



A COMPARATIVE RANDOMIZED STUDY OF NITROFURANTOIN AND FOSFOMYCIN IN THE TREATMENT OF URINARY TRACT INFECTIONS IN NON-PREGNANT WOMEN AT A TERTIARY CARE RURAL HOSPITAL, KARNATAKA.

Obstetrics & Gynecology

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ABSTRACT

Introduction: Urinary tract infections are the most common infections seen in the hospital setting and take the second lead after respiratory tract infection in community acquired infections. Nitrofurantoin and Fosfomycin are older drugs that are being revived and recommended as first-line agents in treating uncomplicated UTI.

Aims And Objectives: To assess the comparative efficacy of 5day nitrofurantoin versus single dose fosfomycin for clinical resolution in uncomplicated UTI.

Materials And Methods: This randomized clinical trial was conducted from January 2019 to September 2019 at the Department of Obstetrics and Gynaecology, AIMS, B G Nagara, Mandya, Karnataka. Patients were randomized to either oral nitrofurantoin 100mg twice daily for 5 days or single dose of oral fosfomycin 3g. Baseline urine routine was done. They were followed up at 14(+/-2) and 28(+/-7) days after completion of antibiotic therapy which was considered at day 5 as fosfomycin has long half-life. The data was entered in Microsoft Excel and outcomes were analysed using Epi Info software.

Results: Out of total 92 patients screened, 63 were enrolled and randomized. Thirty-two (50.7%) were given nitrofurantoin and 31 (49.2%) received fosfomycin. Of total enrolled after screening 3 (4.7%) patients were lost to follow-up, so only 60 patients (n=92, 65.2%) comprised the study population.

Conclusion: Five-day nitrofurantoin is superior to single dose fosfomycin in treatment of acute uncomplicated UTI.

KEYWORDS

Nitrofurantoin, Fosfomycin, contraception, hygiene

INTRODUCTION

Urinary tract infections are the most common infections seen in the hospital setting and take the second lead after respiratory tract infection in community acquired infections. Up to one-third of all women are found to experience UTI at least once in their lifetime.⁽¹⁾

The predominant pathogen in both uncomplicated and complicated UTI remains pathogenic Escherichia Coli, although Klebsiella and Proteus appears with increased frequency in complicated UTI. Most often, bacteria cause UTI by ascending means through urethra to bladder. Host defence factors that predispose women to UTI include urinary stasis, abnormal urinary tract anatomy, diabetes mellitus, oestrogen-related issues, sexual activity, and change of birth control measures, inadequate and poor-quality sanitation, previous UTI, debility and aging.^(2,3)

Dysuria, burning micturition, hematuria, persistent and frequent urge to pass urine, pressure or cramping pain in the groin or lower abdomen is the most common presenting complaints in uncomplicated UTI. Although urine culture with >10⁵ colony forming units/mL in the symptomatic women remains the diagnostic gold standard, correlation of patient's history and urine analysis usually suffice to diagnose UTI. If not adequately diagnosed and treated, UTI can lead to complications such as recurrent infection, permanent kidney damage, and increased risk in pregnant women of delivering low birth weight and premature infants and sepsis.^(1,2,3)

Trimethoprim-sulfamethoxazole are currently used world-wide to treat uncomplicated UTI. Fluroquinolones are being reserved for resistant and complicated cases. Antimicrobial resistance is increasing worldwide, resulting in infection that are more difficult to treat and associated with higher mortality, morbidity and cost. Nitrofurantoin and fosfomycin are now recommended as first-line agents in treating uncomplicated UTI. They both are older drugs that are being revived for the treatment of UTI since they possess unique features such as, achieving high concentrations in the urinary tract, minimal impact on gastrointestinal flora, low propensity for resistance and a favourable safety profile.^(4-3,10)

Hence the study is aimed at re-exploring the older drugs-nitrofurantoin and fosfomycin for the management of uncomplicated

UTI. Urine routine and clinical resolution is considered to assess the efficacy of the drugs rather than relying on urine culture as that is more significant to patient, cost effective and less time consuming.⁽¹⁻³⁾

Aim

To assess the comparative efficacy of 5-day nitrofurantoin versus single dose fosfomycin for clinical resolution in uncomplicated UTI.

