Original Article

http://journals.sbmu.ac.ir/jpn
https://doi.org/10.22037/jpn.v9i3.34181

Comparative Study of Prophylactic Antibiotic Twice a Week Versus Every Night in Recurrent Urinary Tract Infections in Children

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Received: February, 2021
Revised: September, 2021
Accepted: October, 2021

Abstract

Background and Aim: Urinary tract infection is one of the most common childhood diseases. The results of studies investigating discontinuation or continuation of antibiotics in children with recurrent urinary tract infections and urinary reflux are controversial. Therefore, this study was conducted to compare prophylactic antibiotic treatment twice a week versus every night in the recurrence of urinary tract infections in children.

Methods: This clinical trial was conducted using non-random simple sampling. Group A was given a single daily dose of cephalexin 10 mg/kg and group B was given cotrimoxazole at a dose of 5 mg/kg. Both groups were followed for ten months. Recurrences of urinary tract infections were compared between the two groups.

Results: The mean age of the participants was 3.53±2.04 years. Most of the subjects were female (n=37, 61.7%). Urinary reflux was unilateral in 65% of the cases (n=39) and bilateral in the rest. There was no significant difference in age distribution, sex, and type of reflux between groups A and B. The frequency of recurrent urinary tract infection was 8.3% in group A and 6.7% in group B indicating no significant difference (p = 0.500).

Conclusion: The results of this study showed that the frequency of recurrence of urinary tract infections in children who received prophylactic antibiotic treatment twice a week was not significantly different compared to the group of children who received continuous antibiotic prophylaxis.

Keywords: Urinary Tract Infection; Antibiotic Prophylaxis; Pediatrics; Cotrimoxazole.

Conflict of interest: The authors declare no conflict of interest.
Please cite this article as: Taheri A, Azarfar A, Ravanshad Y, Sahebkari A. Comparative Study of Prophylactic Antibiotic Twice a Week Versus Every Night in Recurrent Urinary Tract Infections in Children. J Ped Nephrol 2021;9(3):1-5.
https://doi.org/10.22037/jpn.v9i3.34181

Introduction

Urinary tract infection is one of the most common childhood diseases that may lead to severe complications such as scarring if not diagnosed and treated in time. Prompt diagnosis and treatment are necessary to prevent the complications. Urinary reflux is the most important underlying cause of urinary tract infections in children. Oral antibiotics at lower than therapeutic doses (one-third to one-fourth) are used as prophylaxis to prevent urinary tract infections; however, this will be a long-term and costly preventive measure that may not be possible. The other adverse effects in this regards are nausea, vomiting, and allergic skin reactions (1-3). Urinary tract infection is also the most common bacterial infection after respiratory infections. As a result, large amounts of antibiotics are used to treat urinary tract infections, which impose very high costs on the health system and patients. Misuse of antibiotics to treat urinary tract infections also increases drug resistance (4). Studies on discontinuation or continuation of antibiotics in children with recurrent urinary tract infections and urinary reflux are controversial.

While some physicians insist on continuing the medication, others point out that it is safe to discontinue these medications (5-9). In addition, some still make decisions subject to further study (10, 11). The results of a study by Weiss et al. showed that antibiotics were effective in preventing the recurrence of urinary tract infections in children with urinary reflux (12). However, Cooper et al. found that antibiotic discontinuation was safe (13).

In a study by Ohata et al. performed on children that were unable to tolerate daily antibiotics, oral TMP / SMX 8 mg/kg on two non-consecutive days of the week was compared to daily injectable and inhaled pentamidine regimens. The effect of these two regimens on the prophylaxis of Pneumocystis jiroveci pneumonia (in children receiving stem cell transplants or receiving chemotherapy) was evaluated in the same way (14).

Keiko Ono et al. performed a study on patients with non-Hodgkin's lymphoma receiving high-dose TMP-SMX for PCP (Pneumocystis pneumonia) prophylaxis. In this study, TMP-SMX 800 mg two days a week and 400 mg daily were compared. The median follow-up time was 29.4 months and the median duration of antibiotic use was 5.7 months. During this time, none of the 291 monitored patients showed any signs of Pneumocystis jiroveci pneumonia (15).

One of the most common reasons for patients to discontinue medication is the daily administration of medication, which sometimes causes arbitrary discontinuation of medication. On the other hand, the literature suggests the use of cotrimoxazole twice a week. Therefore, given the fact that cotrimoxazole is also used in PCP prophylaxis and several articles have been recently published on reducing the dose of cotrimoxazole in PCP prophylaxis to decrease drug side effects and improve compliance, this study was conducted to compare the effect of prophylactic antibiotic twice a week versus every night on the recurrence of urinary tract infections in children. Reducing the number of drug doses will increase the acceptance of the family and the child; on the other hand, this measure will reduce treatment costs imposed on the family and the health system.

