A study to compare the safety and efficacy of levofloxacin versus cefuroxime axetil in patients with uncomplicated lower UTI in a North Indian Medical College and Hospital.

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ABSTRACT

Background and Objectives: Uncomplicated lower UTI accounts for around 150 million cases worldwide, every year. Antibiotics commonly used for the treatment of uncomplicated lower UTI include fluoroquinolones, trimethoprim-sulphamethoxazole, nitrofurantoin, cephalosporins, and amoxicillin. No comparative study between levofloxacin and cefuroxime axetil in patients with uncomplicated lower UTI could be searched. So, this randomized study was designed to compare the efficacy and tolerability of levofloxacin 500 mg once daily with cefuroxime axetil 250 mg twice daily in the treatment of uncomplicated lower UTI in adult Indian patients.

Methods: This prospective, parallel group comparative study was conducted in 100 patients with uncomplicated lower UTI. Patients were assessed for clinical and bacteriological success over the study period.

Results: 89 patients of the total of 100 patients enrolled in the study completed the study. E.coli was the most common organism isolated in both the groups. Patients in levofloxacin group showed improvement in clinical symptoms by 95.35 percent, as compared to 89.13 percent in the cefuroxime group. However, the intergroup difference was not statistically significant ($p>0.05$). Levofloxacin group showed decrease in bacteriological scoring by 95.35 percent, and cefuroxime group showed decrease by 86.96 percent. The difference in bacteriological scoring between the two treatment groups was not significant ($p>0.05$).

Conclusion: The results of our study show that cefuroxime axetil in a dose of 250 mg twice daily and levofloxacin 500 mg once daily for three days, are equally efficacious in treating patients with uncomplicated lower UTI. The comparative clinical and bacteriological successes between the two groups were statistically not significant, and both drugs were well-tolerated by the patients.

Introduction

Urinary tract infections (UTI) include a heterogeneous group of clinical syndromes and diseases with a worldwide incidence of at least 150 million cases annually. (1) UTI can be broadly divided into lower UTI, which involves urethra, bladder; and upper UTI that involves kidney, ureter, and prostate. Patients with lower UTI present with features of frequency of micturition, dysuria, urgency, suprapubic pain and tenderness, foul smelling urine and hematuria(2), whereas patients of upper UTI present with loin pain and tenderness, fever and systemic upset.(3)

Escherichia coli are the most common organism (71 to 78 percent) causing uncomplicated UTI, followed by Proteus (4-12 percent), Klebsiella, Enterococcus faecalis and occasionally Pseudomonas and Staphylococcus.(2,4,5) Diagnosis of UTI depends on the symptoms and urine culture. Treatment of acute, uncomplicated lower UTI includes mainly oral or parenteral antibiotics. Antibiotics commonly used for the treatment of uncomplicated lower UTI include fluoroquinolones, trimethoprim-sulphamethoxazole, nitrofurantoin, aminoglycosides, cephalosporins, and amoxicillin.(5,6,7,8)

Levofloxacin, the S-isomer of ofloxacin is active against a wide range of gram negative and gram positive organisms including Staphylococcus spp., Streptococcus, H. influenzae, Escherichia coli, Klebsiella spp, Proteus, Pseudomonas aeruginosa and atypical bacteria accountable for causing lower UTI.(9, 10) Comparative studies in lower UTI have demonstrated similar or significantly better results with levofloxacin versus ciprofloxacin, norfloxacin or ofloxacin, and other conventionally used antibiotics e.g. amoxicillin, trimethoprim-sulphamethoxazole (TMP-SMX).(5,11,12,13) The drug levofloxacin is well-absorbed, its bioavailability approaches 100 percent, and it is widely distributed throughout the body.(14) The drug is well-tolerated with a low incidence of resistance.(15,16)