Objectives

Primary Outcome- clinical response in 14 days after completion of therapy.

Secondary Outcome- clinical response at 28 days of completion of therapy, duration of symptoms after treatment initiation, incidence of progression to pyelonephritis, incidence of adverse events, emergence of bacterial resistance or recurrence throughout the study period.

METHOD

Study Design And Population

This randomized clinical trial was conducted from January 2019 to September 2019 at the Department of Obstetrics and Gynaecology, AIMS, B G Nagara, Mandya, Karnataka. A simple random sampling method was used with inclusion criteria being of women aged >18 years, presenting with at least 1 symptom of acute lower UTI (dysuria, urgency, frequency or suprapubic tenderness) and a urine routine examination positive for leukocytes.

Main exclusion criteria were pregnancy and lactation; suspected upper UTI (presence of fever, chills, or flank pain); antibiotic use or history of UTI in previous 4 weeks; complicated UTI; immunosuppression due to corticosteroid intake or on-going chemotherapy or radiotherapy. The patients were recruited on OPD basis. Participants were well informed about the trials in their understandable language and a written consent was taken. The clinical trial was constantly reviewed by the institutional ethics committee. Among 92 patients screened, 63 were enrolled, randomized and taken as sample size. The data was entered in Microsoft Excel and outcomes were analysed using Epi Info software.

Procedure

After approval of ethical clearance, patients were randomized to either

oral nitrofurantoin 100mg twice daily for 5 days or single dose of oral fosfomycin 3g. Baseline urine routine was done. They were followed up at 14(+/-2) and 28(+/-7) days after completion of antibiotic therapy which was considered at day 5 as fosfomycin has long half-life.

Laboratory Test

Voided mid-stream urine specimens were collected in sterile container and transported within half an hour to central laboratory, AIMS, B G Nagara. Microscopic analysis (sensitive for detection of 105 cfu/ml) was done as it has a positive predictive value of 100% for the presence of pyuria (defined as > 8 WBC/mm³). As the number of cells/hpf increases, the positive predictive value for bacteriuria increases.

RESULTS

Out of total 92 patients screened, 63 were enrolled and randomized. Thirty-two (50.7%) were given nitrofurantoin and 31 (49.2%) received fosfomycin. Of total enrolled after screening 3 (4.7%) patients were lost to follow-up, so only 60 patients (n=92, 65.2%) comprised the study population.

Of the total number of patients, 38.1% (n=24) were falling in the age group of 31-40 years, while a significant of them comprised in the age group of 21-30 years group comprising of 34.9% (n=22). Hence considering both these groups, the median age of the study population was 32 years. Of the total of 63 patients enrolled, multigravida accounted for 68.2% (n=43), indicating increased risk in this group. Primigravida accounted 31.7% of the total study group.

| Age in Years | Range | Frequency | Percent |
|--------------|-------|-----------|---------|
| | ≤20 | 1 | 1.6 |
| | 21-30 | 22 | 34.9 |
| | 31-40 | 24 | 38.1 |
| | >40 | 16 | 25.4 |

| Parity | Parity Score | Frequency | Percent |
|--------|--------------|-----------|---------|
| | Primigravida | 20 | 31.7 |
| | Multigravida | 43 | 68.2 |

| Employment status | Occupation | Frequency | Percent |
|-------------------|-------------------|-----------|---------|
| | Accountant | 1 | 1.6 |
| | Clerk | 1 | 1.6 |
| | Daily Wage Worker | 6 | 9.5 |
| | Employee | 5 | 7.9 |
| | Farmer | 13 | 20.6 |
| | Housewife | 15 | 23.8 |
| | Maid | 1 | 1.6 |
| | Shopkeeper | 3 | 4.8 |
| | Skilled Worker | 1 | 1.6 |
| | Sweeper | 8 | 12.7 |
| | Teacher | 1 | 1.6 |
| | Vendor | 8 | 12.7 |

