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Single Dose of Fosfomycin Trometamol versus five days Norfloxacin In The Treatment Of Lower Uncomplicated urinary tract infections

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Abstract :
Objective: *To evaluate the safety and efficacy of a single 3 g dose of Fosfomycin trometamol in the treatment of lower uncomplicated UTI compared with those of a 5 day course of Norfloxacin (400 mg, bid).*
Methods: *Patients attending gynecological OPD at PESIMSR Kuppam with a clinical diagnosis of lower urinary tract infection were studied. Urine samples were taken for microscopy and culture sensitivity . Patients in group 1 received single dose of 3 gm fosfomycin trometamol , patients in group 2 received 5 day course of 400 mg bid norfoxacin . Patients were evaluated at the end of 10 days for symptomatic relief, side effects, bacteriological clearance. If patient persists to have clinical or microbiological evidence of infection after course of therapy then antibiotics was changed according to culture and sensitivity report . Primary outcome was clinical cure.Secondary outcome was bacteriological cure.*
Results: *94 % of people in Fosfomycin group and 88 % of people in norfloxacin group had symptomatic clearance. Follow up urine analysis showed no infection in 92 % of Fosfomycin group and 86 % of norfloxacin group.All the organisms responded well in Fosfomycin group , follow up culture in the fosfomycin group showed no growth, except in case of Pseudomonas Among 4 patients with UTI whose culture was positive for Pseudomonas only two patients responded well by showing no growth on follow up culture. The other two patients had persistent growth.*
Keywords: *lower uncomplicated urinary tract infections, Fosfomycin, norfloxacin.*

I. Introduction

Background

Uncomplicated UTIs are defined as infections occurring in a structurally and neurologically normal urinary tract. Complicated UTI refers to infection in urinary tract with abnormalities[1] . One in two women suffers from UTI at least once in her life. The young and sexually active are particularly affected.[2] This situation is further complicated by the fact that accurate diagnosis depends on both the presence of symptoms and a positive urine culture, although in most outpatient settings this diagnosis is made without the benefit of culture[3]. If left untreated, UTIs can develop into very serious and potentially life-threatening kidney infections (pyelonephritis) that can permanently scar or damage the kidneys. The infection may also spread into the bloodstream (called sepsis) and elsewhere in the body. In some adults, recurrent UTIs may cause scarring in the kidneys, which over time can lead to renal hypertension and eventual kidney failure [4]. Common pathogens E .coli and Staphylococcus Saprophyticus account for 80% of community acquired UTIs particularly in a women under 50 years age. Other gram negative organisms including Pseudomonas, Enterobacter, Serratia, Citrobacter and urease producing Klebsiella, Proteus, Corynebacterium, Ureolyticum and Providencia are also involved.[5] This topic has been chosen to prove that treatment of uncomplicated urinary tract infection in females with single dose antibiotic is as effective as conventional regimes.Single dose therapy has several advantages: significantly improves the compliance to the treatment, reduces the risk of emergence of resistance, and reduces side effects.

II. Method

A study was conducted among 100 patients with uncomplicated lower UTI at PESIMSR, Kuppam over a period of 1year from 1st January 2013 to 31st January 2014. Inclusion criteria included Females of reproductive age with clinical (history of dysuria, urgency, frequency, pain abdomen) and/or microbiologically diagnosed uncomplicated, lower urinary tract infection. Exclusion criteria were Known hypersensitivity to the drug, Pregnant and lactating women ,Pyelonephritis or perinephric abscess, UTI with structural or functional abnormality.satisfying the inclusion criteria patients were randomized into 2 groups alternatively urine samples were taken for microscopy and culture sensitivity examination. Observed for 48 hours for growth of the bacteria more than 10^5 colony forming units was considered as positive culture.[6]Patients in group 1 received single dose of 3 gm fosfomycin trometamol, they were asked to mix fosfomycin sachet in one glass of water and consume. Patients in group 2 received 5 day course of 400 mg bd norfloxacin . Patients are evaluated at the end of 10

days for symptomatic clearance , side effect, bacteriological clearance.If patient persist to have clinical or microbiological evidence of infection after course of therapy then antibiotics is changed according to culture sensitivity.

