



# Evaluation of the relationship of the time of vesicoureteral reflux between renal scar development and endoscopic treatment success in early childhood

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## Abstract

**Aim:** It is aimed to evaluate the effect of reflux time in primary VUR in terms of predicting endoscopic treatment success and treatment timing in VUR management. Vesicoureteral reflux (VUR) is an important cause of urinary tract infection and chronic renal disease. Voiding cystourethrography (VCUG) is the gold standard diagnostic test in the diagnosis of VUR. In recent years, new parameters related to VCUG have been more objectively studied to evaluate the clinical prognosis.

**Materials and Methods:** In our study, the records and imaging findings of children with primary VUR who underwent VCUG examination between 2012 and 2019, who were treated with endoscopic injections, were retrospectively reviewed. Forty-one children (67 renal units) were included in our study. Patients with preoperative VCUG, urinary ultrasonography, dimercaptosuccinic acid (DMSA) renal scan, and post-operative control VCUG were included in this study.

**Results:** Patients with preoperative VUR grade 1-2 were divided into two groups as “low grade” and patients with stage 3-4-5 as “high grade”. In the general patient population, endoscopic success rates in terms of renal unit deficit were found to be 46.3% (31/67). When the subgroup was analyzed, the endoscopic treatment success rate was 72.2% (13/18) in the low-grade group, versus 36.7% (18/49) in the high-grade group ( $p = 0.010$ ). In the multivariate logistic regression analysis performed to identify independent predictors of scarring, reflux degree and reflux time were found to be independent predictors of scarring.

**Conclusion:** In our study, we found that in VCUG evaluated preoperatively, VUR time as well as VUR grade were effective on endoscopic success rate and scar development. Based on these results, it could be thought that VUR time may be effective in selecting the best candidates for surgery and in the management and timing of treatment of VUR patients.



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## Introduction

Primary vesicoureteral reflux (VUR), seen in 0.4-1.8% of childhood, is a congenital anomaly originating from the vesicoureteral junction [1]. The gold standard test in the diagnosis of VUR is voiding cystourethrography (VCUG). VCUG grading is done according to International Reflux Study criteria. Although there are some determinants that could lead to impaired clinical outcomes, including age,

bilateral or unilateral involvement of VUR, the most frequently used one is still reflux grade [2]. The first option in treatment is endoscopic injection. In high-grade bilateral reflux, endoscopic injection therapy may be useless, and reimplantation surgery may be required [3-6].

Management of VUR remains controversial because of difficulties in identifying potential risks, unnecessary surgical treatments, or inadequate interventions [2]. Renal scarring associated with VUR is known as reflux nephropathy (RN) [7]. In recent studies, it has been reported that the probability of the occurrence of focal DMSA cortical defects in children younger than 1 year is lower and the probability of

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having focal DMSA defects increases with advancing age [8-10]. In recent years, new parameters related to VCUG have been studied to evaluate the clinical prognosis more clearly, and one of them is reflux onset time, accepted as a predictor of spontaneous resolution in VUR [11]. Nasrallah et al. [12] showed the relationship between resistance to spontaneous resolution and low bladder volume in their study with radionuclide cystography. In another study, it was stated that, after endoscopic injection, the timing of VUR could be a predictor of VUR resolution in children with primary VUR [13]. Papachristou et al. [14] found that children diagnosed with VUR in infancy, with a bladder pressure of less than 20 cm H<sub>2</sub>O at the onset of reflux, or with a bladder volume less than 45% of total bladder capacity, were more likely to have VUR after 3 years of age, and stated that it is an important prognostic factor for reflux resolution. It is aimed in our study to evaluate the effect of reflux time on renal scar development and endoscopic treatment success and its contribution to treatment management in VUR detected in early childhood.