The UTI seemed to be more prevalent among specific group based on certain factors such as their occupation, lifestyle, social factors, economic factors, availability of toilet, etc. In our study it was observed that, most of the women were Housewife/Homemaker by occupation (n=15, 23.8%) followed by farmers (n=20.6%), where most of women in the study population belonged to Lower class as per Modified B.G Prasad Classification.

| Modified B.G Prasad Classification | Socioeconomic status | Frequency | Percent |
|------------------------------------|----------------------|-----------|---------|
| | Upper Class | 4 | 6.3 |
| | Middle Class | 26 | 41.3 |
| | Lower Middle Class | 4 | 6.3 |
| | Lower Class | 29 | 46.0 |

| Area of House (sq.ft) | Area of house | Frequency | Percent |
|-----------------------|---------------|-----------|---------|
| | <150 | 29 | 46.0 |
| | >250 | 25 | 39.7 |
| | 150-250 | 9 | 14.3 |

Based on the area of house per square feet, nearly, 46% (n=29) of the study population lived in a house of less than 150 square feet, while 39.7% (n=25) lived in house with more than 250 square feet area, which mainly coincides with the population belonging to lower class. Of them, nearly 55.6% had access to bathroom/toilet located outside the house. More than half the study population were deprived of the facility of having a personal toilet/bathroom for their use, as the access which they had was to only public toilet used by the community. Females having access to bathroom/toilet inside their house accounted

less than half the study population accounting 44.4%. Hence this adds to increased risk of acquiring urinary tract infections. Out of the total patients, nearly 31.7% (n=20) mentioned of having difficult in accessing community bathroom/toilet as it was far from their homes.

| Access to Bathroom/toilet | Location | Frequency | Percent |
|---------------------------|---------------|-----------|---------|
| | inside house | 28 | 44.4 |
| | outside house | 35 | 55.6 |

| Distance of community toilet from home | Distance | Frequency | Percent |
|--|----------|-----------|---------|
| | far | 20 | 31.7 |
| | near | 15 | 23.8 |
| | neutral | 28 | 44.4 |

Almost 90.5% women were sexually active, with 9.5% being inactive sexually. Most of the sexually inactive women were widow, few had personal reasons. Nearly 39.7% women had sexual contact 1-2 times per week, with 30.2% (n=19) 3-4 times per week. Of these most of them complained associated white discharge per vaginum with many other chief complaints indicating Urinary tract infection. The patients presented with a permutation and combination of several complaints, but however,

increased frequency with burning micturition was the commonest complaint in 49.2% (n=31). Overall the single most common symptom they presented with was increased frequency of micturition in among 82.5% (n=52). Suprapubic pain was noticed only in 27% of patients (n=17). Of 90.5% sexually active females, 1.6% used Copper T (n=1) while 31.7% (n=20), used natural barrier method (male condom), of which 39.7% (n=25) underwent tubectomy while only 1.6% (n=1) did not undergo tubectomy. However, 25.4% (n=16), did not mention the method of contraception used by them, either due to they being widow or they did not use any contraceptive measures, or their family was not complete.

| Sexual History | Sexual History | Frequency | Percent |
|----------------------------|----------------|-----------|---------|
| | Active | 57 | 90.5 |
| | Not Active | 6 | 9.5 |
| Sexual contact as per week | 1-2 Times | 25 | 39.7 |
| | 2-3 Times | 13 | 20.6 |
| | 3-4 Times | 19 | 30.2 |
| | Neutral | 6 | 9.5 |