Data analysis :

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ±SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

III. Results

During the study period 100 women with UTI were taken. Incidence of UTI was high in the age group 20 – 29 years (% - 52.0 , N – 52) and multiparas (% - 90, N – 90). Most of the women belonged to low socio economic status (70%) as shown in table 1

Most common symptoms among patients studied were dysuria along with frequency(41 %) followed by frequency and urgency(32 %). Abdominal pain along with dysuria was noted in 15%, 11 % presented with abdominal pain alone and hematuria was noted in 1 % . 44 % of the patients with dysuria and frequency received fosfomycin and 38 % received norfloxacin. There was no significant difference between the two groups.table 2

Among 100 cases of UTI most common organism isolated was E.coli which constituted about 62 %. Out of these 31%) received Fosfomycin and 31 % received norfloxacin. Enterococcus was isolated in 14 % Fosfomycin was given in 7 % and Norfloxacin was given in 7 %. Pseudomonas was found in 7 % , 4 % received Fosfomycin and 3 % received Norfloxacin. Klebsiella was found in 5 %, 3 % received Fosfomycin and 2 % received Norfloxacin. NFGNB and CONS were found in 1 % each both of which received Fosfomycin. There was no significant difference in organism pattern in both the groups. (P value 0.787) table 3

Table 4 compares symptomatic clearance before and after treatment with both the drugs. Both Fosfomycin and norfloxacin were effective in producing symptomatic clearance in UTI patients. P value is < 0.001 which says that the symptomatic clearance was significant with both the drugs.

Table 5 shows symptomatic clearance with both drugs when compared to each other on follow up that is after ten days of completion of course. 94 % of the people who received Fosfomycin showed symptomatic clearance and only 6 % were not relived symptomatically. In Norfloxacin group symptomatic clearance was seen in 88 % and 12 % showed no improvement. There is no difference in symptomtic relief among two groups after treatment when compared to each other (P value – 0.487) . Table 6 compares microbiological clearance by urine microscopy P value is < 0.001. This indicates that there was significant microbiological clearance with both the drugs. Both the drugs were effective in clearing the bacteria.

microscopic examination at follow up that is ten days after the course of treatment in both the groups when compared to each other. Microbiological clearance was seen in 92 % of the people in Fosfomycin group and 86 % of the people in norfloxacin group. P value is 0.913 which suggests that the microbiological clearance with Fosfomycin and Norfloxacin was not statistically significant when compared to each other. Among 50 patients of Fosfomycin group there was complete clearance that is follow up culture showed no growth in E.coli, enterococcus, Klebsiella, Staphylococcus, NFGNB and CONS. 50 % (n – 2) of pseudomonas responded well to Fosfomycin and the other 50 % (n -2) showed persistent growth.

In Norfloxacin group there was complete clearance in enterococcus, Klebsiella and Staphylococcus. Persistent growth was seen in 6.5 % of E.coli and 66.7 % of Pseudomonas. 93.5 % of E.coli and 33.3 % of Pseudomonas responded well to Norfloxacin. P value is < 0.001 which shows both the drugs were effective in producing microbiological clearance. During the study period patients were enquired about side effects at the time of follow up. In Fosfomycin group 94 % of people did not have any side effects and 6 % had diarrhea. In Norfloxacin group 90 % had no side effects and 4 % had diarrhea, 4 % had nausea and 2 % had headache(table 7)

IV. Discussion

Urinary tract infection is one of the commonest bacterial infections encountered in daily clinical practice Consequently, the prevalence of urinary tract pathogens and their resistance to the different antibiotics may have changed over the years in the study area. Hence, studies are needed as a guide in the community and hospital health care settings.[7] A study conducted by Devanand Prakash showed that females of the age group 26–36 years were found more susceptible (90.69%) to UTI followed by 15–25 years (82.93%), 37–47 years (58.82%), and ≥48 years (45.45%).The factors of this increasing incidence of UTI in young age females are associated with high sexual activity, recent use of a diaphragm with spermicide, and a history of recurrent UTIs[8]. In our study highest incidence of UTI was found in the age group 20 – 29 years, which is consistent with other studies. study by KC Arul prakasam etal Among 200 patients 68% presented with dysuria, 60.5% with

fever, 46.5% with urgency and 29% with lower abdominal pain.[9] In our study most of the women with UTI presented with dysuria along with frequency, 41 % followed by 32 % with frequency and urgency. Abdominal pain along with dysuria was noted in 15 % . 11 % presented with abdominal pain alone and hematuria was noted in 1 % . Study done by Suman Kumar Majietal in West Bengal with a large sample size with a total number of 1,190 samples revealed positive bacterial growth. Seven types of dominant organisms were isolated as causative agents like Escherichia coli (63.44%), Klebsiella sp. (14.62%), Pseudomonas aeruginosa (4.53%), Proteus sp. (4.62%), other Gram negative bacteria (5.79%), Staphylococcus aureus and coagulase negative Streptococci (5.21%), and other Enterococcus sp. (1.76%). E.coli was the most common pathogen of UTI in tribal population with female susceptibility predominantly more than male patients.[10] In our study most common organism isolated was E.coli which constituted about 62 %, Enterococcus was isolated in 14 %, Pseudomonas was found in 7 %. Klebsiella was found in 5 %, NFGNB and CONS were found in 1 % each. The results were consistent with various other studies .11 of the 17 studies reported that at least 90% of the isolates were susceptible to fosfomycin. 1604 (96·8%) of 1657 Escherichia coli isolates producing ESBL were susceptible to fosfomycin. Similarly, 608 (81·3%) of 748 Klebsiella pneumoniae isolates producing ESBL were susceptible to fosfomycin.[11]

In our study Both the drugs were equally effective in symptomatic and microbiological clearance. But the Fosfomycin has the advantage of being given in single dose which is responsible for better compliance, tolerability and decreased resistance among uropathogens.

