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ORIGINAL ARTICLE

Comparison of 3-day and 7-day ciprofloxacin regimen for the treatment of uncomplicated urinary tract infection in women: A randomized double-blind clinical trial

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ABSTRACT

Background: Urinary tract infections (UTIs) are among the most commonly bacterial infections in clinical practice. Almost half of all women experience at least one urinary tract infection in their lifetime. This study compared efficacy and safety of 3-day and 7-day ciprofloxacin regimen for the treatment of uncomplicated urinary tract infection in women.

Patients and methods: A total of 76 patients were randomly assigned to two treatment groups. One group received ciprofloxacin, 250 mg twice a day for 3 days (n=39) and the other group received ciprofloxacin 250 mg twice a day for 7 days (n=37). Subjects were visited and assessed three times during the study period (baseline, end of treatment, and test for cure). Clinical and bacteriological responses to the treatment were compared between the two groups.

Results: There was no significant difference between the two groups in terms of age distribution and clinical signs/symptoms during the baseline visit. There was no significant difference between clinical or bacteriological responses between the two groups. Three-day regimen of ciprofloxacin showed high microbiological eradication rate for *E. coli* (66.7%) which was similar to the eradication rate observed for 7-day regimen (64.8%). No statistically significant difference was found in adverse effects between the groups, except for nausea (p=0.041).

Conclusion: A 3-day ciprofloxacin regimen appeared to be safe and effective for the treatment of UTI in women. Therefore, shorter therapy duration with ciprofloxacin can potentially improve patient compliance and decrease costs.

Keywords: *Urinary tract infections, Ciprofloxacin, Women*.
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INTRODUCTION

Urinary tract infections (UTIs) cause over 7 million physician office visits (mostly for cystitis) and one million emergency visits per year in the United States (1,2). Trimethoprim-sulfomethoxazole (TMP-SMX) is currently the first-line treatment for uncomplicated UTIs. Given increasing bacterial resistance to TMP-SMX (3,4), fluoroquinolones are now recommended as first-

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line treatment in areas with high bacterial resistance. Ciprofloxacin is a fluoroquinolone antimicrobial agent with a broad spectrum activity against gram-negative and gram-positive bacteria. It is an effective treatment for a wide variety of bacterial infections, including UTIs. However, gastrointestinal side effects such as nausea and diarrhea are the most common causes of discontinuation of ciprofloxacin therapy (5,6).

This study compared the efficacy and safety of a 3-day ciprofloxacin and 7-day ciprofloxacin for the treatment of uncomplicated urinary tract infection in women.

PATIENTS and METHODS

Study design: This study is a randomized double-blind clinical trial, comparing 3-day and 7-day ciprofloxacin regimen for the treatment of uncomplicated UTI in women. Study subjects were randomly selected from female patients with clinical evidence of acute uncomplicated UTIs. All subjects were requested to complete an informed consent prior to study. Eligible patients were randomly assigned, in a double blind, double-dummy manner to either ciprofloxacin 250 mg twice a day for 3 days, or ciprofloxacin 250 mg twice a day for 7 days in a ratio of 1:1.

Eligibility and accrual: The following inclusion criteria were applied at baseline: non-pregnant female adult (≥18 years old) with clinical evidence of acute uncomplicated UTIs (dysuria, urgency, frequency of urination and/or suprapubic pain), and onset of symptoms less than 72 hours prior to study. Patients must have a positive pretreatment clean-catheter midstream urine culture defined as $\geq 10^5$ CFU/ml of an identified single uropathogen (7). It should be noted that all patients, who initially entered the study and had clinical presentations of UTI, were tested for urine culture and subsequently treated with ciprofloxacin. If the urine culture results did not meet the above-mentioned criteria ($\geq 10^5$ CFU/ml of an identified single uropathogen), they were excluded from the study. Meanwhile, the following exclusion criteria were applied at baseline: three or more UTIs in previous year, signs or symptoms of vaginal infections, overt pyelonephritis, structural abnormalities, an indwelling catheter, renal insufficiency, gastrointestinal disorder, and gynecologic disorder (8) as well as receiving medications containing products such as antacids, sucralfate, calcium, iron or zinc supplements and/or any antimicrobial treatments within two days prior to the study.