| Chief complaints | Frequency | Percent |
|--|-----------|---------|
| Burning Micturition | 1 | 1.6 |
| Dysuria | 7 | 11.1 |
| Dysuria, Burning Micturition | 1 | 1.6 |
| Dysuria, Frequency, Burning Micturition, Suprapubic Pain | 14 | 22.2 |
| Dysuria, Frequency, Urgency | 4 | 6.3 |
| Dysuria, Frequency, Urgency, Suprapubic Pain | 1 | 1.6 |
| Frequency, Burning Micturition | 31 | 49.2 |
| Frequency | 2 | 3.2 |
| Suprapubic Pain | 2 | 3.2 |
| Total | 63 | 100.0 |

| Contraception method used | Contraception method used | Frequency | Percent |
|---------------------------|---------------------------|-----------|---------|
| | Copper T | 1 | 1.6 |
| | Male Condom | 20 | 31.7 |
| | Neutral | 16 | 25.4 |
| | Not tubectomized | 1 | 1.6 |
| | Tubectomized | 25 | 39.7 |

| Urinalysis: bacteria/hpf | Urinalysis: bacteria/hpf | Frequency | Percent |
|--------------------------|--------------------------|-----------|---------|
| | Absent | 20 | 31.7 |
| | Present | 43 | 68.3 |

Because of cost effectiveness, the urine routine and microscopy was done to evaluate the degree of infection among our patients, besides urine culture and sensitivity was avoided due to time constraint as it usually provides results after 4 days, and also affordability factor. Bacteria were present in nearly 68.3% (n=43) patients, while 31.7% (n=20) did not have any trace of bacteria present, however 31.7% patients had RBC's/hpf and 22.2% (n=14) had more than 20 pus cells/hpf.

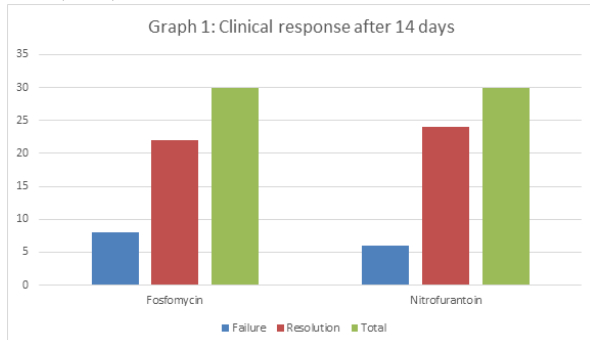
A total of 63 patients were enrolled of which 3 patients did not follow up, hence of total 60 patients, 50% (30) patients were treated with Fosfomycin and 50% were treated with Nitrofurantoin (n=30), of which the clinical response at 14th day and 28th day was noted.

Clinical resolution is complete resolution of symptoms and signs of UTI without prior failure.

| Table no 12 | | Clinical response at 14 days | | Total | Chi square value | P value |
|-------------|----------------|------------------------------|------------|-------|------------------|---------|
| | | Failure | Resolution | | | |
| Drug given | Fosfomycin | 8 | 22 | 30 | 0.373 | 0.542 |
| | Nitrofurantoin | 6 | 24 | 30 | | |
| Total | | 14 | 46 | 60 | | |

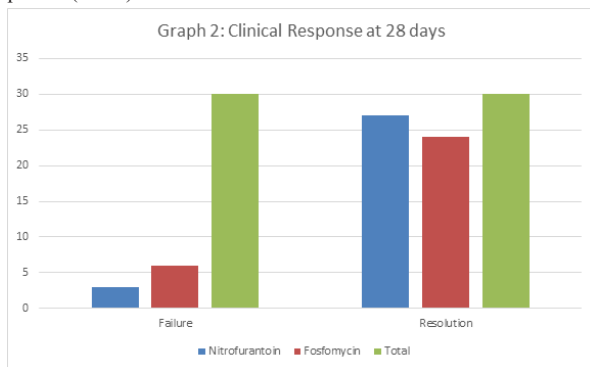
Clinical failure is need for additional or change in antibiotic treatment due to UTI or discontinuation due to lack of efficacy.