Study by Stein GE reported twenty patients (5.3%) who received fosfomycin had 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%).[12]

In present study in Fosfomycin group 94 % of people did not have any side effects and 6 % had diarrhea. In Norfloxacin group 90 % had no side effects and 4 % had diarrhea, 4 % had nausea and 2 % had headache. Side effect profile of Fosfomycin is very minor and it can be safely administered to the patients.

V. Conclusion

In this study Fosfomycin produced similar symptomatic and microbiological clearance compared to Norfloxacin. Advantage of Fosfomycin is given as a single dose, hence better compliance. The major advantage is that the emergence of resistance is less with Fosfomycin which can also be attributed to its single dose administration which is curative . Single dose Fosfomycin is as effective as multiple dose conventional regimens and can be given as an empirical therapy in people with lower uncomplicated Urinary tract infections

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Table 1 Demographic data of the two treatment groups

Age group (years)	Treatment drug					
	Fosfomycin		Norfloxacin		Total	
	N	%	N	%	N	%
20 - 29	28	56	24	48	52	52
30 - 39	18	36	17	34	35	35
40 - 49	4	8	9	18	13	13
Parity						
Primi	7	14	3	6	10	10
Multi	43	86	47	94	90	90
SES						
Low	33	66	37	74	70	70
Middle	14	28	12	24	26	26
High	3	6	1	2	4	4

Table 2 Comparision of symptoms among two treatment groups

Symptoms	Treatment drug					
	Fosfomycin		Norfloxacin		Total	
	N	%	N	%	N	%
Abdominal Pain	4	8	7	14	11	11
Dysuria, Abdominal Pain	9	18	6	12	15	15
Dysuria, Frequency	22	44	19	38	41	41
Frequency, Urgency	14	28	18	36	32	32
Hematuria	1	2	0	0	1	1
Total	50	100	50	100	100	100

Table 3 Various species isolated in two treatment groups

Culture (Species)	Treatment drug					
	Fosfomycin		Norfloxacin		Total	
	N	%	N	%	N	%
E Coli	31	62	31	62	62	62
Entrococcus	7	14	7	14	14	14
Pseudomonas	4	8	3	6	7	7
Klebsiella	3	6	2	4	5	5
Staphylococcus	3	6	7	14	10	10
NFGNB	1	2	0	0	1	1
CONS	1	2	0	0	1	1
Total	50	100	50	100	100	100

Table 4 –Symptomatic relief before and after treatment with both the drugs

Treatment drug	Symptoms	Symptoms relieved or not					
		Relieved		Not relieved		Total	
		N	Row %	N	Row %	N	Row %
Fosfomycin	Abdominal Pain	4	100	0	0	4	100
	Dysuria, Abdominal Pain	9	100	0	0	9	100
	Dysuria, Frequency	20	90.9	2	9.1	22	100
	Frequency, Urgency	14	100	0	0	14	100
	Hematuria	0	0	1	100	1	100
	Total	47	94	3	6	50	100
Norflxacin	Abdominal Pain	6	85.7	1	14.3	7	100
	Dysuria, Abdominal Pain	6	100	0	0	6	100
	Dysuria, Frequency	17	89.5	2	10.5	19	100
	Frequency, Urgency	15	83.3	3	16.7	18	100
	Total	44	88	6	12	50	100

Table 5 – Comparision of symptomatic clearance with both the drugs

Symptoms clearance present or absent	Treatment drug					
	Fosfomycin		Norfloxacin		Total	
	N	%	N	%	N	%
Present	47	94	44	88	91	91
Absent	3	6	6	12	9	9
Total	50	100	50	100	100	100

Table 6 – Comparision of follow up urine microscopy in the two treatment groups

	Treatment drug					
	Fosfomycin		Norfloxacin		Total	
Follow up U/R	N	%	N	%	N	%
Less than 4	46	92	43	86	89	89
5 or more	4	8	7	14	11	11
Total	50	100	50	100	100	100

Table 7 – Side effects in the two study groups

	Treatment drug					
	Fosfomycin		Norfloxacin		Total	
Side effects	N	%	N	%	N	%
Nil	47	94	45	90	92	92
Diarrhoea	3	6	2	4	5	5
Nausea	0	0	2	4	2	2
Headache	0	0	1	2	1	1
Total	50	100	50	100	100	100