

## Comparing Intermittent and Continuous Antibiotic Administrations for the Treatment of Children with Vesicoureteral Reflux

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### Abstract

**Background:** Vesicoureteral reflux (VUR) is a high-prevalence and dangerous urinary system disorder. So, this study was performed to investigate the comparison between intermittent and continuous administration of antibiotics for the treatment of children with VUR.

**Methods:** In this study, 27 children with VUR referred to a nephrology clinic were included in the study. Children received cephalexin at 15 mg/kg once a day for 6 months, and after a 48-hour washout period, children received cephalexin at 15 mg/kg intermittently every other day for 6 months. Before the start of each treatment period, kidney and urinary tract ultrasounds and urine tests were performed for patients. In case of fever, dysuria, and frequent urination, urine test and culture were performed immediately, and in case of no symptoms, urine test and culture were performed monthly.

**Results:** Out of 27 children, 4 children (14.8%) had abnormal dimercaptosuccinic acid (DMSA) results, 18 (66.7%) had bladder reflux grade 4-5, 9 (33.3%) were less than 12 months, and 4 (14.8%) had recurrent urinary tract infections (UTI). The incidences of urinary tract infection did not differ, significantly, in continuous and intermittent antibiotic treatments ( $p>0.05$ ). There were no ultrasound changes after the treatment period.

**Conclusion:** There was no difference between intermittent and continuous administrations of antibiotics in the improvement of UTI symptoms in children with VUR. Therefore, the intermittent method can be used as a method with fewer toxicity or adverse effects in the treatment of these patients due to lower doses of antibiotic administration.

**Key Words:** Antibiotic, Urinary tract infection, Vesicoureteral reflux.

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## 1- INTRODUCTION

Reflux is important with respect to predisposing the kidney to infection and scarring. Large renal scars lead to renal dysfunction, renin-dependent hypertension, chronic renal failure, stunting, and even nephropathy (1). Vesicoureteral reflux (VUR) is abnormal urine flowing backward from the bladder to one or both ureters or toward the kidneys. It is a common congenital urinary tract congenital defect and its prevalence is approximately 0.4–2% in the general population (2, 3). VUR is an important risk factor for recurrent UTIs that cause kidney damage (reflux nephropathy), and is a major cause of chronic renal failure in children (1, 4). Therefore, the prevention of UTIs in patients with urinary reflux is very important to prevent reflux nephropathy (5). For prophylaxis, oral antibiotics including cephalexin, nitrofurantoin, and cotrimoxazole are used in doses lower than the therapeutic dose (1/3 once daily) (6). Indications of antibiotic prophylaxis in these children include primary VUR grade 4-5, primary VUR of any degree with recurrent urinary tract infection or with impaired bladder and intestinal function, and primary VUR of any degree in infants younger than 1 year (7).

In this regard, studies have shown that antibiotic prophylaxis is as effective as surgical treatment for the prevention of VUR and recurrent UTIs (8, 9). But some studies revealed that antibiotic prophylaxis increases the risk of infection due to antibiotic resistance (10) and long-term antibiotic prophylaxis cannot completely prevent urinary tract or wound infections and may be associated with unpleasant side effects (11). So controversies exist considering antibiotic prophylaxis in the management of children affected with VUR. Therefore, this study was performed to compare intermittent and continuous

administrations of antibiotics for the treatment of children with VUR.

## 2- MATERIALS AND METHODS

In this study, 30 children with primary VUR referred to Hajar Educational Medical Center and nephrology clinics in Shahrekord in 2021-2022 were enrolled. They were treated for 2 periods. In the first step, cephalexin was administered at 15 mg/kg once every night (for 6 months). After a 48-hour washout period, the second phase of cephalexin was administered at 15 mg/kg intermittently once every night (for 6 months) (12).

Before the start of each treatment period, renal and urinary tract ultrasounds as well as urine tests and cultures were performed. In case of symptoms of fever, burning urination, and frequent urination, urine test and culture were performed immediately, and in case of no symptoms, urine test and culture were performed monthly. Then, the two treatments were compared for UTIs by examining clinical symptoms and performing urine cultures and tests.

