Effectiveness and tolerability of short course co-trimoxazole, norfloxacin and levofloxacin in bacteriological cure of uncomplicated urinary tract infection in outpatient setting. An open label, parallel group, randomized controlled trial

INTRODUCTION

Urinary tract infection (UTI) is characterized by the presence of >10^5 microorganisms per milliliter of urine with pus cells and red blood cells [1]. It is commonly caused by Gram negative organisms like Escherichia coli, Klebsiella, Proteus, Pseudomonas, Enterobacter and also less commonly by gram positive organisms like Staphylococcus saprophyticus and Streptococci [2]. Empirical antimicrobial therapy for 7-10 days is the main stay treatment [3]. Co-trimoxazole, β-lactams, aminoglycosides, and fluoroquinolones are the groups of antimicrobials commonly prescribed for treatment of UTI [4]. Most of the time, broad spectrum antimicrobials are prescribed before the availability of bacterial culture and sensitivity test reports. Some studies have shown that three days treatment with antimicrobials is as effective as seven days therapy in clinical and bacteriological cure of urinary tract infection [5]. Short duration treatment leads to better patient compliance, less adverse effects and cost reduction. In the present study, we evaluated effectiveness of short course treatment with three commonly prescribed antimicrobials (co-trimoxazole, norfloxacin and levofloxacin) for treatment of uncomplicated urinary tract infection in a tertiary care hospital of Gujarat, India.

PATIENTS AND METHODS

The study protocol was approved by the Institutional Review Board (IRB), Government Medical College, Bhavnagar (IRB No. 360/2013, dated 3rd September, 2013). This open label, randomized clinical trial was registered in Clinical Trial Reg-
The study was conducted at the outpatient Department of Medicine at Sir Takhatsinhji General Hospital, Bhavnagar, Gujarat, India. International Conference on Harmonization and Good Clinical Practice (ICH-GCP) guidelines were followed. Written informed consent was obtained from each study participant.

Patients aged 18-65 years with symptoms of dysuria or frequency/urgency of micturation, burning micturation, fever and urine culture showing >10^5 colony forming unit (CFU) per milliliter (CFU/ml) were included in the study. Patients with urine culture showing less than 10^5 CFU/mL, symptoms of upper urinary tract infection, benign prostatic hypertrophy, prostatitis, recurrent UTI or per urethral discharge were excluded from the study. Patients having diabetes, ECG abnormality, abnormal liver and renal laboratory parameters, haemoglobin <8 g/dL, pregnant women were also excluded from the study. At the time of screening, blood samples were collected for total blood count, liver and renal function test; urine samples were collected for routine and microscopic examination.

All the screened patients were randomized. Randomization was done with random software to recruit patients in 1:1:1 ratio into three different study groups (Group A, B and C). Randomization was done by a person not involved in the study and randomized codes were kept in sealed envelopes and opened at the time of patient recruitment. Group A patients received co-trimoxazole 960 mg twice a day; Group B patients received norfloxacin 400 mg twice a day, and Group C patients received levofloxacin 250 mg once a day for 3 days. Patients were called for follow-up on day 4; urine was collected for culture report. Laboratory persons from National Accreditation Board for Testing and Calibration Laboratories (NABL) of the institution were blinded for assigned treatment.

Outcome measures: Effectiveness of each treatment group was evaluated by bacteriological cure rate. Bacteriological cure rate was defined as conversion of pre-treatment positive bacterial urine culture into negative urinary culture on day 4. The treatment failure was defined as positive culture at the end of treatment period. Adverse drug reactions were recorded at follow up visit and compared between the treatment groups.

**Statistical analysis:** Data were expressed in proportions. Chi square test was applied for comparison of bacteriological cure rate between the study groups. P value <0.05 was considered as statistically significant. All the statistical calculations were performed using SPSS (version 21) software (International Business Machine, IBM - America).