Methods

This clinical trial was conducted in Dr. Sheikh Medical Research and Training Center affiliated with Mashhad University of Medical Sciences from June to March 2015. The participants included children with urinary reflux presenting to the Nephrology Clinic of Sheik Hospital. After an initial visit, the patients were selected by a pediatrician or a nephrologist according to the following items, and their data were collected using interviews, examinations, and a designed checklist including data such as age, sex, and grade of reflux. Then, the patients were divided into groups A and B using envelopes (simple random method). The pediatrician was not aware which package belonged to group A or B.

Inclusion criteria

1. Obtaining consent from parents
2. Reflux grade 2 or higher requiring prophylactic antibiotic
3. Good general condition
4. Living in Mashhad or near cities for easy follow-up
5. Age between one and eight years

Exclusion criteria

1. Withdrawal from study
2. Migrating to a distant city
3. Impaired consciousness or mental retardation
4. Living in an orphanage
5. A positive history of urinary tract stones, hypersensitivity, reaction to cotrimoxazole or cephalexin, and antibiotic resistance
6. Loss to follow-up

After explaining the study objectives to participants (or legal guardians in children under 7 years based on the research ethics guide in vulnerable groups) and obtaining informed consent (from the children or their legal guardians), the participants were included in the study. To observe the research ethics in vulnerable groups such as children, in addition to obtaining consent from the children's guardians or parents, an attempt was made to obtain the children's consent separately. The Ethics Committee of Mashhad University of Medical Sciences approved the study (IR.MUMS.REC.1394.298). The study was registered in International Clinical Trials Registry Platform (ICTRP) (IRCT20201112049368N).

Patients group A received a single daily dose of cephalexin 10 mg/kg while patients in group B were given cotrimoxazole 5 mg/kg twice a week on Saturdays and Tuesdays. Both groups were followed for ten months. The patients' urine samples were analyzed and cultured monthly and

the patients were monitored for recurrence of urinary tract infections (urine culture containing 100,000 colonies or 10,000 colonies with symptoms of cystitis). UTI recurrence was compared between the two groups. Other patients' characteristics such as the degree of urinary reflux and the age were also analyzed. A schematic overview of the experimental design is presented in Figure 1. Data were analyzed using the SPSS software version 16. Independent t-test, Mann-Whitney U test, and chi-square test were used to compare the parameters between the two groups.

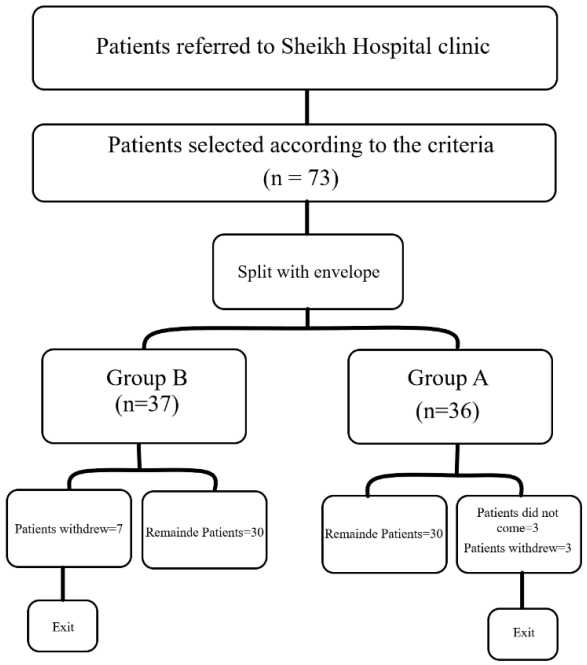

Figure 1. Schematic overview of experimental design

Results

The mean age of participants was 3.53±2.04 years (range: 1-8 years).

The mean age of the children was 3.56±2.17 years in group A and 3.13±1.92 years in group B. Since age did not have a normal distribution, Mann-Whitney U was used to compare the age difference between the two groups, which showed no significant difference (p=0.467).

Most of the subjects were female (n=37, 61.7%) Chi-square showed no significant difference in the frequency of gender distribution between the two groups (Table 1).

Table 1. Comparison of gender frequency distribution between study groups

		Group A	Group B	Chi-square test
	Male	12 (20%)	11 (18.3%)	
	Female	18 (30%)	19 (31.7%)	

*p value is not significant (p>0.05)

Urinary reflux was unilateral in 65% of the cases (n=39) and bilateral in the rest. The frequency of unilateral reflux was 70% in group A and 60% in group B, indicating no significant difference between the two groups (p = 0.659). (Table 2)

Table 2. Comparison of the frequency distribution of urinary reflux type between study groups

		Group A	Group B	Chi-square test
Reflux type	Unilateral	21 (35%)	18 (30%)	p=0417*
	Bilateral	9 (15%)	12 (20%)	

*p value is not significant (p>0.05)

Therefore, there was no significant difference in age distribution, sex, and type of reflux between groups A and B.

The prevalence of urinary tract infections was 15% (n=9).

The frequency of recurrence was 8.3% in group A and 6.7% in group B, and the Fisher's exact test showed no significant difference in the recurrence frequency between the two groups (p = 0.500) (Table 3).