### 2-1. Inclusion and Exclusion Criteria

Children with primary VUR grades 4-5, infants under one year of age with primary VUR of any degree, children with primary VUR of any degree with recurrent urinary tract infection, and children with primary VUR of any degree with bladder and bowel dysfunction were included in the study.

Children with secondary VUR and children with VUR grades 1-3 without recurrent UTIs or intestinal and bladder dysfunction were excluded from the study.

### 2-2. Data Analysis

Descriptive analyses were reported as number (%), mean $\pm$  SD, or median (IQR) for qualitative, quantitative with normal distribution, and quantitative data without normal distribution, respectively. Statistical analyses were performed using

the McNemar test in SPSS version 20 and P-value <0.05 was considered statistically significant.

### 3- RESULTS

In this study, 30 children with VUR were enrolled and finally, 27 children completed the study. The mean age of children was 25.61 (2-96) months. Twenty-five (92.6%) children were girls and 2 (7.4%) were boys. Four children (14.8%) had abnormal dimercaptosuccinic acid (DMSA) results consisting of 2 cases of left kidney scar, 1 case of decreased

uptake of right kidney upper pole, and 1 case of multicystic dysplastic kidney.

Also, 18 patients (66.7%) had VUR grade 4-5 (the right ureter in five children, the left ureter in nine children, and both ureters in four children). Of the 27 children studied, 9 (33.3%) were under 12 months old and 4 (14.8%) had recurrent UTIs. Bladder and bowel dysfunction was not observed in any of the patients (**Table 1**). None of the 27 children studied had ultrasound changes after the treatment period.

**Table-1:** Descriptive statistics of demographic variables

| Variable                           | Subgroup   | Frequency (%) |
|------------------------------------|------------|---------------|
| Gender                             | Female     | 25 (92.6%)    |
|                                    | Male       | 2 (7.4%)      |
| Age category                       | < 12 month | 18 (66.7%)    |
|                                    | > 12 month | 9 (33.3%)     |
| DMSA scan result                   | Normal     | 23 (85.2%)    |
|                                    | Abnormal   | 4 (14.8%)     |
| Vesicoureteral Reflux              | 4-5 degree | 18 (66.7%)    |
| Recurrent urinary tract infections | No         | 23 (85.2%)    |
|                                    | Yes        | 4 (14.8%)     |

No cases of urinary tract infection were observed during the continuous prophylaxis period, and only 2 cases (7.4%) of UTIs were observed during the intermittent prophylaxis period, indicating that intermittent prophylaxis is as effective as continuous prophylaxis for prevention of UTIs. One patient under 12 months had recurrent UTIs.

The other patients were 5 years old, had grade 4-5 reflux, and developed urinary tract infection during treatment with intermittent antibiotics (**Table 2**). The rate of parental satisfaction with intermittent prophylaxis was 81.48%.

**Table-2:** Comparing the results between the groups of Intermittent and Continuous antibiotics

| Variable                 | Intermittent antibiotics | Continuous antibiotics | P-value |
|--------------------------|--------------------------|------------------------|---------|
| Positive urinary culture | 2 (7.4%)                 | 0 (0%)                 | 0.50    |
| Fever                    | 2 (7.4%)                 | 0 (0%)                 | 0.50    |
| Frequent urination       | 1 (3.7%)                 | 0 (0%)                 | 0.99    |
| Pyuria                   | 2 (7.4%)                 | 0 (0%)                 | 0.50    |

#### 4- DISCUSSION

In this study, no cases of fever, pyuria, frequent urination, and positive urine culture were observed during the period of continuous prophylaxis, and in the period of intermittent prophylaxis, only 2 cases (7.4%) of fever, pyuria, and positive urine culture were observed, which shows that intermittent prophylaxis is as effective as continuous prophylaxis for prevention of UTIs, although further studies are needed due to our small sample size. In this regard, a review study also showed that the administration of continuous and intermittent antibiotics had similar results in the treatment of UTI (13).