## Materials and Methods

Our study was a retrospective, single-center study between 2012 and 2019. It was approved by the Inonu University Health Sciences Non-Invasive Clinical Research Ethics Committee (Decision no: 2021/2156) and planned in accordance with the Declaration of Helsinki. The records and imaging findings of children with primary VUR who underwent VCUG examination and endoscopic injection therapy in our institution were retrospectively reviewed. A total of 41 children (67 renal units with VUR) with preoperative VCUG, urinary ultrasonography, dimercaptosuccinic acid (DMSA) kidney scan and post-operative control VCUG were included in this study. In order to reduce the effect of late diagnosis age on the sequelae changes, children under 5 years of age were included in the study (8-10). Those with previous VUR surgery, congenital urinary tract pathologies that can cause anatomical VUR, and patients with neurological disorders were not included in the study. To detect an effect size of 0.10 at alpha error of 0.05 and statistical power of 0.80, 39 participants are required for our study.

Patient age, gender, preoperative VUR grade, laterality (unilateral or bilateral), reflux onset time at diagnosis were recorded. In all cases, DMSA examination was performed at least 3 months later in patients with signs of infection to exclude a transient focal ischemic image due to acute pyelonephritis. In the preoperative DMSA, scar formation was recorded as positive in the presence of hypoactive focal area, contour irregularity compatible with sequelae, and lobulation. Impaired differential uptake was considered abnormal if there was more than 10% difference between renal units [15]. Concurrent USG findings with the preoperative first VCUG were evaluated according to the urinary tract dilatation (UTD) classification.

A negative urine culture was obtained for VCUG application. A single anterior-posterior view was obtained covering the kidneys, ureters, and bladder. Bladder capacity was calculated as  $[\text{age} + 2] \times 30 \text{ ml}$  and  $\text{kg} \times 7$  for those younger than 2 years (16). During the filling of the bladder, in addition to the standard images of the

anterior-posterior, right and left oblique positions and the urethra during voiding, initial reflux images were evaluated. According to the images of the bladder full of reflux, it was evaluated over three groups as (i) less than 50%, (ii) 50% and more, (iii) during voiding (17). Each kidney unit was evaluated separately in VCUG bilateral reflux cases. As the control VCUG, the first examination performed at least 3 months after the endoscopic injection was evaluated. Absence of reflux according to control VCUG was accepted as radiological success.

## Statistical analysis

All statistical analyzes have been conducted using the JASP 0.14.1 software. Continuous variables were given as mean and standard deviation, categorical variables as numbers and percentages. The Shapiro-Wilk test was used to determine whether the data fit the normal distribution. Differences between groups were evaluated according to the type of data, with t test, Mann-Whitney U test and one-way analysis of variance (ANOVA) for continuous variables, and with chi-square test, Fisher's exact test and Kruskal-Wallis test for categorical variables. We also used cross-tabulation with chi-square test to compare our categorical data. Pearson or Spearman correlation analysis was used according to the data type to evaluate the correlation of the data. The followings were included as variables affecting the presence of DMSA scarring: age at first complaint, gender, reflux degree, reflux time, urethra and laterality were included in the Cramer's V test as univariate analysis. A P value of <0.05 was considered statistically significant.

## Results

Forty-one children (67 renal units) with endoscopic treatment for primary VUR were recruited to our study. Demographic data of the patients are shown in Table 1. According to the preoperative VUR grade, the patients were divided into two groups as grade 1-2 as "low grade" and

**Table 1.** Demographic data of the patients.

Parameters	Value
Age, month	25.6 ± 19.2
Gender, male	24 (58.5%)
Laterality, bilateral	52 (77.6%)
Grade n,%	
GRADE I	2 (3.0%)
GRADE II	16 (23.9%)
GRADE III	27 (40.3%)
GRADE IV	18 (26.9%)
GRADE V	4 (6.0%)
Time n,%	
Early	28 (41.8%)
Late	25(37.3%)
Voiding	14(20.9%)
Function, %	47.8±24.5

