A comparative study of fosfomycin trometamol and nitrofurantoin in acute uncomplicated urinary tract infection

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Abstract

Background: Acute urinary tract infection is stressful situation for women. Uncomplicated urinary tract infections are considered to be the most common bacterial infection in women. For treating these uncomplicated UTIs, susceptibility is of critical importance in selecting an appropriate antimicrobial agent. Material and Methods: A case control study carried out in department of obstetrics and gynecology in tertiary care teaching institute in north India. Total 100 female non pregnant patients aged 18 – 65 years with acute uncomplicated UTI were taken in two groups each having 50 cases. The 50 patients of study group were given single 3 gram dose of fosfomycin trometamol orally, while the 50 patients of control group were given 100 mg tab of nitrofurantoin twice daily after food for 7 days, treated on OPD basis. Clinical and microbiological reassessment performed in 7-8 days after the start of treatment and long term follow up at one month from the start of the treatment were done. Results: Mean age of the patients in fosfomycin group was 31.6 years and in nitrofurantoin group was 33.8 years. The most frequently isolated microorganism in both the groups were E coli 88% and 86 % respectively based on antibiotic susceptibility of all uropathogens, fosfomycin (91.8%) was the most active antibiotic followed by nitrofurantoin (91.2%) and norfloxacin. Bacterial eradication after 7 days follow up was obtained in 90 % in fosfomycin group as compared to 85% in control group. And long term follow up at one month gave eradication in 81 % in fosfomycin group as compared to 80 % in nitrofurantoin group. Conclusion: This study concludes that fosfomycin trometol in a single 3-4 gram dose is as effective as 7 day regimen of nitrofurantoin for the treatment of uncomplicated lower urinary tract infection in women. So based on comparable microbiological cure and cost effectiveness and less adverse effects, we conclude that single dose fosfomycin trometol is a good alternative in the treatment of women with acute uncomplicated UTI.

Keywords: Urinary tract infections, Fosfomycin Trometamol, Nitrofurantoin.

Introduction

Urinary tract infections (UTIs) are among the most commonly occurring human infections [1, 2]. It is estimated that approximately 50% of women will experience at least one UTI during their lifetime and that 25% will suffer recurrent infection [3]. Uncomplicated cystitis, the most common presentation for UTI, occurs in adult, premenopausal women with a normal, unobstructed, genitourinary tract where symptoms are confined to the urinary bladder and urethra. Females with cystitis typically present with dysuria and increased urinary urgency and frequency, as well as suprapubic pain, hematuria, and nocturia. Pyelonephritis is distinct from cystitis and is commonly associated with fever (>38°C) and flank pain. The majority of cases of community-acquired cystitis are attributable to uropathogenic Escherichia coli (75–90%) and Staphylococcus saprophyticus (5–15%), with Klebsiella spp, Enterococcus spp., Streptococcus agalactiae and Proteus mirabilis accounting for most other cases [1, 2, 4, 5]. Pseudomonas aeruginosa, Staphylococcus aureus and Candida spp. are infrequent causes of acute uncomplicated UTIs.

Current guidelines published by the Infectious Diseases Society of America (IDSA) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) recommend fosfomycin, nitrofurantoin, and
trimethoprim-sulfamethoxazole (TMP-SMX) as first-line agents to treat acute uncomplicated UTIs in adult females, reserving fluoroquinolones, amoxicillin-clavulanate, and other β-lactams as second-line agents [6]. Elevated rates of resistance (>10–20%) to TMP-SMX, as well as fluoroquinolones, are now widely reported for uropathogenic isolates of E. coli in Canada and elsewhere [7, 8]. The most recently published Canadian study, describing antimicrobial resistance rates among E. coli isolated from patients with urinary tract infections, reported on isolates collected from 2010 to 2013 and found susceptibility rates of 74.7% to TMP-SMX, 77.4% to ciprofloxacin, 81.3% to amoxicillin-clavulanate, 96.1% to nitrofurantoin, and 99.4% to fosfomycin [9]. The increasing identification of extended-spectrum beta-lactamase- (ESBL-) producing E. coli across Canada and internationally has been associated with concomitant resistance to amoxicillin-clavulanate, ciprofloxacin, and TMP-SMX [7, 8]. Rates of susceptibility among E. coli of <80% for one or more first- or second-line agents should prompt local reevaluation of empiric treatment strategies for acute uncomplicated UTIs [6]

