

CORRELATION OF SEVERITY OF VESICO-URETERAL REFLUX WITH RENAL SCARRING IN CHILDREN WITH RECURRENT URINARY TRACT INFECTIONS

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ABSTRACT

Objective: To find out the correlation of severity of vesico-ureteral reflux with the frequency of finding renal scar in children with recurrent urinary tract infections.

Study Design: Correlational study.

Place and Duration of Study: Department of Paediatrics Nephrology, Children Hospital, Lahore, from Jan 2016 to Jun 2017.

Methodology: Seventy children (140 kidney units) of 1 month to 10 years of age with ≥ 2 episodes of urinary tract infection within a period of 1 year and having vesico-ureteral reflux of Grade III, IV and V were included. Data of each kidney unit was taken regarding grades of vesico-ureteral reflux, number of urinary tract infection episodes, presence or absence of renal scar on dimercaptosuccinic acid scan. Data was analyzed using SPSS-22. Correlation between vesico-ureteral reflux severity and renal scarring was seen by Spearman rank correlation coefficient.

Results: Out of total 70 patients, 37 (52.9%) were males and 33 (47.1%) were females. Out of 140 kidney units, 53 (37.8%), 48 (34.3%) and 39 (27.9%) had a vesico-ureteral reflux of grade-III, grade-IV and grade-V respectively. Renal scarring was present in 51 (36.4%) kidney units. Out of these, 11 (7.8%) were grade-III, 19 (13.6%) were grade-IV and 21 (15%) were grade-V vesico-ureteral reflux kidney units. With increasing severity of vesico-ureteral reflux, presence of renal scar increased (correlation coefficient = 0.279, p -value 0.001). Renal scarring was present in 25 (35.8%) of right sided and 26 (37.1%) of left sided kidneys. The positive correlation between vesico-ureteral reflux severity and renal scarring was significant in left kidneys ($p=0.002$) but insignificant in right kidneys ($p=0.11$). Study also revealed significant positive correlation between vesico-ureteral reflux severity and number of urinary tract infection episodes ($p<0.001$).

Conclusion: There was a significant positive correlation between degree of vesico-ureteral reflux severity and presence of renal scarring in children with recurrent urinary tract infections. The vesico-ureteral reflux severity was also significantly correlated with number of urinary tract infection episodes a kidney unit suffered from.

Keywords: Renal scar, Urinary tract infection, Vesicoureteral reflux.

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INTRODUCTION

Urinary tract infection (UTI) is one of most common diseases of kidneys and also the biggest causes of morbidity in children especially in a developing country like Pakistan^{1,2}. In children, UTI may lead us to suspicion that any structural abnormality is there in UTI which have caused UTI episode to occur. Although, urinary tract infection can be the first symptom of obstructive uropathy or bladder dysfunction, the most common abnormality that can cause UTI is vesico ureteral reflux (VUR)³. VUR is a condition of the urinary tract in which urine flows in the opposite direction abnormally, from the bladder, through the ureter to kidney. One or both ureters may be involved. It is one of the most common urological anomalies in children⁴. Its prevalence rather varies. In healthy children it is 1.3% while after urinary tract infection, it is 8-50%². The incidence of VUR is more in infants and newborn children after UTI i.e. 36-49%². VUR is graded into

different grades according to severity from grade-I as mild to grade-V as severe⁵. Renal cortical scar may occur by either recurrent UTI with VUR or VUR without UTI, irrespective of their grading. Higher the grade of VUR in children having UTI, higher the chances that their kidneys (one or both) may develop renal scarring².

Ultrasonography (USG) has been used to detect VUR in several studies⁶, but it failed to detect lower grades in many studies⁷. That is why VUCG (voiding urethrocytogram) is the primary diagnostic modality for identifying vesicoureteral reflux^{5,8}. The test which is accepted gold standard for diagnosing renal scar is now a days dimercaptosuccinic acid renal scan (DMSA Renal Scan)⁹.

In the case of unavailability of Doppler ultrasonography, DMSA renal scan is used for ruling out of acute pyelonephritis according to NICE clinical guidelines¹⁰. Sensitivity of ultrasonography and DMSA for detecting VUR were 75% and 84% respectively.

