

# Comparison of Efficacy of Fosfomycin and Ceftriaxone in the Treatment of Urinary Tract Infections in Children

Arshia Munir<sup>1</sup>, Muhammad Aqeel Khan<sup>1</sup>, Muhammad Bilal Khattak<sup>2</sup>, Kalimullah Khan<sup>3</sup> and Irum Naz<sup>4</sup>

## ABSTRACT

**Objective:** To compare the efficacy of oral Fosfomycin and Intravenous ceftriaxone in the treatment of urinary tract infections (UTIs) in children upto 16 years of age.

**Study Design:** Randomized Clinical Trial (RCT)

**Place and Duration of Study:** This study was conducted at the Department Pediatrics, MTI HMC Peshawar from November 2016 to April 2017.

**Materials and Methods:** 390 children with UTI were randomly allocated in two groups A (195) to receive fosfomycin and B (195) to receive ceftriaxone. Urine culture was done at the 5<sup>th</sup> day of the start of therapy to determine the effect of drug.

**Results:** We found the mean age group of our whole sample was  $9.4 \pm 2.3$  years. The mean age of children in group A was  $9.4 \pm 2.4$  years while in group B it was  $9.3 \pm 2.2$  years ( $p = 0.949$ ). There were 61.5% males in group A compared to 67.7% in group B ( $p = 0.204$ ). On follow up, repeat urine culture was performed in all children and it was observed that 72.3% children in fosfomycin group and 60% children in ceftriaxone group were having negative urine culture (efficacy)  $p = 0.01$ .

**Conclusion:** Fosfomycin is effective compared to ceftriaxone in the treatment of UTIs (urinary tract infections) in children.

**Key Words:** Urinary Tract Infection, Urine Culture, Pyrexia, Fosfomycin, Ceftriaxone, Abbreviations: HMC: Hayatabad Medical Complex, C & S: culture and sensitivity, UTI: Urinary tract infection.

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## INTRODUCTION

Infants and young children are prone to multiple problems. UTIs are quite common in these age groups leading to acute, recurrent and chronic illnesses. UTIs occur approximately in 8% of girls and 1.7 % of in their first seven years of life, with a recurrence rate of 10% to 30%<sup>1</sup>.

In pediatric age group the sample collection varies depending upon the age of the child from infants to adolescent<sup>2</sup>. The clinical manifestations of urinary tract infection (UTI) in young patients are most of the time not specific and taking a urine sample in critical patients is extremely difficult<sup>3</sup>. In most of the cases UTI is missed and not diagnosed in time at primary care center<sup>4</sup>. Therefore it is recommended that clinicians at all level should obtain urine sample for routine examination and culture in acutely ill young children<sup>5</sup>.

Several pathogens cause urinary tract infections and the most frequent occurring is *Escherichia coli*. Other pathogens causing UTIs in children are *Klebsiella*, *Proteus*, *Enterobacter*, *Citrobacter* and *Enterococcus*<sup>6</sup>. Amoxicillin has been used as first line antibiotic for UTI and as an empirical therapy for a long time but due to increasing *E. coli* resistance this is no more favorable choice<sup>7</sup>. The growing resistance has been documented for cephalosporins for *Enterobacter* species in children<sup>8</sup>. Fosfomycin has not been used frequently for the treatment of urinary tract infections in the recent years. But its use has increased very recently because of increasing resistance to the routine used antibiotics in the treatment of the UTIs<sup>9</sup>. Though an old antibiotics, Fosfomycin has been used only for the treatment of uncomplicated urinary tract infections in routine<sup>10</sup>. Now a day, studies have defined the role of this medicine in several clinical condition and not merely uncomplicated UTIs<sup>11,12</sup>. Fosfomycin has been used orally in treating young children with clinical diagnosis of cystitis<sup>13</sup>. One of the reasons of the high efficacy of the oral formulation of fosfomycin for the treatment of UTIs is its rapid absorption and achievement of high urinary concentrations and presence for several days in the blood<sup>14</sup>.

<sup>1</sup>. Department of Pediatrics, MTI HMC/KMC, Peshawar.

