



ISSN: 2277- 7695

TPI 2016; 5(6): 47-52

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www.thepharmajournal.com

Received: 10-04-2016

Accepted: 11-05-2016

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A prospective study comparing nitrofurantoin vs fluoroquinolones in the therapy of uncomplicated urinary tract infection

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Abstract

Urinary Tract Infection is one of the most common diseases encountered in humans today, especially in women and children. *E. coli* has consistently been reported to be the major cause of this disease. Nitrofurantoin, Fluoroquinolones and Trimethoprim-Sulfamethoxazole are the most commonly used classes of drugs for the therapy of Urinary tract infection. However uropathogens have become greatly resistant to these drugs. The aim of this study was to assess the comparative effectiveness between Nitrofurantoin and Fluoroquinolones, to determine the resistance to drugs reported as well as to analyze the change in Quality of Life trends upon contacting urinary tract infection. Overall, Nitrofurantoin appears to be the best option to manage UTI, in light of the increasing reports of Fluoroquinolone resistance. *E. coli* continues to be the major pathogen responsible which increases the chances of resistance development. The Quality of life was found to decrease in all subclasses when the participants developed the infection. This disease is not to be taken lightly as the associated decrease in quality of life is significant. Thus, it is the need of the hour to use the most rational antibiotic therapy to manage UTI.

Keywords: Nitrofurantoin, Comparative effectiveness, *E. coli*, resistance, quality of life, urinary tract infection, women.

1. Introduction

Urinary Tract Infection is one of the most common diseases encountered in medical practice today with approximately 150 million patients suffering from it per annum all over the world. These are infections of the urinary tract caused by microorganisms that cannot be accounted for by contamination, usually producing an inflammatory response. The infection may progress from the faecal flora and spread by an ascending process to the urinary tract or from another primary source by the haematogenous route following a descending path^[1]. UTI is usually bacterial in aetiology, although other infectious agents can also cause UTI. These include viruses, fungi, and Chlamydia. Frequent urinary tract infections can result in chronic kidney disease and hypertension, especially in childhood^[2]. It may be either acute or chronic, and may affect any part of the upper or lower urinary system. It usually results in painful burning sensation during urination (dysuria), increased frequency or urgency to urinate with or without blood /pus in urine and a host of other symptoms.

UTI is characterised by its high recurrence rate. Recurrent UTI may be caused by either relapse due to treatment failure or reinfection. Patients who never improve or who immediately relapse following completion of treatment may be said to have persistent infection^[3]. Generally, UTIs are treated with various antibiotics and fluid supplementation.

1.1 Pharmacological Therapy

Antimicrobial therapy for UTI may follow either the prophylactic or the therapeutic approach depending on the recurrence of infection in the patient. The therapeutic approach attempts to relieve the existing symptoms and prevent the development of further complications^[4]. Empirical Antimicrobial therapy can be done for acute uncomplicated UTI whereas, selection of antibiotics for treatment of relapsed UTI should be done based on results of culture and susceptibility testing, and the duration of antibiotic therapy could be as long as 2 weeks. Recurrent UTI which occurs more than 2 weeks after the original infection is treated as a new infection and managed with therapeutic considerations similar to those for the initial infection. Those with frequent infections (3 or more/year) may be considered for chronic prophylactic therapy.

Consensus clinical guidelines recommend Nitrofurantoin monohydrate/macrocrystals 100 mg bid for 5 days or Trimethoprim-sulfamethoxazole 160/800 mg (one DS tablet) bid for 3 days or Fosfomycin trometamol 3 gm single dose or Pivmecillinam 400 mg bid for 5 days as preferred first-line antibiotics for treatment of uncomplicated UTI. Fluoroquinolones or β -lactams are to be used only when the first line drugs cannot be used [5]. For many years, trimethoprim-sulfamethoxazole (TMP-SMX) was the preferred antibiotic for the treatment of UTI, given its efficacy and low cost [6]. However, development of a high prevalence of TMP-SMX resistance among uropathogens [7-9] has discouraged use of this drug in many communities. An effective alternative for many clinicians has been the fluoroquinolone class of antibiotics, which achieve high concentrations in the urine and have excellent activity against most uropathogens [6].