Resolution of symptoms were noted in 73.3% (n=22), while failure of treatment towards day 14 in 26.6% (n=8) in patients treated with Fosfomycin. While those treated with Nitrofurantoin, showed resolution of symptoms in 80% (n=24), and failure rate of 20% (n=6), towards the end of Day 14, with the chi square value (0.373) and p value (0.542).



| Table no 13 | | Clinical response at 28 days | | Total | Chi square value | P value |
|-------------|----------------|------------------------------|------------|-------|------------------|---------|
| | | Failure | Resolution | | | |
| Drug given | Fosfomycin | 6 | 24 | 30 | 1.176 | 0.278 |
| | Nitrofurantoin | 3 | 27 | 30 | | |
| Total | | 9 | 51 | 60 | | |

With respect to clinical response at day 28, complete resolution of symptoms were noted in 80% (n=24), while failure of treatment in 20% (n=8) in patients treated with Fosfomycin. While those treated with Nitrofurantoin, showed complete resolution of symptoms in 90% (n=27), and failure rate of 10% (n=3) with chi square value (1.176) and p value (0.278).

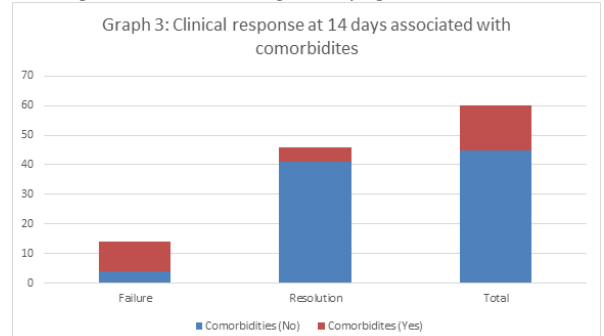


Thus based on our results, Nitrofurantoin had comparatively better clinical resolution and low failure rates compared to Fosfomycin toward day 14, but however both the drugs failed to achieve complete resolution towards the end of Day 28, with Nitrofurantoin having slightly an upper hand in the race.

| Table no 14 | | Clinical response at 14 days | | Total | Chi square value | P value |
|----------------|-----|------------------------------|------------|-------|------------------|---------|
| | | Failure | Resolution | | | |
| Co morbidities | No | 4 | 41 | 45 | 20.994 | 0.000 |
| | Yes | 10 | 5 | 15 | | |
| Total | | 14 | 46 | 60 | | |

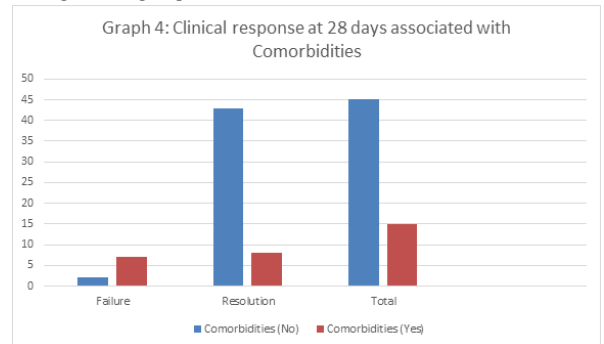
However in anticipating response with respect to resolution, we suspected certain comorbidities to pose some hinderances which was statistically significant based on chi square test value of (20.994); P value of 0.000 towards day 14 and chi square test value (15.730). Irrespective of the treatment provided, a total of 15 patients had

comorbidities of which 50 % (n=5); 8.6% (out of 60 patients), had immediate resolution towards days 14. By the end of day 28, 11.6% (n=7) had comorbidities who were enlisted in failure of treatment, while 13.3% (n=8) of enlisted cases had resolution with comorbidities. Hence of a total 15 patients who had comorbidities, 53.3% (n=8) had resolution of symptoms and signs of UTI associated with comorbidities. To summarize, by day 14, only 5 (8.3%; 33.3%) patients of 15 patients having comorbidities showed positive outcome of treatment given irrespective of drug used, while by day 28, 13.3% (n=8; 53.3%), of 15 patients with comorbidities of the total patients, showed positive resolution of signs and symptoms.



