled into the study, and 408 patients were microbiologically confirmed chronic bacterial prostatitis, who were randomized to either oral levofloxacin (500 mg q.d.) or ciprofloxacin (500 mg b.i.d.) for 4 weeks. Bacterial clearance rate, clinical symptoms/signs, adverse reactions and disease recurrence were assessed. The clinical symptoms and signs (including dysuria, perineal discomfort or pain) and bacteria cultures in 209 patients treated with levofloxacin and 199 patients treated with ciprofloxacin were similar. The most common bacteria were *Escherichia coli* and *Staphylococcus aureus*. One to four weeks after the end of 4 weeks treatment, the bacterial clearance rate (86.06% *vs.* 60.03%; $P<0.05$) and the clinical efficacy (including clinical cure and clinical improvement(93.30% *vs.* 71.86%; $P<0.05$)) were significantly higher in the levofloxacin-treated group than in the ciprofloxacin-treated group. The microbiological recurrence rate was significantly lower in the levofloxacin-treated group than in the ciprofloxacin-treated group (4.00% *vs.* 19.25%; $P<0.05$). Rates of adverse events and treatment-related adverse events were slightly lower in the levofloxacin-treated group than in ciprofloxacin-treated group. Levofloxacin showed some advantages over ciprofloxacin in terms of clinical efficacy and disease recurrence, with a low rate of adverse events, for the treatment of chronic bacterial prostatitis in Chinese patients.

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INTRODUCTION

Chronic prostatitis is a common disease that occurs in all age groups, although it predominantly affects young adults and greatly affects the quality of life of patients.[1] Definitive diagnosis of chronic bacterial prostatitis is usually established by the Meares–Stamey '4-glass test'.[2] It has been demonstrated that the most common pathogenic bacteria associated with this disease are aerobic Gram-negative bacteria such as *Escherichia coli*, while the presence of Gram-positive bacteria in chronic bacterial prostatitis remains controversial.[3–5] Nevertheless, the significance of Gram-positive bacteria, such as *Enterococcus faecalis* and *Staphylococcus epidermidis*, in the prostate is receiving increasing attention.[6,7]

Most urologists treat prostatitis empirically using antibiotics;[8] therefore, administration of broad-spectrum drugs that are effective against both Gram-positive and Gram-negative bacteria is very important. Accordingly, quinolones are considered particularly useful for the treatment of chronic bacterial prostatitis because of its broad-spectrum activity and marked accumulation in prostate secretion.[9]

Levofloxacin is a synthetic fluoroquinolone that is widely used to treat severe or potentially life-threatening bacterial infections, particularly those that have failed to respond to other classes of antibiotics. Several randomized controlled studies have demonstrated that oral levofloxacin is an effective and well-tolerated treatment for chronic bacterial prostatitis.[10–13] However, most of these studies were conducted in Europe or North America and very few studies have investigated the efficacy and safety of levofloxacin in Asian subjects. Therefore, in this multicenter, open-label, randomized controlled non-inferiority study, we compared the efficacy and safety of oral administration of levofloxacin 500 mg q.d. with that of ciprofloxacin 500 mg b.i.d. for the treatment chronic bacterial prostatitis in Chinese patients.

MATERIALS AND METHODS

Patients

All the patients with a history of chronic bacterial prostatitis, symptoms and signs of prostatitis and laboratory evidence for

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prostatitis were eligible for this study. History of prostatitis included the presence of one symptom within the last 4 weeks or two or more symptoms in the past 12 months. Symptoms and signs of prostatitis include mild tenderness of the prostate (no obvious nodules), dysuria, suprapubic discomfort, ejaculation pain, lower back pain, perineal discomfort, urinary frequency, urgency, delayed urination, urine thinning, urinary retention, digital rectal examination pain, fever and chills. The exclusion criterions include severe complications, such as severe disease of heart, lung, liver and kidney, psychotic disorders and severe benign prostate hyperplasia, etc.

