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Efficacy of short course versus standard course oral co-trimoxazole in the management of children with lower urinary tract infections.

Bilal Khalid[1], Tehmina Maqbool[2], Sadia Shabir[3], Attiya Fatima[4], Samia Aslam[5], Muhammad Alam Khan[6], Muhammad Ahsan[7]

1. MBBS, FCPS (Peads)
Senior Registrar Pediatric Medicine
King Edward Medical University
Lahore.
2. MBBS, FCPS (Peads)
Assistant Professor Pediatric Medicine
King Edward Medical University
Lahore.
3. FCPS (Peads)
Assistant Professor Pediatric Medicine
King Edward Medical University
Lahore.
4. MBBS, FCPS (Peads)
Senior Registrar Pediatric Medicine
King Edward Medical University
Lahore.
5. MBBS, FCPS (Peads)
Senior Registrar Pediatric Medicine
King Edward Medical University
Lahore.
6. MD (Peads)
Senior Registrar Pediatric Medicine
King Edward Medical University
Lahore.
7. MBBS, PGPN
Medical Officer Pediatric Medicine
Govt General Hospital, Faisalabad.

Correspondence Address:
Dr. Muhammad Ahsan
Department of Pediatric Medicine
Govt General Hospital, Faisalabad.
ahsanjahangir194@gmail.com

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ABSTRACT… Objective: To compare the efficacy of short course versus standard course oral co-trimoxazole in the management of children presenting with lower urinary tract infections. **Study Design:** Randomized Controlled Trial. **Setting:** Department of Paediatric, Federal Government Polyclinic, Islamabad. **Period:** 6 months from January 2017 to June 2017. **Material & Methods:** Patients were randomly allocated to two therapy groups by lottery method i.e. oral co-trimoxamole for 3 days (Group A) and oral co-trimoxazole for 10 days (Group B). The antibiotic course was started according to child weight and stopped after 3 and 10 days according to study group allocation. The patients were followed up after 7 days in the short course group and 10 days in the standard therapy group to assess for clinical resolution of UTI. The outcome was noted as clinical cure or relapse/recurrence of UTI. The children with recurrence were sent home after change of therapy to next generation of antibiotic therapy and in case of severe condition, patient was admitted for parenteral therapy. **Results:** In this study efficacy of short course was seen in 41(85.4%) patients while patients who were given standard course among they m efficacy was seen in only 14(29.2%) patients only. Efficacy of short course treatment was significantly higher as that of that of standard course i.e. p-value=0.000. Efficacy of both treatment regimens was seen in terms of age, gender and duration of symptoms. Stratification of these variables showed that short course efficacy was significantly higher as that of standard course for all these stratified variables. **Conclusion:** Results of this study demonstrated that short course of oral co-trimoxazole is more effective than standard course in the management of children presenting with lower urinary tract infections. However short course is not only beneficial in terms of cost as well as it cures in a short time span and minimal side effects.

Key words: Efficacy, Lower Urinary Tract Infections, Oral Co-trimoxazole, Paediatric, Septran, Short Course, Standard Course, Septran, UTI.

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INTRODUCTION

Urinary infections are quite prevalent in childhood population. It has been estimated that around 8% girls and 2% boys have it atleast once till the age of 7 years.[1,2] It presents with pain, irritability, anxiety and inconvenience to the victim and to the family. Early diagnosis and treatment have good clinical outcome.

Clinical signs & symptoms varies with age, but all febrile children of age 2 months to 24 months with no obvious infection etiology should be evaluated for UTI (with the exception of circumcised boys older than 12 months). Evaluation of other older children should be done according to signs like leukocyte esterase or nitrite on dipstick; pyuria of at least 10 white blood cells per high-power field and bacteriuria.[3]

Most common pathogen is Escherichia coli, accounting for approximately 85 percent of UTI in children.[1] The commonly used diagnostic methods are routine urine examination, urine cultures, ultrasonography, cystography and a renal cortical scan. For infants and children with lower urinary tract infection, treatment is oral antibiotics for 10 days.[4] The recommended initial antibiotic for children is trimethoprim / sulphamethoxazole (septran). Alternative include amoxicillin/clavulanate or third generation

cephalosporins. Prophylactic antibiotic use can be done but there is no reduction in the risk of subsequent UTI, even in children with mild to moderate vesicoureteral reflux (VUR). Constipation is also one of the risk factors and it should be avoided while managing UTI.[3]

The guidelines for diagnosis, management and follow-up of children with urinary tract infections (UTIs) continue to evolve and therapy duration is controversial.[5] Short-course 3 days treatment is equally effective for acute-uncomplicated cystitis.[6]

There is scientific evidence which suggests that a 3-day course of oral antibiotics appears to be as effective as a 10 days course in children with lower UTIs.[6] A previous study by Johnson et al reported therapy failure of 45.0% with short course antibiotic therapy compared to 17.6% with standard therapy in the management of UTIs in children.

