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Comparison of Recurrent Urinary Tract Infection in Children with Different Grades of Vesicoureteral Reflux

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ABSTRACT

Background and Objective: Urinary reflux is the most common urological abnormality in children. About half of the children with urinary infection have urinary reflux at the same time. Considering the importance of urinary reflux in children and contradictory results reported regarding the relationship between different grades of vesicoureteral reflux and recurrent urinary tract infection, this study was conducted with the aim of comparing recurrent urinary tract infection in children with different grades of vesicoureteral reflux.

Methods: This cross-sectional study was conducted on 150 children with pyelonephritis and vesicoureteral reflux who refered to Amirkola Children's Hospital in 2011-2019. Reflux grades were determined by voiding cystourethrogram (VCUG) or direct radionuclide cystography (DRNC). Children were followed up for 2 years and in case of clinical symptoms with positive urine culture, they were considered as recurrent urinary tract infection.

Findings: Of the 150 children studied, 126 (84%) were girls and 24 (16%) were boys with a mean age of 27.17±11.53 months. 95 people (63.3%) had once, 37 people (24.7%) twice, 8 people (5.3%) three times, and 10 people (6.7%) four times experience of recurrent urinary tract infection. The odds ratio of recurrent urinary tract infection was more than two times higher in children with grade 3 and 4 reflux involvement than in children with grade 1 and 2 reflux (OR=3.20, 95% CI=1.05-9.75, p=0.041). However, there was no significant difference in recurrent urinary tract infection in children based on age at diagnosis, gender, and whether the reflux was unilateral or bilateral.

Conclusion: The results of the study showed that children with moderate and severe involvement of vesicoureteral reflux experience higher recurrent urinary tract infection compared to mild involvement.

Keywords: *Urinary Reflux, Urinary Infection, Pyelonephritis, Children*.

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Introduction

Vesicoureteral Reflux (VUR) is the most common urological abnormality in children (1-4) and 30-40% of children with urinary tract infections have urinary reflux (5-6). The most common reason for radiological examinations in children to determine the possibility of urinary reflux is urinary infection (7, 8), because reflux will cause recurrent urinary tract infection (7). Urinary reflux refers to the abnormal return of urine from the bladder to the upper part of the urinary system and is caused by dysfunction of the ureterovesical junction (9).

This backflow of urine from the bladder to the kidneys may cause urinary infection, kidney disease, chronic kidney failure, and hypertension. As reflux facilitates the transfer of microbes from the bladder to the kidneys, the presence of reflux can be a more predisposing factor in children with reflux compared to children without reflux (10).

In the study of Sorkhi et al., the results showed that urinary tract infection in 253 children led to hospitalization for about ten days (11). The reports of researchers are contradictory regarding the effect of different grades of reflux on the frequency of urinary infection recurrence. Dias et al. (12) and Chang et al. (13) showed that the rate of urinary infection in high grades is significantly higher than in low grades of reflux in children. On the other hand, Smellie et al. (14) reported that there is no significant difference between the recurrence of urinary infection in children with grade one to three reflux and children with grade four and five.

In the study of Mohammadi et al. among 220 children with urinary tract Infection and vesicoureteral reflux, the findings showed that more than half of the children had kidney scarring and complications (15). There are diverse opinions regarding the follow-up and treatment of children with vesicoureteral reflux. In a study, Sorkhi et al. showed that a high percentage of children under one year of age with reflux had spontaneous recovery, and early surgery at this age should be reconsidered (16). Medical treatment and the use of oral antibiotics until complete recovery or the use of surgical methods are the things that have been considered by researchers. The usual and effective treatment to prevent urinary infection is the use of oral antibiotics to prevent urinary infection, which must be considered due to the possibility of bacteria becoming resistant to the drug (17). Therefore, considering the importance of urinary reflux in children and the limited studies and contradictory results regarding the relationship between different grades of reflux and the frequency of recurrent urinary tract infection, as well as the lack of extensive studies in Iran, the present study was conducted to evaluate recurrent urinary tract infection in different grades of reflux during the years 2011-2019 among children who referred to the clinic and nephrology department of Amirkola Children's Hospital.

Methods

After approval by the ethics committee of Babol University of Medical Sciences with the code IR.MUBABOL.REC.1399.485, this cross-sectional study was conducted on children with pyelonephritis and urinary reflux referring to the clinic or nephrology department of Amirkola Children's Hospital in 2011-2019. Children between the ages of one month and 18 years with pyelonephritis and urinary reflux who underwent VCUG or DRNC urinary system radiography and the presence of VUR was confirmed, were included in the study. Children with cystitis, children whose VCUG or DRNC results were not available or did not refer for follow-up, and children with secondary VUR (VUR following neurogenic bladder or anatomical obstructions such as posterior urethral valve in which reflux is associated with high urinary system pressure) were excluded from the study.