In Pakistan almost no studies have been conducted to find out a correlation of VUR with presence or

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absence of renal scarring. Internationally, the DATA in this regards have been very much less. In one study by Supavekin *et al*¹² it was observed that DMSA scan proven renal scar had a significant correlation with recurrent UTI as well as VUR. Hence it was recommended that DMSA scan should be done in all children having Vesicoureteral reflux and/or re-current urinary tract infections irrespective of their age and sex in order to detect renal scarring and follow up future complications.

In Pakistan, despite of high disease burden of UTI in children, there is almost no available DATA regarding correlation of VUR with absence or presence of renal scar in patients having UTI. So we wanted to conduct a study to find out the correlation of severity of VUR with the frequency of finding renal scar in children affected with recurrent urinary tract infections.

METHODOLOGY

It was a descriptive correlational study in which non probability, purposive sampling was done. This study was conducted in the department of Paediatric Nephrology, Children Hospital Lahore from Jan 2016 to June 2017. Sample size of 140 kidney units was calculated by using 90% confidence interval and 7% margin of error with expected population proportion of UTI patients detected to have VUR as 51.39% in previous study².

A total of 70 children of ages between 1 month to 10 years presenting with recurrent UTI (two or more than two episodes) and those having VUR of Grade III, IV and V were included in the study. Children having UTI with immunocompromised status, those with asymptomatic bacteriuria, and with Grade I and II VUR were excluded from the study. As each child was having two kidney units, so total 140 kidney units (including right and left kidneys) were under study.

Recurrent UTI was defined as two or more than two symptomatic UTI within 12 months following clinical resolution of each previous UTI after therapy. For labeling UTI, Urine culture was said to be positive depending upon method of collection. In midstream urine, culture was taken positive if pus cells were $\geq 100,000$ CFU/ml. In case of suprapubic aspiration, if gram +ve then few thousand organisms were taken as positive culture and if gram -ve organism, then any number was taken to be positive. In catheterized specimen 50,000CFU/ml pus cells were taken as positive culture. Renal Scar was defined as focal or diffuse areas of diminished uptake of isotopes on DMSA¹¹⁻¹³.

VUR was divided into five grades according to international classification⁵. Urine refluxing into a non-dilated ureter was taken as grade-I VUR. Still non dilated ureter with reflux of urine into upper collecting system was taken grade-II. Grade-III VUR was defined as Reflux into dilated ureter as well as blunting of calyceal fornices while grade-IV was a VUR that caused ureter to dilate grossly. Grade-V was massive reflux causing significant dilatation and tortuosity of ureters as well as loss of papillary impression⁵.

Voiding cystourethrography (VUCG) of all the children was done at the end of antimicrobial therapy (given for 10-14 days) or after urine became sterile in urinalysis or urine culture. Those who were having VUR of grades-I and grade-II in VCUG were excluded.

Dimercaptosuccinic acid (DMSA) renal scan was performed for each patient (so for each kidney unit) after 3-6 months of diagnosis. The scan was performed by injection of technetium 99 dimercaptosuccinic acid and views were taken by low energy high resolution gamma camera, keeping the patient in prone position. Renal scar were defined by focal or diffused areas of diminished uptake of isotopes¹⁴.

The data were analyzed by using software SPSS-22. The variables under study were age, gender, grades of VUR, presence or absence of renal scar and side of kidney (left or right). The variables were analyzed through simple, descriptive statistics. Quantitative variables like age were presented by mean and standard deviation. Qualitative variables like gender, grades of VUR, presence or absence of renal scar were represented as frequencies and percentages.

Each group having different grades of VUR severity i.e. grade-III, grade-IV and grade-V were looked and compared for presence or absence of renal scarring. Frequencies of the absence or presence of renal scarring were then correlated with increasing grades of severity of VUR using spearman rank correlation test. Correlation between VUR severity and renal scar was also seen in both kidneys separately by Spearman rank correlation test. Moreover spearman rank correlation test was also applied between number of UTI episodes and VUR as well as UTI episodes and presence of renal scar to reveal any correlation if present. A *p*-value ≤ 0.05 was considered as a significant value.