There is variable data regarding the efficacy of antibiotic duration, moreover, there are very fewer studies done recently on children with UTI in terms of antibiotic therapy duration. The probable benefits of short course antibiotic therapy could be less adverse effects, reduced cost and duration on therapy. However, this needs to be evaluated. Thus, we plan to conduct a randomized controlled trial to assess the efficacy of short course therapy compared to standard course oral of co-trimoxazole in the management of children with lower urinary tract infection. The fresh evidence will inform healthcare workers and programme managers related to child health regarding appropriate choice of antibiotic therapy duration.

MATERIAL & METHODS

This Randomized controlled trial was conducted at the Paediatric Department, Federal Government Polyclinic, Islamabad for 6 months after approval. The aim of this study was to compare the efficacy of short course versus standard course oral co-trimoxazole in the management of children presenting with lower urinary tract infections in the paediatric medicine department of Federal Government Polyclinic, Islamabad. Lower Urinary Tract Infection. UTI was characterized by fever, painful urination or increased frequency of micturition with the culture of a pure growth of organisms $>10^5$ organisms/ml of urine sample. Alternate Hypothesis was defined as 'There is difference in efficacy between standard and short course of oral Co-trimoxazole in the management of lower UTI in children.' Standard Course was Oral co-trimoxazole therapy for 10 days was given in twice daily dosage as per child weight and Short Course was oral co-trimoxazole therapy for 3 days was given twice daily dosage as per child weight. Study efficacy was defined in terms of complete clinical cure after 3 days and 10 days of antibiotic treatment that is disappearance of above mentioned symptoms along with negative urine culture reports after completion of both courses of therapy.

Sample Size was calculated using WHO sample size calculator taking Power of the Test = 90%, Alpha error = 5%, Anticipated population proportion in short course group = 45.0% and in standard course group = 17.6%. The study sample size was 48 cases in each study group. A total of 96 children with UTI were enrolled in this study with the inclusion criteria which states that 'All children of both genders of age 1 to 5 years having clinical picture as mentioned in operational definition of urinary tract infection were included in the study.' Exclusion Criteria for this study was: Children with chronic kidney disease, Children with end stage renal disease, renal scarring, occult pyelonephritis, malformation of urinary tract and spinal cord dysfunction/ Atonic bladder.

Before initiation of the study, ethical clearance was sought from hospital ethics committee. The patients presenting with UTI signs and symptoms and fulfilling study criteria were selected from outpatient department. A written informed consent was administered to all study patients/ caretakers after explaining the purpose of the study. A structured study proforma was used for data collection.

Patients were randomly allocated to two therapy groups by lottery method i.e. oral co-trimoxamole for 3 days (Group A) and oral co-trimoxazole for

10 days (Group B). The patient demographic characteristics were noted in terms of sex and age. The signs and symptoms along with laboratory findings were entered in the proforma. The antibiotic course was started according to child weight and stopped after 3 and 10 days according to study group allocation.

The patients were followed after 7 days in short-course group while those in the other group were followed after 10 days to assess for clinical resolution of UTI. The outcome was noted as clinical cure or relapse/recurrence of UTI. The children with recurrence was sent home after change of therapy to next generation of antibiotic therapy and in case of severe condition, patient was admitted for parentral therapy. All the study related procedures and data collection was done by the researcher himself to decrease selection bias and data quality. The study outcome was determined in terms of efficacy of oral co-trimoxazole when given in either short course (3 days) or standard course (10 days).

All records and variables were entered and later analyzed using statistical package for social sciences (SPSS) 11.0. Effect modifiers (age, gender, duration of symptoms) were controlled by stratification and the post stratification chi-square test was applied. A p-value of < 0.05 was considered significant. The results were described and also presented as tables and graphs.