Considering the diversity in the frequency difference of at least 12% in the recurrence of infection in first, second, fourth, and fifth grade reflux in previous studies (18, 19) and the formula for comparison of ratios, 95% confidence interval and 80% power, the sample size was estimated as 150 people. Convenience sampling was used and it was based on the inclusion criteria. The grade of urinary reflux in children was classified into 5 grades according to the International Reflux Study Committee:

Grade 1: Reflux into the non-dilated ureter

Grade 2: Reflux into the pelvis and calyces without dilatation

Grade 3: Reflux with mild to moderate dilation of the ureter, pelvis and calyces

Grade 4: Reflux along with the twisting of the ureter and expansion of the pelvis and calyces

Grade 5: Reflux along with twisting of the ureter, and severe expansion of the pelvis and calyces (20).

These five grades of reflux were divided into two classes. Grades one and two were classified as mild and grades three to five were classified as moderate-severe. Furthermore, recurrent urinary tract infection once to twice was placed in one class, while three and four times in another class (12, 21). In this study, urinary tract infection was considered in the following cases:

1. The growth of one type of bacteria greater than or equal to 10^5 by mid-stream urine test, along with a complete active urine test (such as pyuria or positive nitrites) and clinical symptoms (including fever, chills, side and lower abdominal pain, burning and frequent urination)
2. The growth of one type of bacteria greater than or equal to 10^3 through catheterization along with a complete active test and with clinical symptoms.
3. The presence of at least one type of bacteria in suprapubic aspiration, along with a complete active urine test and with clinical symptoms (11).

All urine samples were cultured in the usual culture medium of blood agar or chocolate agar and the type of microorganisms was identified. Children received prophylactic antibiotics with a dose of 1.2-1.3 every night, and U/A and U/C tests were repeated every 1-2 months. During the 2-year follow-up period, if there were clinical symptoms with a positive urine culture, it was recorded as recurrent urinary tract infection.

Children's information was extracted from existing files. Demographic information including age, gender and place of residence, medical information including medical history, age of urinary reflux diagnosis by month, grade of reflux (grade 1 to 5), and unilateral or bilateral reflux were recorded. In addition, the information related to the follow-up of children, including the frequency of urinary tract infection, the amount and type of receiving antibiotic prophylaxis was also recorded. Data were analyzed using SPSS software (Version 22.0, Chicago, IL, USA) and using descriptive and analytical indicators. T-Test and ANOVA were used to analyze quantitative data, and chi-square tests and Fisher's exact test were used to analyze qualitative data. In addition, logistic regression was used to adjust the effect of variables and $p<0.05$ was considered significant.

Results

The mean age of the studied children was 27.17±11.53 months. Of 150 children, 126 were girls (84%) and 24 were boys (16%). In evaluating the grade of reflux by separating left and right kidney, 117 children had left kidney involvement and 116 children had right kidney involvement.

Of 150 children, 95 people (63.3%) experienced recurrent urinary tract infection once, 37 people (24.7%) twice, 8 people (5.3%) three times, and 10 people (6.7%) four times. The five grades of reflux were divided into two classes. Grades one and two were classified as mild and grades three to five were classified as moderate-severe. In addition, recurrent urinary tract infection once and twice was placed in one class and

three and four times in another class (12, 21). The results of the study showed that recurrent urinary tract infection more than twice in children with moderate-severe reflux involvement was significantly higher than children with mild involvement (72.2% vs 43.9%) (p=0.024). Recurrent urinary tract infection more than twice in children with moderate-severe urinary reflux involvement on the left kidney was higher than children with mild involvement (63.6% vs 33%), but this difference was not significant. Furthermore, recurrent urinary tract infection more than twice in children with moderate-severe urinary reflux involvement on the right kidney was higher than children with mild involvement (42.9% vs 26.5%), but this difference was not significant (Table 1).

Table 1. Recurrent urinary tract infection in children with mild and moderate-severe reflux with left and right kidney involvement

Frequency of recurrence Degree of reflux	1-2 Number(%)	3-4 Number(%)	Total Number(%)	p-value
Left kidney				
Mild	71(67)	35(33)	106(100)	
Moderate-Severe	4(36.4)	7(63.6)	11(100)	0.054*
Total	75(64.1)	42(35.9)	117(100)	
Right kidney				
Mild	75(73.5)	27(26.5)	102(100)	
Moderate-Severe	8(57.1)	6(42.9)	14(100)	0.20**
Total	83(71.6)	33(28.4)	116(100)	

***Fishers exact test, ****Chi-Square**

Moreover, 83 people (55%) had unilateral reflux and 67 people (45%) had bilateral reflux involvement. There was no statistically significant difference in the frequency of recurrent urinary tract infection in children with moderate-severe reflux as compared to mild cases in terms of being unilateral or bilateral. Logistic regression analysis was used in order to investigate the ratio of the risk of recurrent urinary tract infection relative to the grade of urinary reflux and intervening variables such as unilateral or bilateral reflux, age at diagnosis and gender. As the results show, different grades of urinary reflux (moderate-severe, mild) increase the risk of recurrent urinary tract infection by 3.20 after adjustment with intervening variables (OR=3.20, 95% CI=1.05-9.75, p=0.041) (Table 2). In addition, there was no statistically significant difference in the frequency of recurrent urinary tract infection in children with moderate-severe reflux compared to mild cases according to age, age at diagnosis (less than 2 years and 2-5 years) and gender.