In accordance with the Meares–Stamey '4-glass' test,[2,14] the patients provided urine samples, which were used to count white blood cells (WBCs) under a microscope, for bacterial culture, and to assess drug sensitivity to levofloxacin or ciprofloxacin. VB1, the first 5–10 ml of urine, was discarded while VB2, the mid-segment of urine, was retained for bacterial culture. The prostate was then massaged and prostate secretion (EPS) was collected for bacterial culture. VB3, the first 5–10 ml of urine obtained immediately after prostate massage, was also collected for bacterial culture. The results of bacteria culture and the WBC count were used to determine bacterial infection of the prostate. Bacterial infection was confirmed in patients fulfilling at least one of the following criteria: (i) the WBC count was $\geqslant$10 times higher in VB3 than in VB2; (ii) the number of bacterial colonies in VB2 was $<$100 cfu ml^{-1}, but reached $\geqslant$100 cfu ml^{-1} in VB3 or EPS; (iii) the number of bacterial colonies was $\geqslant$10 times higher in VB3 or EPS than in VB2; (iv) VB3 or EPS contained different species of bacteria from those identified in VB2, and the number of bacterial colonies reached $\geqslant$100 cfu ml^{-1}.

All of the patients were recruited from 15 medical centers. The study was approved by Institutional Review Boards or Ethical Committees at each participating center. All patients signed informed consent forms.

Study design

This multicenter, open-label, randomized, controlled non-inferiority trial comprised six visits. The first visit was a screening visit, which was compulsory for subacute and non-painful patients, but not for acute patients. The patients were then enrolled and randomized at visit 2 and started treatment at visit 3. The fourth 'visit' involved a follow-up telephone call at the end of 4-week therapy. Clinical efficacy and micobiological efficacy were determined at visit 5 (1–4 weeks after end of therapy). Patients entered the final phase at visit 6, 6 months after end of therapy, to determine clinical efficacy and the rate of recurrence, which was defined as the return of pathogenic microorganism. Patients were randomized to the two groups using computer-generated random tables for each center. Levofloxacin (500 mg q.d.) and ciprofloxacin (500 mg b.i.d.) were administered per os at the approved and usual doses for these drugs.

In addition to the post-treatment microbiological evaluations, we also determined the prevalence of clinical symptoms and signs as indices of clinical efficacy. The clinical indices of clinical efficacy included clinical cure and clinical improvement. The clinical cure was defined as the resolution of all symptoms of chronic prostatitis after completing therapy compared with those identified at screening. Clinical improvement was defined as marked reductions in symptoms/signs compared with those identified at screening. The clinical efficacy was defined as patients showing clinical cure or clinical improvement. If the patients could not get the clinical efficacy, the condition was defined as failure.

Statistical analysis

The sample size was calculated essentially as previously described for active-controlled non-inferiority studies.[15,16] To assess whether oral levofloxacin 500 mg q.d. is as effective as oral ciprofloxacin 500 mg b.i.d. during a 4-week treatment course for chronic bacterial prostatitis, the null hypothesis was that the microbiological eradication rate for oral ciprofloxacin minus the microbiological eradication rate for levofloxacin exceeded 20%. The alternative hypothesis of a therapeutically equivalent microbiological efficacy was that the difference in eradication rates was $\leqslant$20%. It was anticipated that approximately 55% of the subjects enrolled will meet the microbiological criteria at entry and 50%–70% of these patients were expected to be microbiologically evaluable. With a one-sided significance level of 0.025, with 55–77 microbiologically evaluable patients per group, the power ranged from 82% to 92% to test the null hypothesis, assuming an 89% success rate for oral ciprofloxacin and an 87% success rate for levofloxacin. Thus, approximately 400 subjects were intended to be enrolled.

The bacterial clearance rate as the clinical cure, and the clinical efficacy as a secondary outcome were compared between the two groups using the Cochrane–Mantel–Haenzel test stratified by center, and the 95% confidence interval was calculated. Changes in symptoms and signs were compared using grouped *t*-tests or Wilcoxon's rank sum test as appropriate. All other data were tested by two-tailed *t*-tests. Values of $P<0.05$ were considered statistically significant, unless specifically indicated. SAS 9.1.3 (SAS Institute, Cary, NC, USA) was used for all analyses.