Nitrofurantoin has been used since long for UTIs without satisfying all the criterias. The drug fosfomycin trometamol shows many fold hope in satisfying all the above criteria for treating UTI. The present study was designed to evaluate the efficacy and safety of drug fosfomycin trometamol versus nitrofurantoin in treatment of acute uncomplicated UTIs in women.

Material and Methods

Study area: The present case control study was carried out in the department of obstetrics and gynecology in tertiary care teaching hospital in north india. A total of 100 cases were taken for study in two groups, each having 50 cases.

Study design – Case control study.

Inclusion criteria: female patients aged 18 – 65 years with acute uncomplicated UTIs with symptoms including dysuria, frequency and urgency were enrolled in the study. A diagnosis of UTI is defined as symptoms of infection and the presence of > 10^5 cfu/ml of a uropathogen in a clean midstream urine sample of < 96 hours were eligible for study enrolment.

Exclusion criteria: female patients with nosocomial and or complicated UTIs (fever, flank pain), pregnant or lactating patients, with known hypersensitivity to fosfomycin and nitrofurantoin, with structural or functional abnormalities of the urinary tract, with renal or hepatic dysfunction or who had received antibiotic within week before the onset of symptoms.

Methods: Total 100 female non pregnant patients aged 18 – 65 years with acute uncomplicated UTI were taken in two groups each having 50 cases. The 50 patients of study group were given single 3 gram dose of fosfomycin trometamol orally before bed time, while the 50 patients of control group were given 100 mg tab of nitrofurantoin twice daily after food for 7 days.

Both groups of patients were treated on OPD basis. A single form per patient was filled including the following data: Age, gender, description and duration of symptoms, past history, data of antibiotic administration etc. From each patient, a urine sample for microscopy and culture sensitivity test was taken before starting the drug dosage. And also a blood sample was taken for CBC, blood sugar, serum creatinine, bilirubin, VDRL and retovirus testing. Out of those patients who fulfilled the selection criteria chronologically odd no. patients were given fosfomycin trometabol single dose 3.0 gm sachet before bed time and even no. patients were treated with tab nitrofurantoin regimen 100 mg tab twice a day after food for 7 days. Clinical and microbiological reassessment performed 7 – 8 days after the start of treatment and long term follow up at one month from the start of the treatment were done.

Clinical success rate was defined as absence or marked reduction of symptoms and failure as exacerbation or no reduction of symptoms.

Microbiological success included eradication that is absence of pathogen or presence of pathogen with <10^3 cfu/ml. No eradication suggested isolation of the initial pathogen with >10^3 cfu/ml while reinfection meaning isolation of different pathogens from that of initial isolation at a concentration of >10^3 cfu/ml. clinical tolerability included absence or presence of side effects.

Analysis of data- The SPSS 11.5 was used for analyzing the data. The mean and standard deviation was obtained for summarizing the Quantitative variables, while the categorical variables were tabulated using frequencies and percentages. A student’s t-test was used for testing continuous variables and a Chi-square test for ordinal variables. A P value of less than 0.05 was considered significant.
Results

A total of 112 female patients with acute UTI symptoms were enrolled in the study & evaluated 12 patients were excluded from the study who failed to follow up. Enrolled odd no. patients were included in fosfomycin trometalol group that is study group and even no. patients were included in nitrofurantoin group that is control group.