Table 2. Status of the odds ratio of recurrent urinary tract infection in the children of the study according to the grade of urinary reflux

Model Variable	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Reflux grade (moderate-severe, mild)	3.31 (1.11-9.83)	3.16 (1.05-9.43)	3.00 (0.99-9.01)	3.20 (1.05-9.75)

Model 1: Adjustment for gender, Model 2: Adjustment for gender plus age at diagnosis, Model 3: Adjustment for gender, age at diagnosis and unilateral or bilateral reflux

Regarding the type of microorganisms found in children's urine cultures, the results of the study showed that the highest frequency was related to Escherichia coli (66%), Klebsiella (4.6%) and Proteus (3.3%), respectively, and there was no significant difference in different grades of reflux.

Discussion

The results of the study showed that after adjustment of intervening variables, recurrent urinary tract infection more than twice in children with moderate-severe reflux involvement was significantly higher than children with mild involvement. However, no statistically significant difference was found in recurrent urinary tract infection in children with different grades of reflux in terms of the side of kidney involvement (right and left), age at diagnosis and gender.

The results of the study showed that recurrent urinary tract infection in children with moderate-severe involvement (three to five) of urinary reflux was significantly higher than mild involvement (one to two) of reflux. After adjusting the intervening variables of gender and age at diagnosis, this difference was significant. In a study by Panaretto et al., after adjusting the intervening variables, the risk of recurrent urinary infection in children with grade three to five reflux was found to be 1.5 times that of children with grade one and two, which was consistent with the present study (21). In the study of Dias et al., in a cohort study with 12 years of follow-up of 740 children, they reported that the high grade of reflux (four and five) is one of the independent factors in recurrent urinary tract infection in children, which is in line with the findings of the present study (12); the rate of urinary infection in high grades was 9.4 people per 1000 people and in lower grades (one to three) 8.7 people per 1000 people (p=0.03) (12). Furthermore, Chang et al. in their study among Taiwanese children showed that urinary reflux and age less than one year are two important factors for the occurrence of recurrent urinary tract infection (13). On the other hand, in the study of Smellie et al., no significant difference was found between recurrent urinary tract infection in children with grade one to three reflux and children with grade four and five, which was contrary to the findings of the present study (14). In addition, the results of the present study showed that the rate of children with moderate-severe involvement of the right kidney experienced a higher rate of recurrent urinary tract infection compared to children with mild involvement (42.9% vs 26.5%). In the involvement of the left kidney, this result was (66.6% vs 33%), although it was not statistically significant, which can probably be attributed to the number of study samples.

During the follow-up period in the present study, of 150 studied children, 95 people (63.3%) had at least one experience of recurrent urinary tract infection, but in the study of Keren et al., the risk of recurrent urinary tract infection in children with urinary reflux was 25% (22). The results of a study by Meena et al., which was conducted as a systematic review of 43 studies that included the examination of 920 children, showed that the frequency of recurrent urinary tract infection in children without urinary reflux was 41% and with urinary reflux was 49%, and no statistically significant difference was found (23). The reason for the difference can be attributed to the different follow-up period in the research and the age of the children in the study.

In the present study, approximately 60% of the children in the study had grades one and two of urinary reflux, and approximately 40% of the children in the study had grades three to five, which is in line with the study by Keren et al. In the study of Keren et al., 55% of children had urinary reflux with grades one and two (22). In addition, in the studies of Al-Ibrahim et al. and Muinuddin et al., about 75% of Saudi and Thai children with reflux problems had grades one to three (24, 25). However, it was not consistent with the

studies of Peru et al., Salih et al., and Zaki et al. In these studies, less than 20% of the children had reflux grade one and two (18, 19, 26). Considering the role of genetics and its autosomal dominant transmission in the occurrence of vesicoureteral reflux (27), this difference can be justified.

In the present study, the highest frequency of organisms found was related to Escherichia coli (65.4%) and Klebsiella (4.6%). In a study conducted by Yılmaz et al., Escherichia coli with a frequency of 73% and Klebsiella with a frequency of 10% were the most common organisms, which was consistent with the findings of the present study (28). Zhu et al. stated that approximately 80-90% of acute cases of recurrent urinary tract infection in children are caused by this organism (29). In this sense, the current study was in line with these studies. Regarding this significant frequency, the reason can be explained that Escherichia coli is a part of the natural intestinal flora.

In the present study, the mean age of children was 27.17 months and most of the patients were girls (83.7%), and at the time of diagnosis, 53.6% of the patients had unilateral reflux. In the study by Chang et al. (13) in Taiwan, 86.6% of children with urinary tract infection were under three years old. In the present study, the limited volume of samples, especially in grades four and five of urinary reflux, and lack of information were among the limitations of this study. It is recommended to examine children at multiple time intervals in the form of cohorts in future studies.

The results of the present study showed that children with moderate-severe involvement experience higher urinary tract infection recurrence compared to children with mild involvement. Due to the limited number of children, especially in grades four and five of urinary reflux, no definite conclusion can be made. Furthermore, there is no significant relationship between the severity of recurrent urinary tract infection and gender, age at diagnosis and side of kidney involvement.

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