Cefuroxime axetil, an oral second generation broad spectrum cephalosporin is also effective against Gram positive and Gram negative bacteria including Staphylococcus spp., Streptococcus, Niesseria, E.coli, Klebsiella, Proteus responsible for causing lower UTI, but not Pseudomonas aeruginosa. Cefuroxime also is well-tolerated, with incidence of resistance similar to levofloxacin and much lower as compared to TMP-SMX and amoxicillin.(15, 17,18) Studies in patients with acute uncomplicated lower UTI treated with cefuroxime axetil, show overall cure rate ranging from 86 percent to 97 percent (19,20) In another study, at one week post therapy, 88 percent of the patients in the cefuroxime axetil group were clinically and bacteriologically cured.(21) Naber and Koch reported a multicentre study done on 163 women with acute uncomplicated lower UTI, with clinical cure and improvement seen in 84.8 percent and 95.2 percent of patients treated with 125 mg cefuroxime axetil twice daily for three days and 100 mg ofloxacin twice daily for three days, respectively.(18) Seven to nine days after therapy, bacteriuria had been eliminated in 80.3 percent and 89.1 percent of the patients receiving cefuroxime axetil and ofloxacin respectively.

No comparative study between levofloxacin and cefuroxime axetil in patients with uncomplicated lower UTI could be searched. So, this randomized study was designed to compare the efficacy and tolerability of levofloxacin with cefuroxime axetil in the treatment of uncomplicated lower UTI in adult Indian patients.

Materials and Methods

Study design and population

This prospective, randomized, comparative, open-label, parallel group study was done in 100 patients suffering with uncomplicated lower UTI visiting the outpatient medicine department of Government Medical College and Hospital, Patiala during the period from 2006 to 2007; conducted in association with department of medicine, microbiology and pharmacology.

Patients of either sex, between 18 to 60 years of age, suspected to have uncomplicated UTI due to typical symptoms of dysuria, frequency, and/or urgency, sensitivity to both levofloxacin and cefuroxime axetil and willing to give written informed consent were included in the study. Patients with signs and symptoms of complicated UTI (fever, flank pain, costovertebral tenderness), pregnancy, diabetes, epilepsy, abnormalities of urinary tract, UTI within the last two weeks, use of antibiotics within the last 3 days, history of hypersensitivity reaction to the test drugs, or unable to give informed consent were excluded from the study. The study was approved by the Institutional Ethics Committee.

Patients visits to the medicine OPD were planned as per the following schedule: During the first baseline visit (Visit 1), detailed history and clinical examination of the patient were performed and urine sample was sent for microscopic examination, culture and sensitivity. The next visit was planned after 2 days (Visit 2), when the urine culture and sensitivity report became available. Based on urine culture and sensitivity report, patients were randomized into group A and group B. Patients in Group A were prescribed tablet levofloxacin 500 mg once daily for 3 days whereas Group B received tablet cefuroxime axetil 250 mg twice daily for 3 days. Patients were then called at the fourth day after starting the treatment (Visit 3), when the symptoms were recorded to assess clinical improvement and urine sample was sent for microscopic examination, culture and sensitivity.

Outcome measurements

The outcome measures used for efficacy variable were clinical success, which comprised of a sum total of clinical cure (improvement in all three symptoms) and clinical improvement (improvement in one or two symptoms); and bacteriological success (complete eradication of infecting organisms on culture).

Statistical analysis

The results were analyzed using Fisher's exact test and unpaired students t test, using Instat Graphpad 3.10 version software. A p-value <0.05 was considered statistically significant.

Results

Of the total of 100 patients (49 on levofloxacin, i.e. Group A and 51 on cefuroxime axetil, i.e. Group B) who were enrolled in the study, 89 patients (43 in Group A and 46 in Group B) completed the study. Eleven patients, six in group A and five in group B did not come for follow-up. The data was calculated for these 89 patients (33 Male, 56 Female) who completed the study.

Demographic and Baseline data

At the baseline visit (Visit 1), there was no significant difference (p>0.05) in demographic and clinical characteristics between the two treatment groups (Table 1). 62.92 percent (67.44 percent in group A and 58.70 percent in group B) of the patients were female. Increase in frequency (all patients in both groups A and B) was the most common symptom, whereas dysuria was the least common symptom at baseline visit. E. Coli (74.41percent in group A, 82.6 percent in group B) was the most common organism in both the groups, as shown in Table 2.

