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Efficacy of Five Days Nitrofurantoin Therapy versus Fosfomycin Stat Dose in Clinical Resolution of Uncomplicated Urinary Tract Infections

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ABSTRACT

Objective: To compare the efficacy of 5-days Nitrofurantoin therapy versus Fosfomycin stat dose in clinical resolution of uncomplicated urinary tract infections in females of reproductive age group.

Study Design: Comparative prospective study.

Place and Duration of Study: Department of Medicine, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Apr 2019 to Mar 2020.

Methodology: A total of 498 females of reproductive age (18 years to 40 years) with lower urinary tract infection symptoms (increased urinary hesitancy, frequent micturition, tenderness at suprapubic region) and positive urine dipstick test for nitrates/leukocyte esterase test were incorporated in the study. Patients were randomly assigned to Group-A and Group-B, comprising 249 patients. Group-A was given tablet Nitrofurantoin 100mg every six hourly. Group-B was given Fosfomycin 3g stat dose. Patients were advised to follow up on days 14 and 28 of treatment to observe the clinical resolution of urinary tract infection symptoms and bacteriologic response.

Results: Clinical resolution of urinary tract infection on the 28th day of treatment was attained in 172(69.1%) patients of the Nitrofurantoin-Group versus 140(56.2%) patients receiving Fosfomycin (*p*-value 0.003). Baseline urine cultures were positive in 286(57.4%) patients. Microbiologic resolution was achieved in 109 of 140(77.9%) and 100 of 146(68.4%) (*p*- value=0.026).

Conclusion: Among the females of reproductive age, five days of Nitrofurantoin therapy is superior to stat dose Fosfomycin in the clinical and microbiologic resolution of uncomplicated urinary tract infections.

Keywords: Fosfomycin, Nitrofurantoin, Uncomplicated urinary tract infection.

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INTRODUCTION

Urinary tract infections are more commonly reported among females, a common cause of antibiotic prescription in Outdoor patient departments and emergency department visits.[1,2] Its overall incidence in the general population is 18/1000 persons per year in the general population.[3] In the United States, there are approximately 10 million OPD visits and an estimated burden of about 2 billion dollars annually.[4]

Most females suffer at least two episodes of UTI in their lifetime, and about one-third of women are diagnosed to be suffering from UTI by the age of 24 years.[5] Worldwide, one of the commonest causes of antibiotic prescription is acute uncomplicated cystitis which has led to the development of multiple drug-resistant bacteria.[6] Etiology of UTI comprises diverse groups of uropathogens. However, the Gramnegative *anaerobe*, *uropathogenic Escherichia coliis* responsible for most cases, accounting for 75 to 80% of cases in women of reproductive age (18-39 years), followed by *Staphylococcus saprophyticus* (15%- 20%).[7,8]

In 2010 Infectious disease society of America (IDSA) updated management guidelines for the treatment of uncomplicated urinary tract infections.[9] IDSA recommended Nitrofurantoin and Fosfomycin as first-line antimicrobials. In our setups, there is a propensity to treat UTI with Fluoroquinolones as the first line and resistance to Fluoroquinolones is increasing.[10] Therefore, treating uncomplicated UTIs with first-line agents having good sensitivity patterns should be preferred. This study aimed to assess the comparative efficacy of first-line drugs, 5-days Nitrofurantoin and single-dose Fosfomycin for clinical resolution of uncomplicated UTI.

METHODOLOGY

The comparative prospective study was conducted at the Department of Internal Medicine, Pak Emirates Military Hospital, Rawalpindi Pakistan, from April 2019 to March 2020. Approval of the Hospital Ethical Review Committee was acquired (PEMH ltr no. A/28 dated 20 Mar 2019). WHO Sample size calculator was used to estimate sample size (clinical resolution 70% vs 58% respectively in two Groups and confidence

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level=95%).[11] The sampling technique was non-probability consecutive sampling.

Inclusion Criteria: Females of reproductive age group (18 to 40 years), with at least one of the symptoms of acute lower urinary tract infection (urinary urgency, increased micturition frequency, dysuria, or pain at supra-pubic region) and a positive urine dipstick test (nitrites/leukocyte esterase) were included in the study population.