**Sample Size calculation:** Overall, 150 participants were needed to achieve 80% power with α level of 0.05 (two tailed), if minimal expected difference in bacteriological cure rate is 20%.

**RESULTS**

One hundred seventy-five out of 203 screened symptomatic patients with uncomplicated UTI were randomized and received the assigned treatment for 3 days. Flow of study participants has been shown in Figure 1. Demographic details and baseline characteristics of patients have been shown in Table 1. Overall, *Escherichia coli* (74.29%) was the most common organism isolated followed by *Klebsiella* spp (11.43%), *Streptococcus* spp (6.29%), *Staphylococcus saprophyticus* (5.14%), and *Pseudomonas* spp (2.86%). At the end of 3 days treatment, bacteriological cure rates were 86.2%, 87.7% and 83.3% for patients receiving co-trimoxazole, norfloxacin and levofloxacin for 3 days, respectively.

As per comparisons for bacteriological cure rates for an individual organism between study groups have been shown in Figure 2, there was no any significant difference noted between the three treatment groups for bacteriological cure rate of an individual organism (p>0.05). 13.6% (6/44), 11.1% (1/9) and 100% (1/1) patients did not respond to the co-trimoxazole in whom *Escherichia coli*, *Klebsiella* and *Pseudomonas* were isolated, respectively. 12.2% (6/49) and 100% (1/1) patients did not respond to norfloxacin against isolated *Escherichia coli* and *Pseudomonas*, respectively. 16.2% (6/37), 28.6% (2/7) and 28.6% (2/7) patients did not respond to levofloxacin in whom *Escherichia coli*, *Klebsiella* and *Streptococcus* spp were isolated, respectively. In all treatment groups, proportions of treatment related adverse drug reactions were found to be similar (Table 2). There were mild adverse reactions reported by the patients. No any serious adverse drug reactions were reported during the trial. Nausea (7.43%) was the most common adverse
drug reaction in all three treatment groups followed by vomiting (5.14%) and headache (1.14%).

**DISCUSSION**

The present study compared the effectiveness and tolerability of co-trimoxazole 960 mg twice a day, norfloxacin 400 mg twice a day and levofloxacin 250 mg once a day for 3 days in patients with uncomplicated urinary tract infection. In the present study, *Escherichia coli* (74.29%) followed by *Klebsiella* spp (11.43%), *Streptococcus* spp (6.29%), *Staphylococcus saprophyticus* (5.14%), and *Pseudomonas* spp (2.86%) were responsible for causing UTI. Gram negative bacteria were predominant com-

![Figure 1 - Flow of patients in present study (CONSORT statement).](image)