Clinical success

At visit 3, patients in group A showed mean percentage decrease in symptoms of increased frequency, urgency and dysuria by 72.09 percent, 70 percent and 94.12 percent,

Table 1: Demographic and clinical characteristics of the two treatment groups at baseline visit (Visit 1)

Characteristics	Group A (Levofloxacin 500 mg od)	Group B (Cefuroxime axetil 250 mg bd)	p-value
No. of patients	43	46	
Age in years (Mean ± SD)	35.65 ± 9.56	35.08 ± 9.36	0.78[a]
Sex (M:F)	14: 29	19:27	0.51[b]
Symptoms			
- Increased Frequency	43	46	
- Urgency	40	42	
- Dysuria	34	38	

a Value determined using two-tailed unpaired student "t" test.

b Value determined using Fisher's exact test.

Table 2:. Distribution of organisms in the two treatment groups seen on bacteriological culture at visit 2

Characteristics	Group A (Levofloxacin 500 mg od) (n=43)	Group B (Cefuroxime axetil 250 mg bd) (n=46)
Culture Organism		
- *E. Coli*	32	38
- *Proteus*	8	6
- *Klebsiella*	2	1
- *Staph. aureus*	1	1

Figure 1: Changes in clinical symptoms among the treatment groups after 3-days treatment