<sup>2</sup>. Department of Medicine/Pediatrics<sup>3</sup>,HMC/KGMC, Peshawar.

<sup>3</sup>. Department of Pediatrics, NTH, Peshawar.

Correspondence: Dr. Muhammad Bilal Khattak, Assistant Professor, Medical C Unit MTI HMC/KGMC Peshawar.

Contact No: 03333-9346838

Email: bilal\_amc1@yahoo.com

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The present study is designed to compare the efficacy of fosfomycin with ceftriaxone in the treatment of UTI in our local pediatric population. UTI among children is not an uncommon in our population and if not treated and managed well in time, it can lead to chronic complication like cystitis. This study is designed keeping in view the importance of treatment for UTI in children. The results of this study will be shared with other local pediatricians and if the efficacy of fosfomycin is found to be significantly more than ceftriaxone, we will recommend fosfomycin for the routine treatment of children with UTI.

## MATERIALS AND METHODS

This RCT (randomized controlled trial) was carried out in the Pediatrics Unit Medical Teaching Institute Hayatabad Medical Complex, Peshawar from November 2016 to April 2017. Consecutive (non probability) sampling technique was used for all those pediatric patient who visited the tertiary level hospital. A total of 195 in each group keeping 77.5% efficacy of fosfomycin<sup>12</sup> and 66.2% efficacy of ceftriaxone<sup>14</sup>, 95% confidence interval and 80% power of the test, using WHO sample size calculations.

All children with urinary tract infection on urine culture with age group 5 to 16 years and either gender were included in the study. Patients with history of intake of any type of antibiotic in the last one week were excluded from the study.

## RESULTS

The study was conducted on 390 children presenting with UTI. The mean age of the whole sample was  $9.4 \pm 2.3$  years. The mean age of children in group A was  $9.4 \pm 2.4$  years while in group B it was  $9.3 \pm 2.2$  years. The difference was statistically not significant after applying independent sample T test with a p value of 0.949. While distributing the patients with regards to gender, we observed that the difference between both the groups was statistically not significant after applying chi square test. (P value 0.204).

**Table No. 1: Age in Categories Between Both Groups (n= 195 each)**

Age Group	Treatment Groups		Total
	Fosfomycin Group	Ceftriaxone Group	
5 to 8 years	63	51	114
	32.3%	26.2%	29.2%
> 8 to 12 years	120	117	237
	61.5%	60.0%	60.8%
> 12 to 16 years	12	27	39
	6.2%	13.8%	10.0%
Total	195	195	390
	100.0%	100.0%	100.0%

**Table No. 2: Gender Distribution in Both Treatment Groups (n=195 each)**

Gender of the Patient	Treatment Groups		P Value
	Fosfomycin Group	Ceftriaxone Group	
Male	120	132	0.204
	61.5%	67.7%	
Female	75	63	
	38.5%	32.3%	
Total	195	195	
	100.0%	100.0%	

**Table No. 3: Comparison of Efficacy Between Treatment Groups (N=195 Each)**

Efficacy of Drug	Treatment Groups		P Value
	Fosfomycin Group	Ceftriaxone Group	
No	54	78	0.01
	27.7%	40.0%	
Yes	141	117	
	72.3%	60.0%	
Total	195	195	
	100.0%	100.0%	

**Table No. 4: Age Groups up to 8.00 Years Wise Stratification of Efficacy**

Efficacy of the drugs	Treatment Groups		P Value
	Fosfomycin Group	Ceftriaxone Group	
No	0	24	< 0.001
	0.0%	47.1%	
Yes	63	27	
	100.0%	52.9%	
Total	63	51	
	100.0%	100.0%	

**Table No. 5: Age Groups 8:01 to 12:00 Years Wise Stratification of Efficacy**

Efficacy of the Drugs	Treatment Groups		P Value
	Fosfomycin Group	Ceftriaxone Group	
No	42	54	< 0.001
	35.0%	46.2%	
Yes	78	63	
	65.0%	53.8%	
Total	120	117	
	100.0%	100.0%	

All the patients in either group were subjected to standard dose of the drug according to international protocols. After 5<sup>th</sup> day of start of regime, repeat urine culture was performed in all children and it was observed that 72.3% children in fosfomycin group and 60% children in ceftriaxone group were having negative urine culture (efficacy). The difference was statistically significant after applying chi square test with a p value of 0.01.