Exclusion Criteria: Patients with prior antibiotic use in the preceding four weeks (either Fluoroquinolones or use of more than two antibiotic classes), patients with recurrent UTIs, signs of complicated UTI (flank pain, fever with chills), urinary tract instrumentation/ catheterization, hematologic disorders, immuno-compromised patients (HIV infection, active chemo-therapy or radiation therapy for neoplasia, patients receiving high dose corticosteroids or other immuno-suppressive therapy), renal disease (creatinine clearance <30ml/min), pregnant and lactating women were excluded.

A total of 498 patients participated in this study. All diagnosed females with uncomplicated UTI were randomly assigned to Group A and B. Patients in Group-A were given oral Nitrofurantoin (macrocrystals), 100mg every 6hours for five days. Patients in Group-B were given a single 3gm dose of oral Fosfomycin.

Baseline urine cultures were collected prior to starting antibiotics. Midstream voided urine specimens were collected and sent to the pathology lab for testing and analysis. Cultures were labelled positive when ≥105CFU/mL of at least one uropathogen was detected. Patients were instructed to monitor symptoms after completion of the antibiotic course till the first follow-up visit. They were asked to report back earlier in case of persistent symptoms, increased severity or medicine side effects. They were also advised to attend two follow-up visits, first on Day 14(±2) and second on Day 28(±7) days after completion of antibiotic treatment. Urine specimens for Culture specificity and Dipstick analysis were collected at all follow-up visits. Patients were grouped successfully treated when the complete resolution of symptoms was experienced 14(±2) days after initiation of treatment. Patients whose symptoms failed to resolve at first follow-up visits or who needed a change of antibiotic treatment were grouped as treatment failure. The microbiologic response was defined as <103 CFU/mL bacteriuria during a follow-up visit and microbiologic failure if bacteriuria ≥103CFU/mL persists after completion of the antibiotic course.[12]

All patient data were recorded on data collection proforma, and contact numbers were taken for correspondence.

Statistical Package for Social Sciences (SPSS) version 21 was used for data analysis. Quantitative variables were documented as mean and standard deviation. Qualitative variables were summarized as frequencies and percentages. The Chi-Square test was used to compare clinical resolution and microbiologic response among both groups. The *p*-value lower than or up to 0.05 was considered as significant.

RESULTS

A total of 498 females diagnosed with uncomplicated UTI were recruited in this study and were distributed in two groups comprising 249 patients in each group. Distribution of age among groups ranged from 18-40 years. The mean age of Group-A was 29.28±5.57 years, while the mean age of Group-B was 30.77±4.70 years. Baseline urine cultures were positive in 286(57.4%) patients. Out of positive cultures, *Escherichia coli* was positive in 223 of 286 cultures reports (44.8%), *Klebsiella spp* in 28(5.6%), *Enterococcus faecalis* 29(5.8%), *Proteus* in 6(1.2%) reports (Table–I).

Table-I: Positive Urine Cultures in Each Group (n=498)

Urine Culture Result	Group-A (Nitrofurantoin) (n=249)	Group-B (Fosfomycin) (n=249)
	n(%)	n(%)
No Growth	109(44.3%)	103(41.4%)
Escherichia Coli	109(43.7%)	114(45.8%)
Klebsiella SPP	13(5.2%)	15(6.0%)
Enterococcus Faecalis	17(6.8%)	12(4.8%)
Proteus	1(0.4%)	5(2.0%)

The clinical and microbiological resolution was checked on days 14 and 28 of the initial visit. Clinical resolution on the 14th day of antibiotic treatment was achieved in 172(69.1%) patients receiving Nitrofurantoin, while 140(56.2%) patients received Fosfomycin (*p*-value 0.003) (Table-II). Micro-biologic resolution was achieved in 109 of 140(77.9%) versus 100 of 146 (68.4%) respectively in each Group (*p*-value=0.026). Adverse effects comprising gastro-intestinal symptoms (nausea, vomiting, abdominal discomfort) were experienced in 13(5.2%) patients in the Nitrofurantoin-Group and 18(7.2%) in the Fosfomycin-Group (*p*-value 0.35) (Table-III).