RESULTS

Patient disposition and general characteristics

Between 12 January 2007 and 21 April 2009, 471 patients were screened with the Meares–Stamey '4-glass' test and 63 pathogen-negative patients were excluded from the trial. Four hundred and eight patients who were pathogen-positive, were randomized and treated with either levofloxacin (n=209) or ciprofloxacin (n=199) according to the intention-to-treat principle. The mean age of the patients was 33.4 years in levofloxacin group and 33.5 years in ciprofloxacin group. Of these, 209 and 199 patients, respectively, completed the 4-week treatment phase. At the end of the study at visit 6, results for 209 patients in the levofloxacin-treated group and 199 patients in the ciprofloxacin-treated group were evaluated. The general characteristics (**Table 1**), clinical symptoms and signs, pathogenesis of chronic prostatitis, and episodes during the last 12 months were similar in both groups. Twenty-two (10.53%) patients in the levofloxacin-treated group and 20 (10.05%) in the ciprofloxacin-treated group used additional agents (no antimicrobials) to treat their prostatitis.

Microbiology findings

Bacteria were isolated in 209 patients from the levofloxacin-treated group and 199 patients from the ciprofloxacin-treated group. The most common bacteria were *E. coli* and *S. epidermidis* (**Table 2**). There were no statistically significant differences between the two groups ($P>0.05$) in terms of types of bacteria isolated. A total of 165 (78.95%) and 123 (61.81%) patients showed sensitivity to levofloxacin and ciprofloxacin, respectively, and was different between the two groups ($P<0.05$).

At visit 5, the bacteria clearance rate in those with confirmed bacterial infection was higher in the levofloxacin-treated group where *S. epidermidis* and *E. coli* were most frequently confirmed (85.65%, 179/209) than in the ciprofloxacin-treated group where *E. coli*, *S. aureus*

Table 1 Characteristics of patients in levofloxacin group and ciprofloxacin group

Characteristic	*Levofloxacin (n=209), mean±s.d.(range)*	*Ciprofloxacin (n=199), mean±s.d.(range)*	P *value*
Age (year)	33.4±8.1 (19.0–54.0)	33.5±8.5 (19.0–54.0)	0.86
Height (cm)	173.0±4.9 (158.0–186.0)	172.4±4.7 (155.0–187.0)	0.19
Weight (kg)	69.3±7.6 (50.0–100.0)	68.1±6.8 (61.5–96.0)	0.063
Pyrexia, *n* (%)			
Yes	38 (18.2)	42 (21.1)	n.d.
No	171 (81.8)	157 (78.9)	

Abbreviation: n.d., not determined.

and *S. epidermidis* were most frequently confirmed (60.30%, 120/199, $P<0.05$). The 95% confidence interval for the difference in the bacterial clearance rate between the two groups was 17.49%–34.02%.

All of the patients were re-evaluated at visit 6 to determine the rate of recurrence. The recurrence rate was lower in the levofloxacin-treated group (4.00%) than in the ciprofloxacin-treated group (19.25%, $P<0.05$).

Clinical outcomes

The clinical efficacy, clinical cure and clinical improvement in patients with confirmed bacterial infection were 93.30%, 55.02%, and 38.28%, respectively, in the levofloxacin-treated group *versus* 71.86%, 34.17% and 37.69%, respectively, in the ciprofloxacin-treated group (**Table 3**). These rates were higher in the levofloxacin-treated group than in the ciprofloxacin-treated group ($P<0.05$) and remained significant after excluding non-evaluable patients from the analysis.

At visit 6, the long-term efficacy was higher in the levofloxacin-treated group (94.22%) than in the ciprofloxacin-treated group (70.70%, $P<0.05$).

Safety

The rates of adverse events and treatment-related adverse events were 3.33% and 2.87%, respectively, in the levofloxacin-treated group, and 6.03% and 5.53%, respectively, in the ciprofloxacin-treated group (**Table 4**). The most common adverse events included dizziness, nausea and digestive tract symptoms, particularly stomach discomfort. Other adverse events were rare. No serious adverse event occurred. Only one patient in the ciprofloxacin-treated group withdrew from the study because of an adverse drug reaction.