RESULTS

Mean age of patients in Group-A and in Group-B was 2.94±1.31 and 2.85±1.39 years. In both groups minimum and maximum age of patients was 1 and 5 years respectively.(Table-I**)** In Group-A there were 32(66.7%) male and 16(33.3%) female while in Group-B there were 27(56.3%) male and 21(43.8%) females.(Table-II) In Group-A mean duration of symptoms was 2.92±1.28 and in Group-B it was 3.08±1.51.(Table-III) In Group-A 26(54.2%) and in Group-B 25(52.1%) children had fever.(Table-IV) In Group-A 39(81.3%) and in Group-B 36(75%) children had pain while micturating.(Table-V) In Group-A 34(70.8%) and in Group-B 41(85.4%) children experiences increased frequency of urine.(Table-VI) In both treatment groups all children urine culture were sent to laboratory.(Table-VII) Urine culture results showed that E.Coli was the pathogen identified in urine culture for all samples.(Table-VIII)

In Group-A efficacy of drug was seen in 41(85.4%) children while in Group-B efficacy of drug was seen in only 14(29.2%) children. P-value showed that efficacy of Group-A patients was significant higher than as that of Group-B patients. i.e. p-value=0.000(Table-IX) In both age groups i.e. 1-2 years and 3-5 years efficacy of treatment was significantly higher in Group-A patients as that of Group-B patients. i.e. 1-2 years (Efficacy): Group-A: 88.2% vs. Group-B:28.6%, p-value=0.000& 3-5 years (Efficacy): Group-A: 83.9% vs. Group-B:29.6%respectivelyp-value=0.000.(Table-X)

Among male and female children efficacy of treatment was significantly higher in Group-A as that of Group-B. i.e. Male (Efficacy): Group-A: 81.3% vs. Group-B:18.5%, p-value=0.000&Female(Efficacy): Group-A: 93.8% vs. Group-B:42.9% respectively, p-value=0.001.(Table-XI)

Patients with symptoms duration 1-2 and 3-5 among them efficacy of treatment was significantly higher in Group-A patients when compared with Group-B patients. i.e. 1-2 (Efficacy): Group-A: 75% vs. Group-B:26.3%, p-value=0.002&3-5 (Efficacy): Group-A: 92.9% vs. Group-B:31% respectively, p-value=0.000.(Table-XII)

	Group-A	Group-B
N	48	48
Mean	2.94	2.85
Standard deviation	1.31	1.39
Min	1	1
Max	5	5

Table-I. Descriptive statistics of age of children

	Group-A	Group-B
Male	32(66.7%)	27(56.3%)
Female	16(33.3%)	21(43.8%)
Total	48	48

Table-II. Gender distribution of patients

	Group-A	Group-B
N	48	48
Mean	2.92	3.08
Standard deviation	1.28	1.51
Min	1	1
Max	5	5

Table-III. Descriptive statistics for duration of symptoms

Fever	Group-A	Group-B
Yes	26(54.2%)	25(52.1%)
No	22(45.8%)	23(47.9%)
Total	48	48

Table-IV. Frequency distribution for fever

	Group-A	Group-B
Yes	39(81.3%)	36(75%)
No	9(18.8%)	12(25%)
Total	48	48

Table-V. Frequency distribution for pain while Micturating

	Group-A	Group-B
Yes	34(70.8%)	41(85.4%)
No	14(29.2%)	7(14.6%)
Total	48	48

Table-VI. Increased frequency of Urine

	Group-A	Group-B
Yes	48(100%)	48(100%)
No	0(0%)	0(0%)
Total	48	48

Table-VII. Urine culture sent to laboratory

	Group-A	Group-B
E.Coli	48(100%)	48(100%)
Total	48	48

Table-VIII. Pathogen type from urine culture

Efficacy	Group-A	Group-B
Yes	41(85.4%)	14(29.2%)
No	7(14.6%)	34(70.8%)
Total	48	48

Table-IX. Efficacy of treatment groups Chi-Square Test=31.03, p-value=0.000

Age Groups	Efficacy	Group-A	Group-B	P-Value
1-2	Yes	15(88.2%)	6(28.6%)	0.000
	No	2(11.8%)	15(71.4%)	
3-5	Yes	26(83.9%)	8(29.6%)	0.000
	No	5(16.1%)	19(70.4%)	

Table-X. Efficacy of treatment groups stratified for age of patients

Gender	Efficacy	Group-A	Group-B	P-Value
Male	Yes	26(81.3%)	5(18.5%)	0.000
	No	6(18.8%)	22(81.5%)	
Female	Yes	15(93.8%)	9(42.9%)	0.001
	No	1(6.3%)	12(57.1%)	

Table-XI. Efficacy of treatment groups stratified for gender of patients

Symptoms Duration	Efficacy	Group-A	Group-B	P-Value
1-2	Yes	15(75%)	5(26.3%)	0.002
	No	5(25%)	14(73.7%)	
3-5	Yes	26(92.9%)	9(31%)	0.000
	No	2(7.1%)	20(69%)	

Table-XII. Efficacy of treatment groups stratified for duration of symptoms

DISCUSSION

Urinary infections are quite prevalent in childhood population. It has been estimated that around 8% girls and 2% boys have it atleast once till the age of 7 years. It presents with pain, irritability, anxiety and inconvenience to the victim and to the family. Early diagnosis and treatment have good clinical outcome. The main idea behind the treatment of these patients is to elevate the symptoms of children in stress and pain, prevention of disease spread with short term and long-term complications.