Table-II: Comparison of Clinical Response & Microbiologic Response of Uncomplicated Urinary Tract Infection (n=498)

Clinical Resolution of Uncomplicated Urinary Tract Infection	Study Group		Total	*p*-value
	A (Nitrofurantoin) (n=249) n (%)	B (Fosfomycin) (n=249) n(%)		
Yes	172(69.1)	140(56.2)	312(62.7)	0.003
No	77(30.9)	109(43.8)	186(37.3)	
Microbiologic Resolution of Uncomplicated Urinary Tract Infection				
Yes	109(77.9)	100(68.4)	209(73.1)	0.026
No	31(22.1)	46(31.5)	77(26.9)	

Table-III: Comparison of Drug Adverse Effects(n=498)

Adverse Effects	Study Groups		*p*-value
	A (Nitrofurantoin) n(%) (n=249)	B (Fosfomycin) n(%) (n=249)	
Yes	13(5.2)	18(7.2)	0.35
No	236(94.8)	231(92.8)	

DISCUSSION

We used clinical parameters and the urinalysis/ dipstick method to establish diagnosis instead of urine culture. In case of suspected pyelonephritis, recurrent UTIs, or atypical symptoms, midstream voided urinary cultures are recommended. Our Results showed that the most common UTI pathogen was E. *coli*, followed by *Klebsiella spp*, *Enterococcus faecalis* and *Proteus.* Nitrofurantoin was superior in efficacy compared to Fosfomycin as a first-line drug in both clinical and microbiologic response at days 14 and 28. These first-line agents are recommended in guidelines for the management of uncomplicated UTIs, as suggested by IDSA-Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Fluoroquin-olones are recommended if other agents are not appropriate.[12,13] Mahnoor *et al.* suggested that in females of the reproductive age group (18-44 years), the most common urinary tract pathogen identified was *Escherichia coli* (49%), *Staphylococcus aureus* (24%), *Klebsiella spp* (17.7%) & *Enterobacter spp.* (4.2%). *E. coli* has the highest sensitivity for Fosfomycin (100%)& Nitrofurantoin (100%).[14] O'Horo *et al.* also concluded that Nitrofurantoin has a superior clinical response in uncomplicated UTIs compared to Fosfomycin (70% vs 58%), emphasizing the role of first-line antibiotics in treatment of UTIs.[15]

However, in clinical practice, almost 50% of prescriptions for uncomplicated UTIs include non-guideline-recommended antibiotics. Further, it was observed that more than >75% of antibiotic prescriptions are different from the practising guidelines of the CDC and are up-to-date.[16] The most common antibiotics being used–fluoroquinolones (FQs), 49% of all antibiotic prescription.[17,18]

Our study assessed treatment efficacy with the clinical response because a significant percentage of patients had negative baseline cultures. The combined clinical and microbiological response would have excluded many patients from the sample. However, microbiologic responses defined as negative or bacteriuria (<103 colony-forming units/mL) were also assessed in the study. Findings were similar to the clinical response of the Fosfomycin-Group in patients with positive baseline cultures. Our study population had no significant adverse effects because all patients with structural genitourinary diseases, pulmonary diseases, renal diseases or other risk factors were excluded.

Although irrational use of non-first-line antibiotics in uncomplicated UTIs leads to the emergence of multidrug-resistant organisms, antimicrobial stewardship must be considered in the antibiotic prescription for uncomplicated UTIs to enhance patient outcomes.

CONCLUSION

This study emphasizes the role of traditional first-line antibiotics in the clinical resolution of uncomplicated UTIs in females. Nitrofurantoin is more effective than Fosfomycin in clinical and microbiologic responses in uncomplicated UTIs in females of reproductive age.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

HBT & MNAK: Conception, study design, drafting the manuscript, approval of the final version to be published.
RK & RT: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.
BA & HWK: Critical review, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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