| Table no 15 | | Clinical response at 28 days | | Total | Chi square value | P value |
|----------------|-----|------------------------------|------------|-------|------------------|---------|
| | | Failure | Resolution | | | |
| Co morbidities | No | 2 | 43 | 45 | 15.730 | 0.000 |
| | Yes | 7 | 8 | 15 | | |
| Total | | 9 | 51 | 60 | | |

During the follow-up visits, no clinically relevant adverse reactions were observed that would warrant exclusion from study or development of pyelonephritis was noted. Median duration of initial symptoms was noted to be one day longer in women receiving nitrofurantoin (4 days versus 3 days for fosfomycin). Adverse reactions in the form of mild gastrointestinal symptoms were noted in 1% of the study population and no significant difference was noted among the two groups.



DISCUSSION

Urinary tract infection is one of the commonly observed infections in day to day clinical practice. One of the serious health problems is threatening rise in the resistance to antimicrobials. It has been observed that antimicrobial resistance is bound to increase as injudicious usage increases.⁽¹⁻³⁾ Therefore, in our present study, older forgotten drugs like nitrofurantoin and fosfomycin are being re-explored.

It was noted in our study that among women with uncomplicated UTI, a 5-day course of nitrofurantoin showed a better clinical and microbiological resolution than compared to single dose fosfomycin when observed at 28 days of therapy completion.⁽³⁻⁵⁾

Although evidence in the form of bacteriological culture was not considered, a purely clinical response was opted for as the mainstay of primary outcome, as that is more relevant to the patient. Also culture and sensitivity is not cost effective and is time consuming.⁽⁶⁻¹¹⁾

Patients who received nitrofurantoin experienced greater clinical and microbiological outcome, the drug's overall response was 90%, as reported by other studies. In a study conducted in Pakistan, showed fosfomycin susceptibility against E. Coli (89.28%) as compared to

nitrofurantoin (96.43%). The resistant rates of fosfomycin and nitrofurantoin against *E. Coli* was 0.3% and 4% respectively in a study conducted in Turkey.⁽¹²⁻¹³⁾

Studies have reported high efficacy of single dose Fosfomycin in the treatment of acute UTI. Double-blind controlled studies as well as randomized open-label studies showed not much difference in the eradication of a uropathogen with fosfomycin and reference drugs. They demonstrated that a single dose of fosfomycin is quite efficacious as compared to 3 day or 7-10 day course of other agents. Although fosfomycin possesses a wide spectrum of activity especially against multidrug resistant organisms, its continued oral administration at an insufficient dose might diminish its usefulness and might necessitate intravenous administration of the drug.

The present study has showed that nitrofurantoin is superior to fosfomycin in the treatment of acute UTI.

Antimicrobial resistance is increasing at an alarming rate and mandates the need for microbiological testing before starting antibiotics. Individualising patient management, reviewing and conducting surveillance on existing guidelines, judicious use of existing antibiotics, development of new antimicrobial agents and strict infection control practices pave way to reduce the spread of resistant organisms.^(3,4,6,7)

CONCLUSION

Cutting the costs in the diagnosis of a UTI can result in significant savings in medical care. Urinalysis is valued as it is an inexpensive alternative to ordering a urine culture and sensitivity on every patient with urinary complaints. Besides these factors, few other major contributing parameters which were of significant value include sexual hygiene and socioeconomic factors and access to clean urinals for women of our Country. Our study not only considered the clinical parameters but also socioeconomic parameters which play a vital role in acquiring infections like urinary tract infection. Poor sanitation can substantially increase morbidities and severity of the various other diseases in women as well apart from urinary tract infections.

However, five-day nitrofurantoin is superior to single dose fosfomycin in treatment of acute uncomplicated UTI. Fosfomycin is a potential treatment option for patients with uncomplicated UTI based on susceptibility results and convenient usage.

Abbreviations:

UTI (urinary tract infections), cfu (colony forming units), *E.Coli* (*Escherichia Coli*)

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