However, the 2011 Infectious Diseases Society of America (IDSA) guidelines on the treatment of UTIs discourage use of fluoroquinolones for acute, uncomplicated UTI as experts are concerned about overuse of fluoroquinolones leading to increased prevalence of fluoroquinolone-resistant pathogens [5]. The fluoroquinolones are more expensive, broader in spectrum, and therefore, should be reserved for communities with high rates of resistance (greater than 10% to 20%) to trimethoprim or in patients who either cannot tolerate trimethoprim-sulfamethoxazole/ Nitrofurantoin or have recurrent urinary tract infections. The use of first-generation cephalosporins or aminopenicillins is generally not recommended because of high levels of resistance and recurrence. Although resistance to the third-generation cephalosporins is lower than to the first generation, these agents are considered -third-line agents because of their high cost and lower efficacy. Most cases of Urinary Tract Infections are uncomplicated and can be treated on an outpatient basis with oral antibiotics

The goal of Comparative Effectiveness Research is to discriminate among clinical interventions on the basis of clinical effectiveness, cost-effectiveness, adverse effects, or other distinguishing factors. Comparative effectiveness may either be analyzed by means of multisite randomized controlled trials or observational studies involving either primary or secondary data collection [10], of which the second method of CER is embraced to achieve a final conclusion.

Many trials that compare two treatment strategies include a quality of life assessment. QOL studies are usually done by asking participants to fill in a standardized and validated questionnaire which tries to link an individual's health with tiredness, weakness, anxiety or depression experienced in everyday activities such as work and its management, home life, exercise and other interactions with the society. Improving a patients' quality of life is often a very important aim of treatment as patients are also more likely to follow a treatment if it has fewer side effects or if they don't have to go to the hospital so often. This study used Optum™ SF-12v2® Health Survey to analyze Quality of Life in participants using just 12 questions to measure functional health and well-being from the patient's point of view [11, 12]. It takes only two to three minutes to complete and is a practical, reliable and valid measure of physical and mental health, particularly useful in large populations or for disease-specific health surveys. Another advantage is its availability in multiple language translations.

In this study, cases of uncomplicated UTI are focused upon as

these are very common but often taken lightly and rarely subjected to pharmacological therapy or management. This study is aimed at identifying the better option among the two commonly used drug classes for the therapy of uncomplicated UTI at the Pushpagiri Medical College in Central Kerala based on their effectiveness. The change in Quality of Life trends among the participants upon contacting the infection was also assessed, along with the most common pathogenic strain in the study population.

2. Materials & Methods

2.1 Study Design and Therapy

A prospective observational study with a 4-6 weeks follow-up was conducted in the General Medicine Department of the Pushpagiri Medical College, Thiruvalla over a period of six months from February to July, 2015. Patients diagnosed with uncomplicated UTI belonging to both sexes of the age group 14-60 years, who were willing to give informed consent, were included in the study. Exclusion criteria used was presence signs and symptoms of complicated UTI (fever, flank pain, costovertebral tenderness), pregnancy, epilepsy, abnormalities of urinary tract, use of antibiotics within the last 3 days and inability to give informed consent.

After getting approval from Ethical committee of the institution, and based on the inclusion and exclusion Criteria, a group of 80 patients diagnosed with uUTI, were divided into 40 each of nitrofurantoin and fluoroquinolone patients upon obtaining Informed Consent. Normal dose of nitrofurantoin (100 mg twice daily for 5 days) to first group and Ciprofloxacin (250 mg twice per day for three days) or extended release 500 mg per day for three days/other fluoroquinolone -administered subjects were included in the study.

2.2 Evaluation of Objectives

A data collection form including patient information such as date of admission, date of discharge, age, gender, duration of hospital stay, and drug information including dose, frequency of administration, duration of therapy was used to collect and record details. At the end of therapy clinical resolution of signs and symptoms of the urinary tract are determined. Effectiveness of the therapeutic strategy was calculated as the sum of clinical cure and clinical improvement [13]. Recurrence rate among the study population is determined based on case file and personal follow-up after 4-6 weeks of beginning therapy.

Quality of Life was assessed using a standard SF-12v2™ questionnaire (Lic.No: QM030058) in malayalam administered to the patients on admission and 4-6 weeks after starting therapy or after complete resolution of symptoms was achieved. This was taken as the control value. Quality Metric Health Outcomes™ scoring software [12, 14] was then used to determine the quality of life scores. The most common causative agent for UTI in the population studied was determined from the culture and sensitivity test.