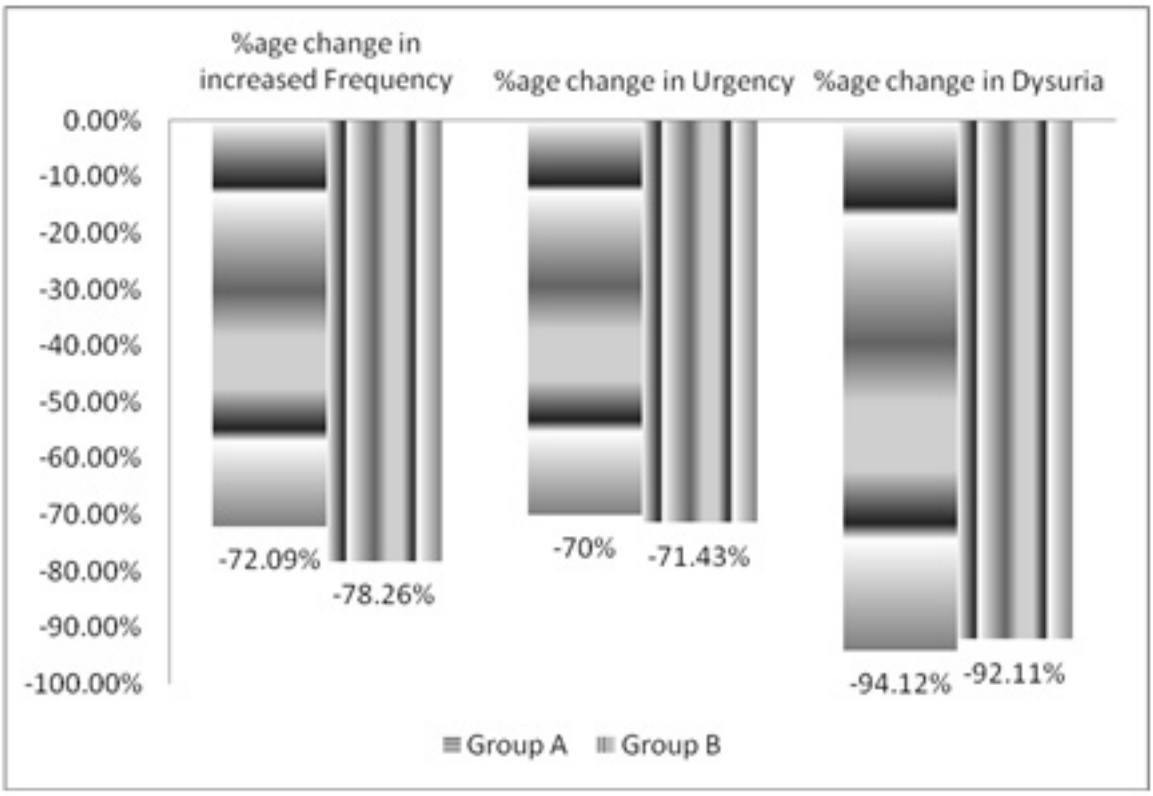
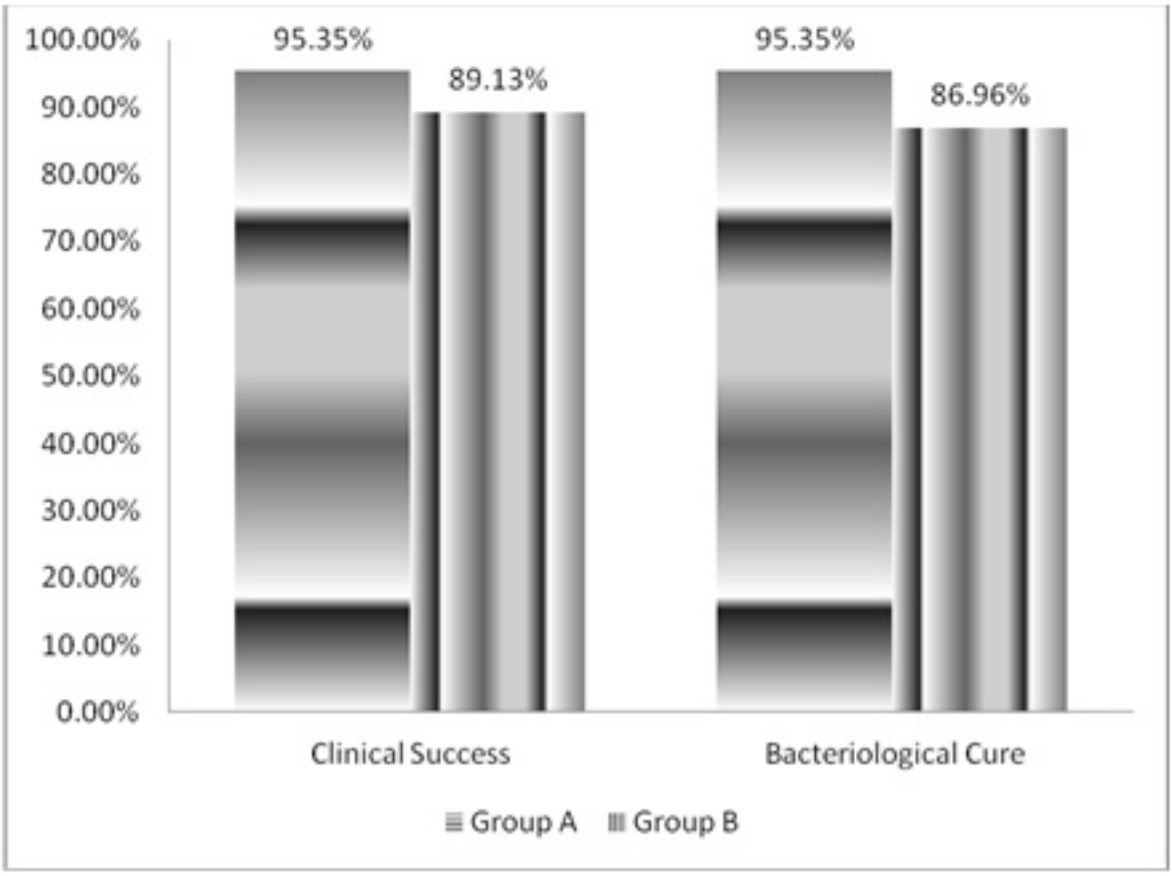


Figure 2: Comparison in clinical success and bacteriological success seen among the treatment groups



respectively. Similarly, patients in group B showed mean percentage decrease in symptoms of increased frequency, urgency and dysuria by 78.26 percent, 71.43 percent and 92.11 percent, respectively (Figure 1). Also, of the total of 43 patients in levofloxacin group A, 23 showed clinical cure, 18 had clinical improvement and 2 patients showed no improvement in any of the symptoms of lower UTI, thus, showing a mean percentage improvement in clinical symptoms by 95.35 percent. In cefuroxime group B, 22 out of the total 46 patients showed clinical cure and 19 showed clinical improvement, however, 5 patients showed no improvement in any of the symptoms. Thus, patients in group B showed a mean percentage improvement in clinical symptoms at visit 3 by 89.13 percent (Figure 2). However, the difference between the two treatment groups was not statistically significant ($p>0.05$), although levofloxacin (95.35 percent versus 89.13 percent) decreased clinical success scores slightly more than cefuroxime (Figure 2).