**Table 1 - Baseline characteristics of study participants.**

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Group A co-trimoxazole N=58</th>
<th>Group B norfloxacin N=57</th>
<th>Group C levofloxacin N=60</th>
<th>Total N=175</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47.68±16.09</td>
<td>47.75±15.66</td>
<td>47.38±13.09</td>
<td>47.93±15.66</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 25 (43.10)</td>
<td>16 (28.07)</td>
<td>24 (40)</td>
<td>65 (37.14)</td>
</tr>
<tr>
<td></td>
<td>Female 33 (56.89)</td>
<td>41 (71.93)</td>
<td>36 (60)</td>
<td>110 (62.86)</td>
</tr>
<tr>
<td>Organism isolated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>44 (75.86)</td>
<td>49 (85.96)</td>
<td>37 (61.67)</td>
<td>130 (74.29)</td>
</tr>
<tr>
<td><em>Klebsiella</em> spp</td>
<td>9 (15.52)</td>
<td>4 (7.018)</td>
<td>7 (11.67)</td>
<td>20 (11.43)</td>
</tr>
<tr>
<td><em>Pseudomonas</em> spp</td>
<td>1 (1.72)</td>
<td>1 (1.75)</td>
<td>3 (5.00)</td>
<td>5 (2.86)</td>
</tr>
<tr>
<td><em>Staphylococcus saprophyticus</em></td>
<td>2 (3.45)</td>
<td>1 (1.75)</td>
<td>6 (10.00)</td>
<td>9 (5.14)</td>
</tr>
<tr>
<td><em>Streptococcus</em> spp</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD and absolute numbers. Values in parenthesis are in percentage.
pared to Gram positive in causing the UTI [6-9]. Antimicrobial spectrum of co-trimoxazole includes Gram negative bacilli like *Escherichia coli*, *Shigella*, *Salmonella*, and *Proteus mirabilis* as well as Gram positive cocci like *Staphylococcus aureus* and *Streptococcus pneumoniae*. Norfloxacin and levofloxacin are a first and a second generation fluoroquinolone, respectively. While their antimicrobial activity against Gram negative is equal, levofloxacin has an extended spectrum against Gram positive and atypical pathogens. In acute and uncomplicated cases, co-trimoxazole 960 mg twice a day, norfloxacin 400 mg twice a day and levofloxacin 250 mg once a day for 5-10 days are equally effective [4]. Various clinical trials showed similar effectiveness of short course antimicrobial therapy (3 days) as compared to standard duration of therapy (5-7 days) [10, 11]. In the present study, co-trimoxazole, norfloxacin and levofloxacin for 3 days resulted in 86.2%, 87.7% and 83.3% bacteriological cure rate, respectively. Other studies have reported 55-91% bacteriological cure rate with co-trimoxazole and 87-91% with norfloxacin short course therapy [12-15]. High level of resistance has been reported to co-trimoxazole, norfloxacin and levo-

**Figure 2** - Response of individual drug against all uropathogens, in each cotrimoxazole and norfloxacin groups, one pseudomonas was isolated but remained untreated.

**Table 2** - Adverse drug reactions noted in study participants.

<table>
<thead>
<tr>
<th>Nature of ADR</th>
<th>Group A co-trimoxazole N=58</th>
<th>Group B norfloxacin N=57</th>
<th>Group C levofloxacin N=60</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>7 (12.07)</td>
<td>4 (7.02)</td>
<td>2 (3.33)</td>
<td>0.208</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (5.17)</td>
<td>3 (5.26)</td>
<td>3 (5.00)</td>
<td>0.994</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (3.45)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0.13</td>
</tr>
<tr>
<td>Total</td>
<td>12 (18.96)</td>
<td>7 (12.28)</td>
<td>5 (8)</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed in absolute numbers, parenthesis shows value in proportion. P value is for Chi-square test.
Effectiveness and tolerability of short course co-trimoxazole, norfloxacin and levofloxacin

floxacín for Gram negative organisms in patients of various regions of India [16-18]. In contrast to an overall resistance of 13.8%, 12.3% and 16.7% reported in the present study, Somashekara et al. reported 75.2%, 62.4% and 51.4% overall resistance to co-trimoxazole, norfloxacin and levofloxacin, respectively [17].

In the present study, co-trimoxazole resistance was found in 13.6% *Escherichia coli*, 11.1% *Klebsiella* and 100% *Pseudomonas* whereas Somashekara et al. reported values of 68.8% in *Escherichia coli*, 52.2% in *Klebsiella spp* and 100% in *Pseudomonas spp* [17]. With regard to norfloxacin, resistance was found in *Escherichia coli* [12.2% vs. 78.6%] and *Pseudomonas* [100% vs. 92%] in contrast to the report of Somashekara SC et al. [17]. Somashekara SC et al reported 76.5% *Escherichia coli*, 82.6% *Pseudomonas spp* and 53.5% *Streptococcus spp* whereas the present study found 16.2% *Escherichia coli*, 28.6% *Klebsiella spp* and 28.6% *Streptococcus* resistant to levofloxacin. All the three patients in whom *Pseudomonas* was isolated got bacteriological eradication with levofloxacin in the present study (Figure 2). All these findings suggest that the 3 days therapy with co-trimoxazole, norfloxacin and levofloxacin are equally effective for bacteriological cure of uncomplicated UTI and that levofloxacin is highly effective, compared to cotrimoxazole and norfloxacin, for treatment of UTI caused by pseudomonas.