**Table 2.** Characteristics of the groups according to time.

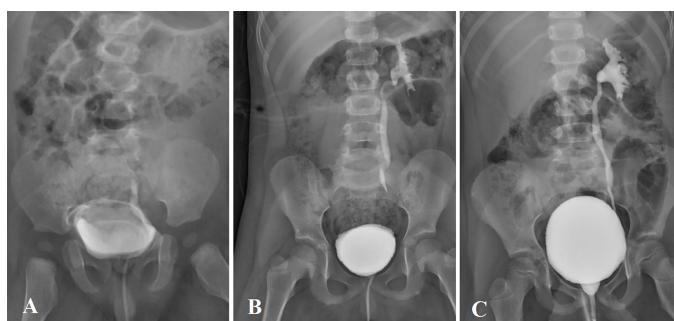
	Group 1 (n=28)	Group 2 (n=25)	Group 3 (n=14)	P value
First complaint, month	17.6±19.3	16±20.2	15.5±17.6	0.929
Function, %	43.4±26.1	51.9±23.2	49.2±23.6	0.443
Scar, positive, (n, %)	19 (67.9%)	12 (48.0%)	2 (14.3%)	0.005 $\beta$
Surgical success, (n, %)	6 (%21.4)	14 (%56.0)	11 (%78.6)	0.001 $\alpha$ , $\beta$
Involvement, bilateral, (n, %)	26 (92.9%)	16 (64.0)	10 (71.4%)	0.035 $\alpha$
VUR grade, high, (n, %)	25 (89.3%)	18 (72.0%)	6 (42.9)	0.005 $\beta$

VUR: Vesicoureteral reflux.  $\alpha$ = p< 0.05 between Group 1 vs. Group 2,  $\beta$ = p< 0.05 between Group 1 vs. Group 3.

**Table 3.** Evaluation of the variables affecting the scar by regression analysis.

	Univariate analysis		Multivariate analysis		
	Cramer's V	P value	OR	%95 CI	P value
Gender	0.138	0.260			
Time	0.400	0.005	0.386	0.161 – 0.925	0.033
Grade	0.462	<0.001	7.473	1.401–39.847	0.019
First complaint	0.544	0.285			
Laterality	0.028	0.820			
UTD	0.127	0.584			

UTD: Urinary tract dilatation.

**Figure 1.** Classification of reflux according to the filling status. A: Early filling (Less than %50), B: late filling (%50 or more), C: voiding.

patients with stage 3 and above as “high grade”. The low-grade group was 18 (26.9%) renal units, and the high-grade group was 49 (73.2%) renal units. In the general patient population, endoscopic success rates for the renal unit were 46.3% (31/67). When the subgroup was analyzed, the endoscopic treatment success rate was 72.2% (13/18) in the low-grade group, versus 36.7% (18/49) in the high-grade group (p = 0.010).

Patients were classified according to the degree of reflux as follows: “early filling group” (Group 1) if the bladder volume is less than half of the expected bladder capacity for age at the time of filling, “late filling group” (Group 2) if the bladder volume is more than half, and if observed during voiding phase of the VCUG, it was defined as the “voiding group” (Group 3) (Figure). When the groups were compared according to reflux time, no significant difference was found between the groups in age at first complaint, DTPA uptake difference, USG findings (according to UTD classification) (Table 2). There was

a significant difference between Group 1 and Group 3 in terms of renal scar development and laterality (p = 0.003, p=0.035, respectively). There were significant differences in endoscopic surgery success rates for group 1 vs. group 2 (p=0.022) and for group 1 vs. group 3 (p=0.001).

The results of the multivariate logistic regression analysis performed to identify the independent predictors affecting the renal scar are shown in Table 3. In the regression analysis, reflux degree (OR:7.473, CI 95% 1.401-39.847, p=0.019) and reflux time (OR:0.386, CI 95% 0.161-0.925, p=0.033) were found to be independent predictors of renal scarring.

## Discussion

The main results of our manuscript are as follows, (i) the success rate was moderate in those who had endoscopic treatment for primary VUR, (ii) the renal scar rate was high in the early filling group in terms of reflux time, but the surgical success rate was low in the same group, (iii) finally, the degree of reflux and time of reflux were determined. were found to be independent predictors of scarring.