2.3 Statistical Analysis

The obtained clinical data was statistically analyzed using SPSS software version 16.00, Wilcoxon Signed Rank Test and Mann-Whitney U test. Significance was determined at 5% level of significance.

3. Results

3.1 Demographic Details of the Study Population

Majority of the patients belonged to the 46-60 years age group.

The mean age of the study population was 51.03(± 12.20) years. Females were found to be more frequently afflicted by uncomplicated UTI (as 68.8% of the study population were women and only the remaining 31.2% were men). Female predominance was maintained in both treatment groups (with 65% females in fluoroquinolone treatment group and 72.5% females in nitrofurantoin treatment group). A greater part of the population had above average education with 35% of study population having at least a degree and 31.3% having a PG. As such, it may be established that education has little to no impact in preventing UTI. A prominent fraction of the study population was married (87.5%). 55% of the population were sexually active. This concurs with the established increase in risk of UTI for sexually active individuals. Post-menopausal women seem to be more susceptible to uncomplicated UTI infection as majority of the women participants (58.5%) belonged to this category. 95% of the population followed a non-vegetarian diet. Drug allergies were reported only among 12.5% patients under study. Only 35% of the population under fluoroquinolone therapy and 27.5% under Nitrofurantoin therapy confessed to having any social habits. Participants were found to be suffering from comorbidities such as Hypertension (40%), Diabetes Mellitus (20%), and Hyperlipidemia, hyponatremia, hyper / hypothyroidism, migraine etc. The most significant associated co morbidity was diabetes although majority of the population reported hypertension. Most common associated symptom was Fever. Overall, 14.06% cases of drug resistance were reported. 12.5% cases of fluoroquinolone resistance and 1.56% cases of nitrofurantoin resistance were reported.

3.2 Clinical Effectiveness

Both treatment regimen groups showed complete clinical response. Clinical Resolution of symptoms occurred slightly more quickly with Nitrofurantoin than with fluoroquinolones, and the difference in time between the two was statistically significant i.e p value was lesser than 0.05. Recurrence Rate was found to be higher in patients with Nitrofurantoin use by 5% than those undergoing fluoroquinolone therapy. The population suffering from recurrence of uncomplicated UTI is a minority (37.5%).

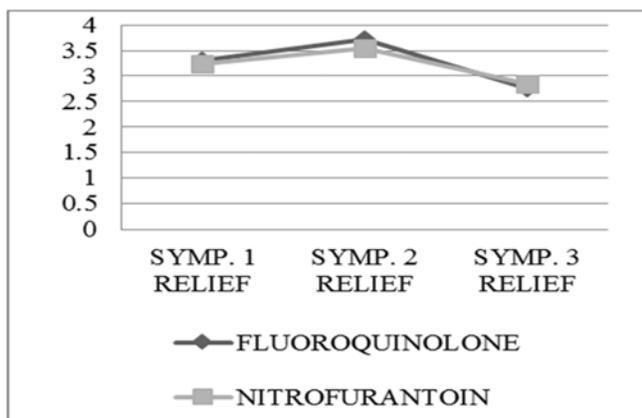


Fig 1: Clinical Improvement

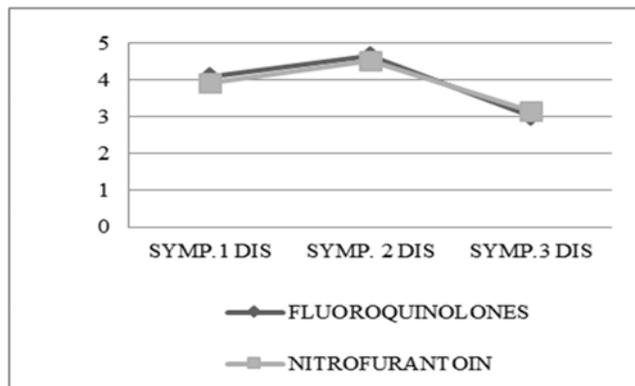


Fig 2: Clinical Cure

3.3 Quality of Life Analysis

Upon analysis of quality of life, both Physical component scores and mental component scores were found to be significantly decreased in patients suffering from UTI, both scores increasing with treatment. PCS and MCS values on comparison had a p value of lesser than 0.05. It was seen that the improvement of Quality of Life scores in relation to the therapeutic regimen employed were similar except for the vitality score in which case significantly greater difference is achieved using Nitrofurantoin therapy.