Table 3. Comparison of frequency distribution of UTI recurrence between study groups

		Group A	Group B	Chi-square test
	Yes	5 (8.3%)	4 (6.7%)	
	No	25 (41.7%)	26 (43.3%)	

*p value is not significant (p>0.05)

The recurrence rate of urinary tract infections was 80% and 20% in boys and girls in group A,

respectively. In group B, however, the prevalence of urinary tract infection was 50% in boys and girls. The mean age of the patients with UTI recurrence was 2.2±2.16 in group A and 1.75±0.95 in group B.

Discussion

Use of prophylactic antibiotics in children with recurrent urinary tract infections has always been controversial. Some studies have suggested that prophylactic antibiotics should not be used in these children, while some other studies suggest that prophylactic antibiotics should be used, especially in children with high-grade urinary reflux. For example, Cooper et al. (2000) found that despite the presence of vesicoureteral reflux, most children had a good prognosis after discontinuation of prophylactic antibiotics (13). Conway et al. (2007) also reported that antibiotic treatment was not associated with a reduced risk of UTI recurrence but was a definite risk factor for developing antibiotic-resistant urinary tract infections in children with recurrent UTIs (16). However, a study by Brandström et al. (2010) concluded that the recurrence rate of febrile urinary tract infections was significantly higher in girls over one year of age with reflux compared to other patients and that antibiotic as well as endoscopic prophylaxis treatment reduced the rate of infection in these patients (17). In addition, Craig et al. found that long-term, low-dose trimethoprim-sulfamethoxazole was associated with a reduction in urinary tract infections in susceptible children (18). A study by Kitchens et al. (2010) showed that discontinuation of antibiotic prophylaxis was associated with an increased risk of urinary tract infection (10). Although the results of a study by Roussey-Kesler et al. (2008) generally supported discontinuation of prophylactic antibiotics, it was not recommended in some treatment subgroups, especially in boys with grade 3 or higher urinary reflux (19). Moreover, long-term daily use of prophylactic antibiotics, in addition to imposing high costs on children's families and the health system, may not be tolerated by children. Long-term use of antibiotics has several side effects. Due to the problems of long-term use of prophylactic antibiotics, studies have been conducted to reduce the dose and frequency of prophylactic antibiotics in different diseases. For example, Ohata et al. compared oral TMP/SMX 8 mg/kg on two consecutive days of the week with daily pentamidine injection in children that could not tolerate daily antibiotics. The effect of these two regimens on the prophylaxis of Pneumocystis jiroveci pneumonia was the same in children receiving chemotherapy or stem cell transplants (14). As for the side effects of high-dose TMP-SMX for prophylaxis of PCP in non-Hodgkin's lymphoma, Keiko Ono et al. compared TMP-SMX 800 mg on two days a week versus TMP-SMX 400 mg daily. The median follow-up time was 29.4 months and the median duration of antibiotic use was 5.7 months. During this period, none of the 291 monitored patients showed any signs of Pneumocystis jiroveci pneumonia. In this study, similar to our study, the decrease in the number of antibiotic use was not associated with an increase in the recurrence of infection (15).

Based on the above and the results of the present study, we recommend that children who have recurrent urinary tract infections due to high-grade reflux and therefore should take prophylactic antibiotics may use antibiotics twice a week instead of daily antibiotic administration.This may increase the child’s acceptance of the drug and reduce the costs for the family and the health system. It may also reduce the side effects of long-term daily antibiotic administration in children with urinary reflux.

The most important limitation of this study was the lack of parental referral for urine tests. Therefore, it was tried to increase the awareness of parents about the importance of this test to maintain the health of their children and to encourage parents to perform this test periodically. In addition, all the costs of the tests were provided from the budget allocated to this project, which improved the participation of the patients.

The authors suggest that high-quality clinical trials with larger sample sizes and a double-blind design be performed to confirm the results.

The authors also suggest that further studies be conducted to identify subgroups of children with urinary reflux who are prone to urinary tract infections and therefore prone to kidney scarring and need antibiotic prophylaxis.

Conclusion

The results of this study showed no significant difference in the frequency of UTI recurrence between children who received prophylactic

antibiotic treatment twice a week and the children who received continuous antibiotic prophylaxis.

Conflict of Interest

Authors declare no conflict of interest.

Financial Support

This research received no external funding.

Ethics

The ethics committee of Mashhad University of Medical Sciences with the code IR.MUMS.REC.1394.298 approved this study also in International Clinical Trials Registry Platform (ICTRP) with code IRCT20201112049368N1 was accepted.

Authors Contributions

Concepts, A.T. and A.A. and Y.R.; Design, A.T. and A.A. and Y.R.; Definition of intellectual content, A.T. and A.A. and Y.R.; Literature search, A.T. and A.S.; Clinical studies, A.T. and A.S.; Experimental studies, A.T. and A.S.; Data acquisition A.T. and A.S.; Data analysis, A.T.; Statistical analysis, A.T.; Manuscript preparation, A.T.; Manuscript editing, A.A. and Y.R.; Manuscript review, A.A. and Y.R.

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