Regarding the diagnosis and treatment of VUR in children, there are still debates about which patients should be evaluated and treated for reflux. The decision for surgery in VUR is made by considering the risk of UTI, the risk of parenchymal scar development, and the possibility of spontaneous recovery. Higher grade reflux is linked with decreased resolution of spontaneous VUR and increased rates of renal scarring [18-20].

Many studies have shown that the duration of VUR is a substantial prognostic factor for spontaneous resolution in primary VUR children (11,14,21). While some studies have found that reflux is probably to resolve spontaneously

in children with reflux at lower bladder volumes, Nasrallah et al. [12] showed an association between resistance to spontaneous resolution and low bladder volume [22,23]. Lee et al. [13] showed that VUR time in preoperative VCUG could be a predictive factor of VUR resolution after endoscopic injection and interpreted that filling reflux more likely requires surgical intervention in children with primary VUR. In our study, endoscopic success rate was found to be lower in early filling reflux, which is consistent with previous studies.

VUR is known to result in urinary tract infection (UTI) and renal scarring. Shaikh et al. reported that VUR patients have higher relative risk for acute pyelonephritis (APN) compared to those without VUR, and children with grade 3 or higher VUR have an increased risk for renal scarring when compared to those with lower grades [24]. In another review, Faust et al. reported an increased risk for renal scar formation after APN in the renal unit with VUR [25]. In this study, the renal scarring rate was lower in mild VUR. In addition, the scar rate was significantly higher in early filling reflux. The reason for more scarring in children with VUR in early filling may be the longer exposure time to bacteria in the presence of urinary tract infection. In another study, early VUR was associated with anatomically inadequate ureteral orifices, which may facilitate the entry of bacteria from the bladder into the upper urinary tract [26]. In our study, bilaterality was more common with early filling reflux. Previous studies have found that filling reflux happens at comparatively lower bladder volume and pressure, and voiding reflux occurs at relatively larger bladder volume and pressure, and these may possibly be associated with immaturity of the lower urinary tract. Therefore, it has been hypothesized that this filling reflux perhaps represents an interior defect that may spontaneously resolve [27,28].

RN may originate from a single pyelonephritis (PN) attack or may develop over time [29,30]. RN may also be caused by abnormal kidney development end up with focal renal hypoplasia or dysplasia [31]. The DMSA scan is the gold standard test in the diagnosis of kidney scar, but it can not identify congenital RN from acquired RN. Many studies have reported that the risk of renal scarring with PN is higher in infants than in older children [32-34]. Some studies have explored this opinion, considering that younger may not have a higher risk for renal scarring [6,7]. Mattoo et al. reported that renal scar formation is more common in older children than younger ones and in those with a second attack of urinary tract infection [35]. In recent studies, there is a lower probability of focal DMSA cortical defects in children younger than 1 year of age, and it has been reported that the probability of having a focal DMSA defect increases with each year of life [8-10]. We think that the fact that we did not find a relationship between the development of renal scar and the age at diagnosis in our study is due to our limited age range.

Our study has several limitations. This retrospective study has small number of patients treated at single center. We studied the factors linked with radiological success after endoscopic surgery on a ureteral rather than a patient basis. Bladder volume evaluation was approximate based on the full bladder and was evaluated by a single

observer. A clearer assessment can be made by recording the contrast dose given during reflux. Without DMSA scintigraphy prior to UTI, it is impossible to definitively distinguish between congenital and acquired damage, and therefore our findings may exaggerate acquired damage.

## Conclusion

In our study, we found that in preoperative VCUG, VUR time, as well as VUR grade, were effective on endoscopic success rate and scar development. Treatment management is critical because of the low success and high scarring rate in children with filling reflux as well as high-grade VUR. Better endoscopic surgical outcomes can be expected in children with VUR with high-grade VUR. It is conceivable that VUR time may be effective in the management and timing of treatment when selecting the best candidates for surgery.

## Ethics approval

Our study was approved by the Inonu University Health Sciences Non-Invasive Clinical Research Ethics Committee (Decision no: 2021/2156).

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