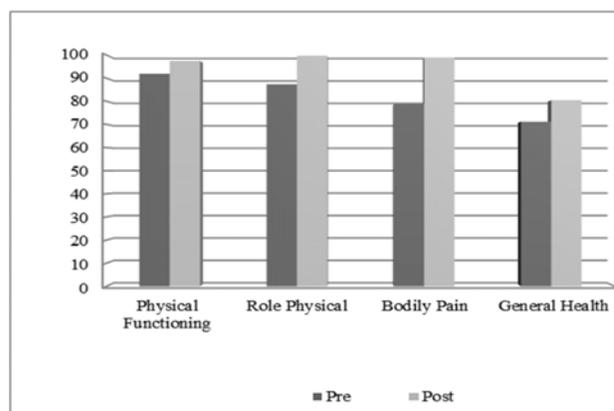


Fig 3: Distribution of Physical Component Scores

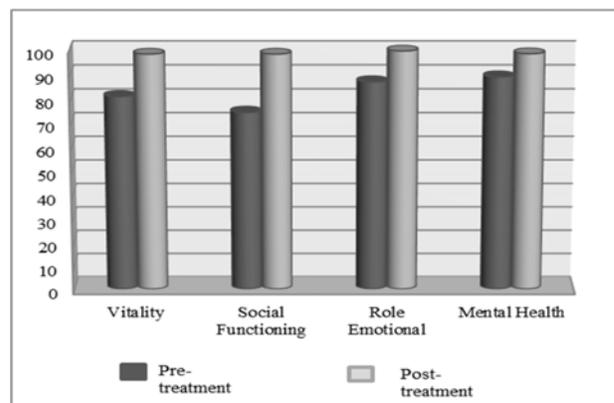


Fig 4: Distribution of Mental Component Scores

Table 1: Comparison of Physical Component Scores and Mental Component Scores

	With uti/ pre-treatment		Without uti/ post-treatment		P Value
	Mean	S.D	Mean	S.D	
Physical Component Scores (PCS)	51.73	5.54	55.31	2.64	0.001
Mental Component Scores (MCS)	55.43	5.35	62.06	2.12	0.001

Table 2: Improvement of Quality of Life on Therapy

Quality Of Life Scores	Fluoroquinolones		Nitrofurantoin		P value
	Mean	S.D	Mean	S.D	
Physical Functioning Change	2.50	17.72	3.75	34.22	0.65
Role Physical Change	10.00	10.28	9.68	26.32	0.11
Bodily Pain Change	16.87	17.34	18.12	29.41	0.27
General Health Change	6.37	18.63	8.25	37.86	0.35
PCS Change	2.66	5.07	1.72	14.43	0.38
Vitality Change	12.50	12.65	17.50	25.44	0.03
Social Functioning Change	23.75	13.80	19.37	32.76	0.43
Role Emotional Change	10.00	10.28	10.31	28.85	0.13
Mental Health Change	6.87	7.98	7.18	25.61	0.184
MCS Change	5.53	3.55	4.63	15.15	0.178

3.4 Pathogenic Evaluation

E. coli was identified as the most common causative pathogen (60%) in the study population.

Table 3: Pathogenic Evaluation

Pathogenic Species	% of incidence
<i>E. coli</i>	60
<i>Klebsiella pneumonia</i>	10
<i>Enterobacter aerogenes</i>	2.5
<i>Enterococcus faecalis</i>	2.5
<i>Proteus vulgaris</i>	1.25

4. Discussion

The predominance of females among those frequently afflicted with uUTI was confirmed with the findings of this study [15]. A predominance was observed in the 46-60 year age group, similar to several studies [16]. The fact that Post-menopausal women seem to be very highly susceptible to uncomplicated UTI infection, as observed in the study, could be a major contributing factor to the prevalence among people older than 40 years. Majority of the population had good education, which goes on to show that sufficient knowledge is not enough overcome an uncomplicated UTI infection. The increased susceptibility of married individuals was observed during the work, supporting the findings of studies conducted by Arul Prakasam K.C [17] *et al.* 55% of the population were sexually active, similar to results observed in the study conducted by Smitha Sood and Ravi Gupta [18]. These observations point towards the need for awareness about following cautious and hygienic sexual practices and how they can help prevent UTI. The prominence of non-vegetarians among the study population validate the findings of Ameer R. Manges *et al* [19] which showed that frequent chicken and pork consumption caused an increased resistance to multiple antimicrobial agents which resulted in greater tendency for UTI. The high percentage of alcoholics among the participants has proven once again that this is habit is a possible risk factor contributing towards multiple drug resistance and UTI [18]. The common associated comorbidity was found to be Diabetes Mellitus as observed in similar studies [17]. Most common associated symptom was Fever as noted by M. Eshwarappa *et al* [20]. The observed high rate of resistance to fluoroquinolones is in accordance with results from all over India [18]. Nearly the same proportion of participants reported a previous history or a recurrence of infection, and as expected [21] both amounted to less than half the participants. Recurrence Rate was higher in patients on Nitrofurantoin therapy.