Treatment procedure: A total of 76 patients were randomly assigned to two groups; one group received ciprofloxacin (Exir Pharmaceutical Co.), 250mg twice a day for 3 days (n=39), and the other group received ciprofloxacin 250mg twice a day for 7 days (n=37). Each subject was visited thrice by a clinician at baseline (visit 1), end of the treatment (visit 2), and 4 weeks following the therapy (visit 3). At the baseline, demographic, and medical and drug history of patients was gathered. Meanwhile, a thorough physical examination and assessment of clinical signs and symptoms of UTIs were performed. Further, a urine sample for pyuria evaluation, culture and susceptibility testing was obtained. During the second visit (3^{rd} and 7^{th} day for respective groups), clinical information concerning the progression or regression of UTIs signs/symptoms along with a urine sample for culture were obtained. At the third visit, response to the therapy was assessed.

Bacterial assessment and outcome measures: Antimicrobial efficacy was evaluated by conventional clinical and laboratory determinants, including serial urine culture obtained by the midstream 'clean-cath' technique at the baseline visit (within 48 hours before the first dose of study drug) and the test for cure visit (one month after treatment). The uropathogens were identified by standard microbiologic techniques and tested for susceptibility to ciprofloxacin using Disk Diffusion Susceptibility Testing (Kirby-Bauer Method)

recommended by the National Committee on Clinical Laboratory Services (NCCLS).

In this study bacteriologic response at the end of treatment (visit 2) was considered as the primary bacteriological efficacy variable. The bacteriologic response was classified as eradication and persistence. Eradication was defined as a reduction of uropathogen colony count from $\geq 10^5$ CFU/ml at study entry to $<10^4$ CFU/ml, only at the second visit. Persistence was defined as growth of the original uropathogen to $\geq 10^4$ CFU/ml from a urine sample taken after therapy completion. These definitions are consistent with prior similar published studies (9,10).

Clinical assessment: Clinical response was evaluated by a clinician at the third visit (4 weeks following the treatment completion) based on clinical UTIs signs and symptoms (dysuria, urgency, frequency of urination and/or suprapubic pain) and patient's primary complaint.

Clinical response was classified as improvement, relative improvement and failure. Improvement was defined as complete relief of all clinical UTIs signs and symptoms. Relative improvement was defined as regression of clinical UTIs signs and symptoms. Failure was defined as persistence or progression of any clinical UTIs signs or symptoms or appearance of new signs or symptoms. It should be noted that these definitions are consistent with prior similar published studies (9,10).

Safety assessment: All study subjects who received at least two doses (1 day) of ciprofloxacin were included in the safety analysis. Medication related adverse effects were obtained by a physician during the final visit.

RESULTS

Approximately, 15-20% of patients in either group were excluded due to drop out and failure to follow up. The most frequent signs and symptoms were frequency (84%), dysuria (59%) and suprapubic pain (51%), followed by nausea (22%), fever (16%) and genital tenderness (4%). Figure 1 shows prevalence of different uropathogens. The most frequent uropathogen was *E. coli* in both therapy groups (69% in 3-day and 73% in 7-day regimen). In this study, antimicrobial susceptibility of uropathogens to ciprofloxacin in 3-day and 7-day treatment groups were 94.9% (37 of 39) and 75.7% (28 of 37), respectively (NS).

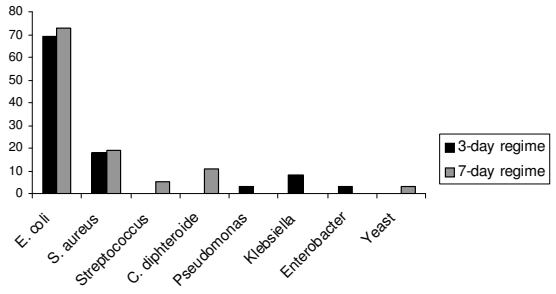

Figure 1. Distribution of pathogens identified in urine sample of patients with UTIs

Overall bacteriological eradication rate for 3-day and 7-day regimen was 74.4% and 64.9%, respectively (p=0.108). Figure 2 shows bacteriological response in both groups according to the uropathogens found in urine. The 3-day regimen showed high microbiological eradication rate for *E. coli* (66.7%) which was similar to the eradication rate observed for 7-day regimen (64.8%).

In our setting, clinical failure rate was 25.6% (10 of 39) and 29.7% (11 of 37), respectively (NS). Figure 3 demonstrates clinical response in both

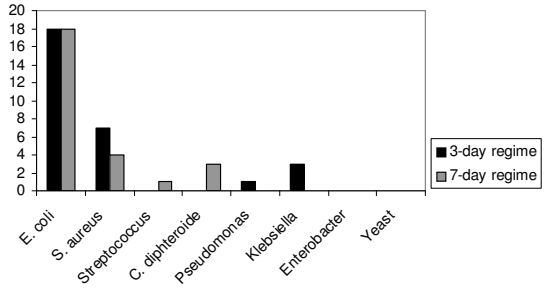

Figure 2. Bacteriological response in both treatment groups at second visit

groups according to patients' signs and symptoms during the third visit.