Table 1 shows age categories, table 2 shows gender wise distribution of the patients while rest of the four tables show efficacy comparison in toto and in separate group respectively.

**Table No. 6: Age Groups 12.01 to 16.00 Years Wise Stratification of Efficacy**

Efficacy of the Drugs		Treatment Groups		P Value
		Fosfomycin Group	Ceftriaxone Group	
No		12	0	< 0.001
		100.0%	0.0%	
Yes		0	27	
		0.0%	100.0%	
Total		12	27	
		100.0%	100.0%	

## DISCUSSION

Acute urinary tract infections (UTIs) are the most frequently occurring pathologies of pediatric age group and causing at least one episode of acute urinary tract infection in 8.4% of the girls and 1.7% of the boys in the first seven years of life. UTIs lead to frequent hospitalization if pediatric age group especially in the first year of life (40%)<sup>15</sup>. UTI is responsible for a majority of transient renal damage (app 40%) of children affected and permanent damage to some extent (about 5%)<sup>16, 17</sup>. The commonest presenting features of UTI in pediatric age group are fever, lethargy, anorexia, and vomiting. The most notorious bug in causing of UTI is *Escherichia coli* in over 80% of cases<sup>18</sup>. Recurrence of UTI is a major issue (app 30%) and the risk factors include vesicoureteric reflux (VUR), bladder instability and previous infections. Recurrence of UTI occurs more commonly in girls than boys<sup>19</sup>. Febrile urinary tract infections have the highest incidence during the first year of life in both sexes, whereas non-febrile urinary tract infections occur predominantly in girls older than 3 years. No doubt UTI management is a real challenging task and involves multidisciplinary approach including pediatricians, and urologists. The important thing is that recurrence of the UTI should be tackled very effectively. The reason is that multiple courses of antibiotic can lead to multi-drug resistance in these kids<sup>20,21</sup>.

Fosfomycin is an old antibiotic agent that has been used for the treatment of uncomplicated urinary tract infections in many clinical settings. In our study we found that Fosfomycin is highly effective in treating the routine urinary tract infections and is introduced orally with easy as compared to most of the antibiotics which needs parenteral administration which is more invasive and needs prolonged hospital stay or close supervision by health professionals. The overall response of UTIs in our study to Fosfomycin was quite encouraging as compared to intravenous administration of ceftriaxone. The infection clearance and course of the antibiotic

therapy was shorter and more effective in Fosfomycin group as compared to cephalosporin group. The duration of Fosfomycin was less than half and the response was 72.3 % as compared to 60% in ceftriaxone group. Efficacy of Fosfomycin has been studied isolated or compared with other antibiotics. The efficacy of this medicine has been found as high as 99 % in urinary tract infections<sup>22</sup>. A study conducted in Turkey by Hosbul T et al found only 2 % resistance to Fosfomycin in uncomplicated urinary tract infections<sup>23</sup>. Florea C found that *E. Coli* urinary tract infections responded very well to Fosfomycin but the response was equally well to third generation cephalosporin as compared to first and second generation cephalosporin which was not encouraging<sup>24</sup>.

## CONCLUSION

Fosfomycin is highly effective compared to ceftriaxone in the treatment of UTI in children. However, the clinical significance of fosfomycin is on a rise not only for UTIs but also for other infections particularly gastrointestinal infections.

**Recommendation:** We recommend more randomized controlled trials with larger sample sizes and involving multiple centers to draw solid conclusions about the best therapy for pediatric UTI.

### Author's Contribution:

Concept & Design of Study: Arshia Munir  
 Drafting: Muhammad Aqeel Khan  
 Data Analysis: Kalimullah Khan, Irum Naz  
 Revisiting Critically: Muhammad Bilal Khattak, Arshia Munir  
 Final Approval of version: Arshia Munir

**Conflict of Interest:** The study has no conflict of interest to declare by any author.

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