Table 1: Shows patient distribution according to age.

| Age of patient | Study Group[50] | Control Group[50] |
|----------------|-----------------|-------------------|
| 18 -30 YRS     | 35              | 33                |
| 30-50 YRS      | 09              | 10                |
| 50-65 YRS      | 06              | 07                |

Table 2: Shows patient distribution according to symptoms.

| Symptoms | Study Group | Control Group |
|----------|-------------|---------------|
| Dysurea  | 40          | 38            |
| Frequency| 48          | 45            |
| Urgency  | 38          | 40            |

The above table shows the distribution of symptoms namely dysuria, frequency, urgency were comparatively same in both study group (fosfomycin trometalol) and control group (Nitrofurantoin).

Table 3: Microorganisms isolated before the beginning of study.

| Microorganisms     | Study group | Control group |
|--------------------|-------------|---------------|
| E.Coli             | 44(88%)     | 43(86%)       |
| Klebsiela          | 03(6%)      | 04(8%)        |
| Pseudomonas        | 01(2%)      | -             |
| Enterococcus Fecalis| 02(4%)   | 03(6%)        |

The above table shows the most frequently isolated microorganisms in both the groups of patients were e.coli 88% and 86% respectively in study and control group. Followed by klebsiela, enterococcus fecalis and pseudomonas in both the groups.

Table 4: Susceptibility of the uropathogens isolated.

| Antibiotic        | Susceptibility | Intermediate | Resistance |
|-------------------|----------------|--------------|------------|
| Fosfomycin        | 91.8%          | 2.3%         | 5.9%       |
| Nitrofurantoin    | 91.2%          | 1.6%         | 7.2%       |
| Norfloxacin       | 89.4%          | 1.3%         | 9.3%       |
| Ciprofloxacin     | 87.4%          | 5.6%         | 7.0%       |
| Cotrimoxazole     | 80.4%          | 7.0%         | 12.6%      |

Antibiotic susceptibility of all uropathogens isolated before the beginning of the study is summarized in table 4. Fosfomycin (91.8%) was the most active antibiotic followed by Nitrofurantoin (91.2%) and Norfloxacin (89.4%), then ciprofloxacin and cotrimoxazole.
Table 5: Clinical evaluation of eradication.

| Clinical eradication        | Study group | Control group |
|----------------------------|-------------|---------------|
| 7 days follow up            | 91%         | 90%           |
| 1 month follow up           | 86%         | 84%           |

The above table shows clinical follow up after 7 days from the end of drug administration. 91% of patients from fosfomycin group were cured and 90% of the patients cured with nitrofurantoin group. At long term follow up (one month) from the start of the regimen, 86% from fosfomycin group and 84% from nitrofurantoin group were cured. The result was statistically significant (p value- 0.01)

Table No 6: Microbiological evaluation of eradication.

| Microbiological eradication | Study group | Control group |
|-----------------------------|-------------|---------------|
| 7 days follow up            | 90%         | 88%           |
| 1 month follow up           | 81%         | 80%           |

The above table shows, Bacterial eradication at 7 days follow up was obtained in 90 % in fosfomycin group as compared to 88% in control group, and long term follow up at one month gave eradication in 81% in fosfomycin group as compared to 80% in nitrofurantoin group. The result was statistically significant (P value- 0.05)

Discussion

Management of acute uncomplicated UTIs has traditionally been based on two important principles, the spectrum of organisms causing acute UTIs and the susceptibility patterns of these organisms. The intention of this study was to describe the current prevalence of uropathogens and their level of antibiotic susceptibility against fosfomycin and nitrofurantoin drug.