As the microbes are developing resistance against most of the antibiotics, rationalisation of prescription patterns with the knowledge of sensitivity patterns of various organisms should be very clear. Another factor is the geographical variations in the sensitivity and resistance patterns, and duration with choice of antimicrobial also varies in various populations. These should be modified with the knowledge of sensitivity pattern of the pathogens in order to minimize the development of resistant strains.[7,8]

For many years, septran and nitrofurantoin have been used as prophylactic in the children with suspected UTI. With the development of restrictions on these substances in early infancy, cephalosporins for oral use are now preferred.[9] These cephalosporins & trimethoprim/co-trimoxazole also work for eradication of gram-

negative microbes in the gut.[9]

The guidelines for diagnosis, management and follow-up of children with UTIs continue to evolve and therapy duration is controversial.[5] Short-course treatment (3 days) is effective for acute uncomplicated cystitis, and it has been proposed as an appropriate regimen for patients with other conditions like spinal cord injury.[6] There is scientific evidence which suggests that a 3-day course of oral antibiotics appears to be as effective as a 10 days course in children with lower UTIs.[6]

In this study efficacy of short course was seen in 41(85.4%) patients while patients who were given standard course among they m efficacy was seen in only 14(29.2%) patients only. Efficacy of short course treatment was significantly higher as that of that of standard course. i.e. p-value=0.000. Efficacy of both treatment regimens was seen in terms of age, gender and duration of symptoms. Stratification of these variables showed that short course efficacy was significantly higher as that of standard course for all these stratified variables.

In a study, Belet et al. reported that the use of either cotrimoxazole, cephadroxil or cefprozil in children as a prophylactic antimicrobial for symptomatic was not statistically different.[10]

Cheng et al. also studied children with symptomatic UTI and found that recurrence rate of UTI in one of two hospitals was significantly more among those who received cotrimoxazole prophylaxis (1.73 cases/100 treatment-months) compared to those who received cephalexin (0.90 cases/100 treatment-months) or cefaclor prophylaxis (1.38 cases/100 treatment-months). In third hospital taken into consideration in this study cotrimoxazole prophylaxis showed recurrence in 1.25 cases/100 treatment-months, which was comparable to the results of cefaclor prophylaxis.[11]

Some trials done on patient of uncomplicated UTIs showed that the short course therapy (3 days) had similar eradication rates with lower incidence of side effects as compared to with longer course of treatment (7 to 10 days).[12]

Infectious Disease Society of America recommended that 3-day short regimens of trimethoprim, trimethoprim-sulfamethoxazole, and fluoroquinolones is better and effective than a single-dose therapy; and single or short course therapy is better tolerated than longer therapies of 7-10 days. Exceptions to this short course therapy include pregnant women, diabetics, and those with symptoms of 1 week or longer.[13]

Uncomplicated cystitis patients treated with trimethoprim-sulfamethoxazole, trimethoprim, or fluoroquinolones for 3 days shout course should eradicate 90% of these infectious agents with minimum adverse effects.[12]

The advantages of this short-course include a better compliance to treatment, decreased side effects of the medication, decreases chances of development of resistance, and decrease in the cost of the treatment. The single dose therapy has not been accepted by the treating physicians because of more chance of development of pyelonephritis and difficulty in diagnosing complications related to upper urinary tract. So the short course of antimicrobial is effective as much as the standard longer 7–14 days treatment with other benefits as well.

CONCLUSION

Results of this study demonstrated that short course of oral co-trimoxazole is more effective than standard course in the management of children presenting with lower UTIs. However short course is not only beneficial in terms of cost as well as it cures in a short time span and minimal side effects.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Bilal Khalid	Paper writing, Data collection.	
2	Tehmina Maqbool	Data entry, Review of paper.	
3	Sadia Shabir	Data analysis, Discussion writing.	
4	Attiya Fatima	Data analysis, Discussion writing.	
5	Samia Aslam	Data analysis, Data entry	
6	Muhammad Alam Khan	Paper writing, Data entry.	
7	Muhammad Ahsan	Paper writing.	