DISCUSSION

Chronic prostatitis is a common disease in men. Although chronic bacterial prostatitis is responsible for only 10% of all cases of chronic prostatitis, most urologists prescribe antibiotics for these diseases to achieve satisfactory clinical outcomes.[17] Quinolones can penetrate the prostate better than other antibiotics and have become the first-choice treatment for chronic prostatitis.[18] It has been reported that the prostate/plasma ratio of levofloxacin in over 70% of the tested population exceeded 1.0, suggesting that the levofloxacin concentration in prostate is higher than that in plasma and that levofloxacin is suitable for prostatic infections.[19] Furthermore, studies in healthy volunteers revealed that, after administration of a single dose, the concentrations of levofloxacin in plasma are higher than those of ciprofloxacin.[20]

The present study compared the efficacy and safety of administration of levofloxacin 500 mg q.d and ciprofloxacin 500 mg b.i.d. in patients with chronic bacterial prostatitis. At enrollment, pathogens were detected in 408 patients subsequently treated with levofloxacin and ciprofloxacin, respectively. Of these, 165 (78.95%) patients were sensitive to levofloxacin and 123 (61.81%) patients were sensitive to ciprofloxacin. The most common Gram-negative bacterium was *E. coli*, while the most common Gram-positive bacteria was *S. epidermidis*. Four weeks after therapy, the bacterial clearance rates was higher with levofloxacin than with ciprofloxacin (86.06% *vs.* 60.30%, respectively; $P<0.05$), suggesting that levofloxacin shows better bacterial clearance in the prostate than ciprofloxacin. The present study also revealed that levofloxacin, like ciprofloxacin, can target multiple bacteria species, including *E. coli*, *Proteus* spp., *Enterobacteriaceae*, *Streptococcus* spp., *S. aureus* and *Ureaplasma urealyticum*, confirming the broad-spectrum activity of levofloxacin. A drug sensitivity test against residual bacteria was conducted 4 weeks after therapy, and

Table 2 Microbiological isolated bacteria from 408 patients*

Bacteria strains	*Levofloxacin*			*Ciprofloxacin*		
	Number	*Frequency of isolation*	*Incidence in 209 patients (%)*	*Number*	*Frequency of isolation*	*Incidence in 199 patients (%)*
Enterococcus	16	19	7.66	16	19	8.04
Atypical pathogens	10	10	4.78	9	9	4.52
Enterobacteriaceae	105	117	50.24	97	107	48.74
Non-fermenting bacteria	7	7	3.35	5	5	2.51
Anaerobes	6	6	2.87	7	7	3.52
Fungi	1	1	0.48	0	0	0
Gram-positive bacteria	3	3	1.44	2	2	1.01
Haemophilus	1	1	0.48	1	1	0.50
Neisseria	1	1	0.48	0	0	0
Staphylococcus	74	82	35.41	79	82	39.70
Streptococcus	10	11	4.78	6	6	3.02

*The 'Number' columns refer to the frequency of bacteria, with two isolated bacteria found in one patient. The 'Frequency of isolation' columns refer to the total frequency of the isolated bacteria, while the frequency of isolation from VB1, VB2 and VB3 may be more than one. The 'Incidence' columns refer to the number of patients from whom the bacteria was isolated as a percentage of the Levofloxacin or Ciprofloxacin groups.

Table 3 Clinical efficacy of levofloxacin and ciprofloxacin in patients with confirmed bacterial infection at baseline

Index	*Levofloxacin* (n=*209*)	*Ciprofloxacin* (n=*199*)
Clinical efficacy, *n* (%)	195 (93.30)	143 (71.86)
Clinical cure, *n* (%)	115 (55.02)	68 (34.17)
Clinically improvement, *n* (%)	80 (38.28)	75 (37.69)
Failure, *n* (%)	13 (6.22)	56 (28.14)
Non-evaluable, *n* (%)	0	0

Cochran–Mantel–Haenszel statistic: including non-evaluable patients, 35.08 (P=0.0000); excluding non-evaluable patients, 35.45 (P=0.0000). The CMH test was conducted twice by including and excluding the non-evaluable patients in both groups. Clinical efficacy, which included clinical cure and clinical improvement, was determined at visit 5 (1–4 weeks after end of therapy).

the results of this test revealed that bacteria that were sensitive to the drug showed mild sensitivity or drug resistance, indicating that alternative antibiotics should be considered to maintain the therapeutic effect if bacteria are still detected after 4 weeks of antibacterial therapy.