Fosfomycin trometamol (fosfomycin tromethamine) [Monuril ®, Monurol ®, Monural ®] is approved in numerous countries worldwide, mainly for the treatment of uncomplicated urinary tract infections (UTIs). Fosfomycin has good in vitro activity against common uropathogens, such as Escherichia coli (including extended-spectrum β-lactamase-producing E. coli), Proteus mirabilis, Klebsiella pneumoniae and Staphylococcus saprophyticus, and the susceptibility of uropathogens to fosfomycin has remained relatively stable over time. A single oral dose of fosfomycin trometamol 3 g (the approved dosage) achieves high concentrations in urine. Results of recent randomized trials indicate that single-dose fosfomycin trometamol had similar clinical and/or bacteriological efficacy to 3- to 7-day regimens of ciprofloxacin, norfloxacin, cotrimoxazole or nitrofurantoin in women with uncomplicated lower UTIs. In addition, single-dose fosfomycin trometamol had similar bacteriological efficacy to a 5-day course of cefuroxime axetil or a 7-day course of amoxicillin/clavulanic acid in pregnant women with asymptomatic bacteriuria, and similar clinical and/or bacteriological efficacy to a 5-day course of cefuroxime axetil or amoxicillin/clavulanic acid or a 3-day course of ceftriaxone in pregnant women with a lower UTI. Single-dose fosfomycin trometamol was generally well tolerated, with gastrointestinal adverse events (e.g. diarrhoea, nausea) reported most commonly. In conclusion, single-dose fosfomycin trometamol is an important option for the first-line empirical treatment of uncomplicated lower UTIs [10].

Similar to our study, A multicenter clinical trial compared single-dose fosfomycin tromethamine with a 7-day course of nitrofurantoin for the treatment of acute uncomplicated lower urinary tract infection (UTI) in female patients. Healthy females with symptoms of acute uncomplicated UTI were enrolled in a double-masked, randomized clinical trial. Assessable patients had >10^5 colony-forming units per milliliter of uropathogen in a clean-voided midstream urine sample. Patients received a single 3-g dose of fosfomycin tromethamine plus 7 days of placebo capsules or a single 3-g dose of placebo plus 7 days of nitrofurantoin monohydrate/macrocystal 100-mg capsules. Treatment efficacy was assessed by both bacteriologic and clinical response 5 to 11 days after the initial treatment dose (visit 2) and 5 to 11 days (visit 3) and 4 to 6 weeks (visit 4) after the last day of medication. Of the 749 patients initially enrolled in the
study. 375 received fosfomycin and 374 received nitrofurantoin. There were no clinical differences in patient characteristics between the 2 groups at study entry. Overall, 94% of pretreatment isolates were susceptible to fosfomycin and 83% were susceptible to nitrofurantoin. Bacteriologic cure rates at the first follow-up visit (5 to 11 days after initiation of treatment) were 78% and 86% for fosfomycin and nitrofurantoin, respectively (P = 0.02). At visit 3 (1 week post treatment), they were 87% and 81% for fosfomycin and nitrofurantoin, respectively (P = 0.17). Both treatment groups had an 80% overall clinical success rate (cure and improvement). Twenty patients (5.6%) who received nitrofurantoin reported an adverse effect related to study medication. The most common side effects related to fosfomycin treatment were diarrhea (2.4%), vaginitis (1.8%), and nausea (0.8%). Both bacteriologic and clinical cure rates observed with a single 3-g dose of fosfomycin were comparable to those achieved with a 7-day course of nitrofurantoin in female patients with acute uncomplicated UTI, results were similar to our study [11].

Results of our study corelated with Van Pienbroek E et al[12] they studied the efficacy and tolerability of a single dose of 3 g fosfomycin trometamol and the conventional treatment with nitrofurantoin 50 mg four times daily for seven days were compared. In a randomized, double-blind, double-dummy trial in 31 general practices in the Netherlands 231 patients with symptoms of acute dysuria, stranguria and/or urinary frequency received treatment. Evaluation was based on resolution of symptoms, dipslide results and side-effects at 4, 9 and 42 days after starting the treatment. The clinical cure rates and bacteriological cure rates were not significantly different between the treatment groups. Side-effects were reported at day 4 by 43% of the women receiving single-dose treatment, compared with 25% of the women in the seven-day treatment group, a significant difference. At day 9 the groups did not significantly differ in the number of patients with side-effects. Almost all side-effects were mild and gastrointestinal complaints were reported most. Taking into account the convenience of taking a single dose we conclude that fosfomycin trometamol is a reasonable alternative to 7 days nitrofurantoin 50 mg four times a day in the treatment of women with symptoms of acute uncomplicated urinary tract infections in general practice [12].