Distribution of meditation related adverse effects is presented in figure 4. No statistically significant difference was found between the two groups, except for nausea (p=0.041).

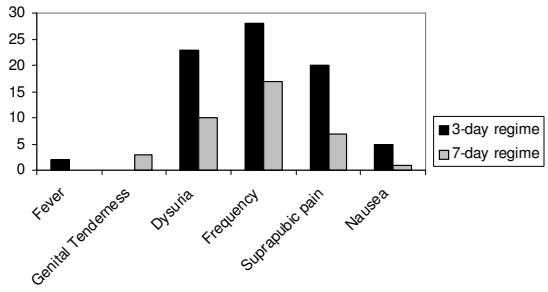

Figure 3. Clinical response in both treatment groups at the third visit

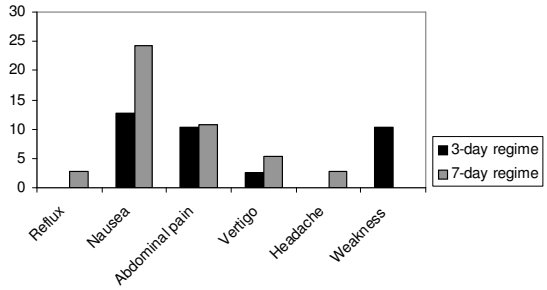

Figure 4. Frequency of adverse drug side effects in both groups

DISCUSSION

Ciprofloxacin was produced by Iranian pharmaceutical companies and introduced to the market in 1990s. Considering the high rate of TMP-SMX resistance for the treatment of UTIs, clinicians in Iran commenced prescribing ciprofloxacin as an alternative choice for the treatment of UTIs. Along with other antibiotics, ciprofloxacin also became resistant to various microorganisms including urinary tract infections pathogens. Factors such as overuse and/or inappropriate use of ciprofloxacin in Iran prompted the authors to conduct this study to investigate and compare efficacy and safety of a 3-day with a 7-day ciprofloxacin regimen for the treatment of UTI.

In this study, there were no significant differences in clinical or bacteriological responses between the two studied groups. In a large, multicenter, double-blind clinical trial, Stein and Philip (9,11) found that a 3-day treatment regimen using a single daily 400mg dose of temafloxacin to be as effective as a 7-day course of ciprofloxacin in women with acute uncomplicated UTI.

Our study showed that microbiological eradication rate of *E. coli* was more or less similar in 3-day and 7-day regimen of ciprofloxacin (66.7% vs. 64.8%). While the resistance of *E. coli* and other gram negative pathogens to TMP-SMX and ampicillin has risen markedly over the past decade, ciprofloxacin has maintained high activity against these organisms (9). Additionally, adverse drug effects such as nausea was significantly lower when the 3-day and 7-day regimens were compared (p=0.041). In a randomized, double-blind study of 891 women with uncomplicated UTI, Henry et al. evaluated the efficacy and safety of extended-release ciprofloxacin 500mg once daily versus immediate-release ciprofloxacin 250mg twice daily, each administered orally for 3 days. The authors reported that the incidence of treatment-related adverse events was 10.4% in women who received extended-release ciprofloxacin and 9.2% among those treated with the immediate-release formulation (10).

Naber et al., in a double-blind, randomized study in adult female patients who received either gatifloxacin (400mg as a single shot or 3 days of 200mg once daily) or ciprofloxacin (250mg given twice daily for 3 days), reported that administration of gatifloxacin 200mg once daily for 3 days, and gatifloxacin 400mg as a single shot is equivalent to ciprofloxacin 250mg twice daily for 3 days for the treatment of acute uncomplicated lower UTIs. They also found that all treatment groups showed a similar safety profile and that the incidence of treatment-related adverse events was comparable,

the majority of adverse events were of mild or moderate intensity and the medications were well tolerated. In our study no serious treatment-related adverse events occurred in either group and only two women in each group stopped treatment because of adverse events. The overall incidence was low, and the most common adverse events were nausea and headache.

This study provides further evidence that a 3-day ciprofloxacin is an effective treatment for patients with UTIs. Furthermore, the patient's compliance for a 3-day ciprofloxacin is better. Hence, this may reduce the emerging and increasing antimicrobial resistance which is highly associated with over use of antibiotics in Iran.

In summary, the results of this study demonstrated that a 3-day ciprofloxacin regimen for the treatment of UTI appeared to be safe and effective. Our findings may suggest that shorter therapy duration of ciprofloxacin regimen can potentially result in improved patient compliance and decreased costs.

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