A study by Hori et al. (1997) on the efficacy and safety of low-dose intermittent trimethoprim-sulfamethoxazole in 35 children with VUR showed that none of the boys had recurrent urinary tract infection, while 2 out of 11 girls had recurrent UTIs during prophylaxis. Both girls were over 3 years old and had mild bladder instability. Finally, it was argued that low and intermittent doses of trimethoprim-sulfamethoxazole seem to be very effective in preventing recurrent UTIs among children with VUR (14). These results are consistent with the findings of our study.

In another study by Reddy et al. (1997), 43 children with VUR were randomly assigned to one of three groups: no antibiotic prophylaxis (control), antibiotic prophylaxis 3 times a week (intermittent prophylaxis), and daily antibiotic prophylaxis (continuous prophylaxis). The incidences of UTIs in the three groups of continuous prophylaxis, intermittent prophylaxis, and the control group were 1.13, 2.14, and 5.16, respectively, showing the effectiveness of continuous and intermittent prophylaxis in preventing UTIs. And, no significant difference was reported between continuous and intermittent prophylaxis (15). Moreover, in

line with our study, Costers et al. (2008) in a meta-analysis reported that continuous antibiotic prophylaxis has no advantage over intermittent antibiotics with respect to the prevention of recurrent UTIs or new kidney damage (16). Yet another study revealed that there were no statistical differences in clinical treatment, infection recurrence, super-infection post-therapy, safety outcomes, and mortality when continuous antibiotic administration was compared with traditional intermittent antibiotics (17).

Shiraishi et al. reported that the mean age at diagnosis of urinary reflux was significantly lower in children who developed an infection during prophylaxis treatment than in children without infection during prophylaxis treatment (18), which is in agreement with our findings; because one case of infection was observed in a child under 1 year of age in our study.

In the study of Hidas et al., in patients with primary VUR, reflux grade 4-5, which is the initial manifestation of urinary tract infection, was found to be the most important risk factor for UTIs while receiving prophylactic antibiotics (19).

In a study on the predictors of UTIs in 288 children with primary VUR under cotrimoxazole prophylaxis, UTIs developed in 38.5% of patients while receiving the prophylactic antibiotic; and gender, renal scar, and the severity of reflux were significantly associated with UTIs (20). Also in other studies, the association between high grade renal reflux and urinary tract infection has been well established (21, 22).

In a multivariate analysis, Soylu et al. observed that renal reflux grade 4-5 was an independent indicator of renal scarring that could potentially lead to urinary tract infection while receiving prophylactic antibiotics (23). Mingin et al. observed that the risk of developing UTIs while

receiving prophylactic antibiotics was higher in children whose DMSA scans showed renal scars (24).

It seems that the prophylactic effect of antibiotics is limited to the period of its use, and considering that children do not have sexual activity (as a precipitating factor of UTIs), intermittent strategy can be used as an effective method.

#### 4-1. Limitations of the study

One of the limitations of the present study is the small sample size, which is due to the limited number of patients with urinary reflux and the lack of cooperation on the part of the patients. It is recommended that in future studies, the effectiveness of continuous and intermittent antibiotic prophylaxis be investigated with larger sample sizes and longer follow-up periods; and if similar results to those of the present study are observed, this prophylaxis method can be suggested to be implemented for reducing antibiotics use and preventing their side effects, e.g., antibiotic resistance in children with urinary reflux in need of antibiotic prophylaxis.

#### 5- CONCLUSION

The incidence of UTIs during continuous and intermittent antibiotic administrations did not differ significantly in children with VUR. Therefore, the intermittent method can be used as an effective method with fewer side effects in the treatment of these patients due to lower doses of antibiotics administration. In addition, by lower antibiotics prescription, fewer costs are imposed on the healthcare system and the cases of antimicrobial resistance will also decrease.

#### 6- ETHICAL CONSIDERATIONS

The study protocol was approved by the ethics committee of Shahrekord University of Medical Sciences (IR.SKUMS.REC.1400.004). After explaining the objectives of the study,

written consent was obtained from the children's parents to participate in the study.

#### 7- ACKNOWLEDGMENTS

This article was derived from a research project approved by the Research and Technology Deputy of the Shahrekord University of Medical Sciences (approval no. 3562). Hereby, the researchers gratefully thank the patients who participated in this study.

#### 8- CONFLICT OF INTEREST

None.

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