Treatment of UTI with placebo has been studied in 2 RCTs [13,14,15]. Christiaens et al[13] performed a blinded RCT of placebo vs nitrofurantoin in 78 young women presenting with symptoms of acute cystitis, excluding those with fever, diabetes, recurrent or recent UTI, and other conditions. Symptomatic cure at 7 days was lower in the placebo group (42%) compared with the treatment group (70%, P = .01). However, these numbers are potentially misleading in favor of the placebo group, because 10 women dropped out of the placebo group for worsening symptoms, compared with 2 such dropouts in the treatment group. One of 38 women in the placebo group developed pyelonephritis (2.6%). The placebo vs pivmecillinam study by Ferry et al[16,17] also favored antibiotic therapy over placebo. One of 855 pivmecillinam treated women developed pyelonephritis, in comparison with 1 of 288 women in the placebo group. A meta-analysis [16,17] of RCTs of antibiotics vs placebo for women with uncomplicated cystitis included these 2 studies as well as 3 earlier studies, 2 of which studied single-dose therapy[18,19] and 1 of which did not report clinical or microbiological cure rates. Antibiotics were superior to placebo when measured by clinical improvement, clinical cure, or bacterial cure, although adverse events (any) were more likely in the women treated with antibiotics [20]. To summarize, available evidence does not support placebo treatment of adult, nonpregnant women who present with symptoms of acute cystitis; placebo is not helpful and may even be harmful (level of evidence A-III).

Acute uncomplicated cystitis is a common condition that can often be successfully diagnosed and treated without a urine culture. Culture-sparing strategies include telephone management, patient self-diagnosis and office visits without urine culture.Clinical trial evidence supports trimethoprim-sulfamethoxazole (160/800mg twice daily for 3days), nitrofurantoin monohydrate/macrocrystals (100mg twice daily for 5-7 days), and fosfomycin trometamol (3 g in a single dose) as first-line therapies for uncomplicated cystitis. The choice between these agents should be influenced by individual factors such as resistance prevalence, cost, and tolerability. The rate of resistance among Escherichia coli to the fluoroquinolones (~20%) is about 10-fold higher than to fosfomycin (1%-2%) and is increasing [21]. An important caveat is that there are limited data on outcomes among women with uropathogens resistant to the treatment drug, and increasing resistance may result in lower efficacy rates in clinical practice compared with what is observed in a clinical trial setting [22].
Conclusions

Immediate antimicrobial therapy with nitrofurantoin, or fosfomycin is indicated for acute uncomplicated urinary tract infection in adult women. Increasing resistance rates among uropathogens have complicated treatment of acute cystitis. Individualized assessment of risk factors for resistance and regimen tolerability is needed to choose the optimum empirical regimen. In this respect, a single dose fosfomycin trometamol is well absorbed and produces a therapeutic concentration in urine for 1–3 days. It is well tolerated and cost effective as compared to nitrofurantoin thus taking into account the convenience of taking a single dose, comparable microbiological cure and cost effectiveness and less adverse effects, we conclude that fosfomycin trometamol is a good alternative in the treatment of women with acute uncomplicated UTI. Educating patients regarding the potential for resistance to the drug they are being prescribed and need for reevaluation and urine culture if symptoms do not improve are also important.

Funding: Nil. Conflict of interest: None. Permission of IRB: Yes

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How to cite this article?

Parate S. A comparative study of fosfomycin trometamol and nitrofurantoin in acute uncomplicated urinary tract infection. Int J Med Res Rev 2016;4(5):787-793. doi: 10.17511/ijmrr.2016.i05.22.