Reports [22] have suggested that Nitrofurantoin may be considered a viable alternative to Fluoroquinolones when the resistance to fluoroquinolone in the population exceeds 12%,

which is true in the study population. The effectiveness of Nitrofurantoin is further proven by their activity against most multi-drug resistance gram negative bacilli and most ESBL producing strains [23] and its good in vitro susceptibility profile [24]. The fact that clinical resolution of symptoms occurred more quickly with Nitrofurantoin in this study, along with all the other findings provide proof which validates the IDSA protocol suggestion that Nitrofurantoin be considered as the first line therapy for acute uncomplicated UTI.

In the Quality of Life assessment, Physical component scores and mental component scores were found to decrease significantly in patients suffering from UTI. It was seen that the improvement of Quality of Life scores in relation to the therapeutic regimen employed were similar except for the vitality score in which case significantly greater difference was achieved using Nitrofurantoin therapy. These results, put together with other studies [25, 21] show that acute uncomplicated UTI must not be taken lightly and be managed with proper therapy. *E. coli* was identified as the most common causative pathogen in 60% of the cases indicating that no change has happened in the major cause of the disease over the years [19, 26].

5. Conclusion

Uncomplicated Urinary Tract Infection is a very common infectious condition in women, children and elderly adult men. The more frequently affected demographic group remains women, especially during pregnancy and in certain populations, during the post-menopausal age. The escalation of drug resistance among pathogens has become a global threat. Before prescribing an empirical anti-microbial therapy for dealing with uUTI, an in-depth knowledge of the aetiology, the predisposing factors, the cultural positivity and the continued evaluation of the susceptibility patterns of uropathogens to the traditional as well as the new antimicrobials, is essential to avoid irrational drug usage and to ascertain the optimal prophylactic therapy. The sixty-eighth World Health Assembly held in Geneva in May 2015 has recognised the importance of this issue and a global action plan to tackle the growing resistance to antibiotics and other antimicrobial medicines has been formulated. Unless the patient has a recurrence or has had a past history of UTI, culture & sensitivity studies are rarely undertaken before starting treatment, which is in accordance with the latest protocol. But, it was observed that at least some of the patients experienced failure/ ineffective therapy which may be attributed to lack of information about the individual's antibiotic sensitivity and resistance pattern exhibited by the pathogen. In several cases such patients needed a change in drug when C&S was done afterwards. Prescribers were of the opinion that fluoroquinolone resistance was very high in the

study setting and as such nitrofurantoin was the first-line therapy for uUTI according to Hospital protocol. Given the increase in resistance in recent times, it is suggested that the possibility of achieving good therapeutic response in a case of uncomplicated UTI, without conducting culture and sensitivity studies, needs to be re-evaluated.

The primary pathogenic source of urinary infection has been always been *E. coli* and this continues to be the case. Nitrofurantoin was found to be slightly more efficacious and less prone to resistance by uropathogens in this study. At the same time recurrence rate of the infection was slightly higher in patients on nitrofurantoin therapy. As such, it may be concluded that nitrofurantoin can be considered a safe alternative to fluoroquinolones in the therapy of acute uncomplicated UTI. Quality of Life assessment showed a significant fall upon developing uncomplicated urinary tract infection. This proves the fact that even acute UTI must not be treated lightly and employing non-pharmacological management strategies alone, such as maintaining sufficient fluid level, are not always enough. It is important that pharmacists, along with other medical personnel, be vigilant in treating acute conditions such as uncomplicated UTI. It is also important to further investigate the field of comparative effectiveness studies so that therapeutic strategies which are able to deal with today's illnesses without posing a threat to an individual's future health and well-being can be decided upon.

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