All the three treatments were well tolerated by the study participants, without occurrence of any serious adverse events. According to the Infectious Disease Society of America (IDSA) guidelines, cotrimoxazole is the current standard therapy for uncomplicated community acquired urinary tract infection (CAUTI) in women [19]. Fluoroquinolones should be reserved as a second line drug for CAUTI [19]. Findings of the present study recommend the use of co-trimoxazole 960 mg twice a day as first line drug for the cases of uncomplicated UTI. There is no added advantage of using norfloxacin and levofloxacin as first line; they can be used as reserved drug. However, we could not measure the effectiveness of short course therapy in preventing UTI relapse.

**CONCLUSION**

In conclusion, co-trimoxazole, norfloxacin and levofloxacin can be recommended for a three days period to reduce bacterial overload in UTI. Co-trimoxazole should be given as a first line drug. There is no added advantage of using norfloxacin and levofloxacin as first line; they can be used as reserved drug.

*Keywords:* urinary tract infection (UTI), co-trimoxazole, norfloxacin, levofloxacin, short-course treatment.

**SUMMARY**

To compare the bacteriological cure rate of short-course (3-day) treatment of uncomplicated urinary tract infection (UTI) using co-trimoxazole, norfloxacin and levofloxacin, patients with uncomplicated UTI were randomized to receive either co-trimoxazole (960 mg) twice a day or norfloxacin (400 mg) twice a day or levofloxacin (250 mg) once a day for three days. Urine culture was done at the end of treatment and evaluated for bacteriological cure rate in each group. Among a total of 175 patients, *Escherichia coli* (74.29%) was the most common organism isolated followed by *Klebsiella* (11.43%), *Streptococcus* (6.29%), *Staphylococcus saprophyticus* (5.14%), and *Pseudomonas* (2.86%). At the end of three days’ treatment, bacteriological cure rates were 86.2%, 87.7% and 83.3% for co-trimoxazole, norfloxacin and levofloxacin, respectively (p>0.05). Therefore short-course treatment with co-trimoxazole 960 mg twice a day, norfloxacin 400 mg twice a day and levofloxacin 250 mg once a day are almost equally effective for treatment of uncomplicated UTI.
Al fine di confrontare il tasso di eradicazione batteriologica conseguente a un ciclo breve (3 giorni) di trattamento per le infezioni delle vie urinarie (IVU) non complicate con cotrimossazolo, norfloxacina e levofloxacina, pazienti affetti da IVU sono stati randomizzati a ricevere uno dei seguenti trattamenti: cotrimossazolo (960 mg) bid, norfloxacina (400 mg) bid o levofloxacina (250 mg) qd per tre giorni. L’urinocultura è stata effettuata al termine del trattamento e il tasso di eradicazione batteriologica è stato valutato in ciascun gruppo di pazienti. Nell’ambito dei 175 pazienti, Escherichia coli (74,29%) ha rappresentato il microrganismo isolato con maggiore frequenza cui hanno fatto seguito Klebsiella (11,43%), Streptococcus (6,29%), Staphylococcus saphrophyticus (5,14%), e Pseudomonas (2,86%). Al termine dei tre giorni di trattamento, i tassi di eradicazione batteriologica sono stati pari a 86,2%, 87,7% e 83,3% per i pazienti trattati con cotrimossazolo, norfloxacina e levofloxacina, rispettivamente (p>0,05). Quindi, cicli di trattamento breve con cotrimossazolo 960 mg bid, norfloxacina 400 mg bid e levofloxacina 250 mg qd presentano una efficacia all’incirca sovrapponibile per il trattamento delle IVU non complicate.

RIASSUNTO

REFERENCES