Bacteriological Success

Mean percentage improvement in bacteriological success score, from baseline to visit 3 of the study period was 95.35 percent for group A (41 had bacteriological cure, 2 had bacteriological failure), and 86.96 percent for group B (40 had bacteriological cure, 6 had bacteriological failure), as shown in Figure 2. The inter-group difference between the two treatment groups A and B was not-significant ($p>0.05$), although levofloxacin decreased bacteriological scores slightly more than cefuroxime.

Safety

Of the 89 patients who completed the study, only three patients (6.98 percent) in the levofloxacin group developed adverse effects with the drug. Two patients (4.65 percent) in levofloxacin group reported nausea and one patient (2.33 percent) complained of headache with the drug. Of the patients on cefuroxime, two patients (4.35 percent) complained of nausea with the drug. The comparison in the incidence of adverse effects between the two treatment groups was statistically non-significant ($p=0.67$), and was done using Fisher's exact test.

Discussion

Urinary tract infections (UTI) are among the most common bacterial infections and the treatment of UTI is aimed at improvement of clinical symptoms and eradication of infection. In uncomplicated acute lower UTI, short-course three-day therapy with cefuroxime axetil or levofloxacin antibiotics is found to be effective, as shown by various studies.(13)

The results of our study show that E.coli was the most common pathogen isolated, similar to the findings seen in other studies.(2,4,5) Also, cefuroxime axetil in a dose of 250 mg twice daily and levofloxacin 500 mg once daily were found to be equally efficacious in treating patients with uncomplicated lower UTI. There was no statistically significant difference ($p > 0.05$) between the clinical and bacteriological success rates of the two treatment groups, and both drugs were well-tolerated by the patients. The levofloxacin group showed slightly better response than cefuroxime axetil, maybe because fluoroquinolones are known to have superior action than cephalosporins against gram negative organisms responsible for causing uncomplicated lower UTI.

In a study by Richard et al, the clinical success rate for levofloxacin vs ofloxacin was 98.1 percent versus 97 percent and bacteriological success rate was 96 percent with levofloxacin and 93 percent for ofloxacin. Our study showed similar response to levofloxacin, although the dose of levofloxacin used in this study was 500 mg od, as compared to 250 mg od in the previous study.(13) In a study by Lee et al in 2011, the susceptibility of E.coli to levofloxacin was 77.5 percent.(22)

The current study shows the effect of cefuroxime axetil was also quite similar to that seen in previous studies. In a study by Naber et al, the clinical success rate for cefuroxime axetil vs ofloxacin was 84.8 percent vs 95.2 percent and bacteriological success rate was 80.3 percent with cefuroxime axetil and 89.1 percent for ofloxacin.(18) The dose of cefuroxime axetil used in this study was 125 mg twice daily for 3 days. Our study was quite similar and showed clinical success rate 89.13 percent and bacteriological success rate 86.96 percent to be slightly better, probably as the dose used was 250 mg twice daily. Another study where patients were prescribed cefuroxime axetil 125 mg twice daily for 7 days, showed clinical success and bacteriological success rate to be 97 percent.(23) The study by Lee et al shows 86.1 percent susceptibility of E. coli to cefuroxime.(22) In another study the susceptibility of E. coli to oral cefuroxime was 68.6 percent versus 97.1 percent to parenteral cefuroxime.(24)

Our study revealed that the two drugs were well tolerated when used for three day therapy. The adverse events of nausea and headache with the test drugs resolved in a few hours in both treatment groups.(12,18) No patient withdrew from the study because of adverse effects, showing good tolerance to study drugs. The adverse effects were lesser in our study in both the groups as compared to earlier studies.

In conclusion, our study shows both drugs cefuroxime axetil 250 mg twice daily and levofloxacin 500 mg once daily to be effective in the three-day treatment of patients with uncomplicated lower UTI, with no statistically significant difference between the efficacy of cefuroxime axetil and levofloxacin, although levofloxacin showed slightly better response than cefuroxime axetil. Both the drugs were well-tolerated.

There are certain limitations in our study: First, more number of patients in each group would make the results more significant. Second, prolonged follow-up visit would have revealed better any cases of relapse or treatment failure.

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