The clinical symptoms and signs of patients were improved in combination with bacterial clearance. After 4 weeks of therapy, the clinical efficacies (i.e., all patients showing clinical cure or improvement) in the levofloxacin- and ciprofloxacin-treated groups were 93.30% and 71.86% ($P<0.05$), respectively, suggesting that levofloxacin may be better than ciprofloxacin in improving clinical symptoms and signs and that the clinical efficacy was positively associated with the bacterial clearance rate. We also found that the higher bacterial clearance rate in the levofloxacin-treated group was associated with higher long-term effectiveness rate and lower rate of recurrence. Taken together, the results presented here were generally consistent with those of earlier studies in European and North American patients.[10–13]

One limitation of the present study is that this study was not performed in a double-blind manner, which may cause some bias in terms of patient selection. Furthermore, some patients received other anti-prostatitis drugs including α-receptor blockers and traditional Chinese medicines, which may relieve the symptoms and improve the clinical outcomes of prostatitis. Because similar proportions of patients in the levofloxacin- and ciprofloxacin-treated groups (10.53% and 10.05%, respectively) used other agents, the difference in efficacy outcomes between the two groups was unlikely to be influenced by the use of other agents.

In conclusion, the present study showed that levofloxacin is better than ciprofloxacin in terms of bacterial clearance rate and resolution of clinical symptoms in Chinese patients with chronic bacterial prostatitis. Although numerous studies have demonstrated similar findings in European and North American patients, our study is the first to demonstrate the efficacy and safety of levofloxacin in Chinese patients with chronic bacterial prostatitis.

AUTHOR CONTRIBUTIONS

ZZC designed the study, conducted the data acquisition, interpreted the data, conducted statistical analysis, drafted and revised the manuscript. GYL also designed the study. ZZC, FSJ, DML, ZJS and YHS conducted the data acquisition, data interpretation and revised manuscript.

Table 4 Overall rates of adverse events and treatment-related adverse events

Items	*Levofloxacin* (n=*209*)			*Ciprofloxacin* (n=*199*)		
	n	*Episodes*	*Incidence (%)*	n	*Episodes*	*Incidence (%)*
All adverse events	7	9	3.33	12	14	6.03
Treatment-related adverse events	6	7	2.87	11	12	5.53
Adverse events						
Skin and auxiliary						
Rash	0	0	0	1	1	0.50
Itching	1	1	0.48	0	0	0
Nervous system						
Headache	0	0	0	2	2	1.01
Dizziness	2	2	0.96	0	0	0
Mental disorder						
Insomnia	1	1	0.48	2	2	1.01
Gastrointestinal system						
Nausea	1	1	0.48	2	2	1.01
Abdominal distention	0	0	0	1	1	0.50
Abdominal discomfort	1	1	0.48	2	2	1.01
Anorexia	0	0	0	1	1	0.50
Hepatobiliary system						
GPT increased	0	0	0	1	1	0.05
GOT increased	1	1	0.48	1	1	0.50
Respiratory system						
Cough	1	1	0.48	0	0	0
WBC and reticuloendothelial system						
Decreased eosinophils	0	0	0	1	1	0.50
Systemic abnormalities						
Drug allergy	1	1	0.48	0	0	0
Others						
Tendinitis	0	0	0	0	0	0

Abbreviations: GOT, glutamic-oxaloacetic transaminase; GPT, glutamic-pyruvic transaminase; WBC, white blood cell.

COMPETING FINANCIAL INTERESTS

The authors have no competing financial interests to declare.

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