RESULTS

Out of a total of 70 patients, 37 (52.9%) were males and 33 (47.1%) were females. Mean age of the study subjects was 5.4 ± 2.5 years. Dividing into age

groups of <1 years, 1-5 years and 5-10 years, frequencies were 3 (4.3%), 28 (40%) and 39 (55.7%) respectively. Regarding fever, mean body temperature of the study population was 101.9 ± 1.2°F. Maximum 35 (50%) patients had fever of 100-102°F followed by 30 (42.9%) patients who were having temperature of >102°F. Dysuria was present in 46 (65.7%) of patients. Dividing into groups according to total leukocyte counts (TLCs), maximum 34 (48.6%) patients had a TLCs between 10000 -15000 (table-I).

Out of total 140 kidney units, 53 (37.8%), 48 (34.3%) and 39 (27.9%) were having VUR of grade-III, grade-IV and grade-V respectively. Renal scarring was

Taking right and left kidney units separately, VUR of grade-III, grade-IV and grade-V were present in 29 (41.4%), 21 (30%) and 20 (28.6%) of right sided kidneys respectively while 24 (34.3%), 27 (38.6%) and 19 (27.1%) of left sided kidneys respectively. Renal scarring was present in 25 (35.8%) of right sided and 26 (37.1%) of left sided kidney units. Applying Spearman rank correlation coefficient between VUR grades and presence of renal scar separately in each sided kidney, there was a significant positive correlation between severity of VUR and presence of renal scar in left sided kidneys ($p=0.002$) but this correlation was not significant in right sided kidneys ($p=0.111$).

Table-I: General characteristics of the study subjects.

		n (%)		n (%)	
Sex	Male	37 (52.9)	Dysuria	Absent	24 (34.3)
	Female	33 (47.1)		Present	46 (65.7)
Age (in years)	<1	3 (4.3)	TLCs	5000-10000	23 (32.8)
	1-5	28 (40)		10000-15000	34 (48.6)
	5-10	39 (55.7)		>15000	13 (18.6)
Fever	<100	05 (7.1)	Total		70 (100)
	100-102	35 (50)			
	>102	30 (42.9)			

Table-II: Correlation of renal scarring with different grades of VUR.

		Vesico Ureteral Reflux			Total n (%)	Spearman Rank Correlation
		Grade-III	Grade-IV	Grade-V		
Renal Scarring Absent	Frequency	42	29	18	89 (63.6%)	Coefficient = 0.279 p -value = 0.001
	%age within VUR group	79.2%	60.4%	46.2%		
	%age within total kidney units	30%	20.7%	12.9%		
Renal Scarring Present	Frequency	11	19	21	51 (36.4%)	
	%age within VUR group	20.8%	39.6%	53.8%		
	%age within total kidney units	7.8%	13.6%	15%		
Total		53 (37.8%)	48 (34.3%)	39 (27.9%)	140 (100%)	

Table-III: Correlation of number of UTI episodes with VUR severity and renal scarring.

Number of UTI episodes	Vesico Ureteral Reflux			Renal Scarring		Total n (%)
	Grade-III n (% within UTI group)	Grade-IV n (% within UTI group)	Grade-V n (% within UTI group)	Absent n (% within UTI group)	Present n (% within UTI group)	
2	19 (55.9%)	12 (35.3%)	3 (8.8%)	25 (73.5%)	9 (26.5%)	34 (24%)
3	25 (43.1%)	21 (36.2%)	12 (20.7%)	37 (63.8%)	21 (36.2%)	58 (41%)
4	8 (19%)	15 (35.7%)	19 (45.2%)	25 (59.5%)	17 (40.5%)	42 (30%)
5	1 (16.7%)	-	5 (83.3%)	2 (33.3%)	4 (66.7%)	6 (4%)
Spearman Rank correlation	Correlation coefficient = 0.388 p -value = <0.001			Correlation coefficient = 0.146 p -value = 0.085		140 kidney units

present in 51 (36.4%) kidney units. Out of these 51 kidneys having renal scar, 11 (7.8%) kidney units were having grade-III VUR while 19 (13.6%) and 21 (15%) were having VUR of grades IV and V respectively. So with increasing severity of VUR chances of finding renal scar increased. Applying Spearman rank correlation test between VUR severity and presence of renal scar, coefficient of correlation was 0.279 and p -value was 0.001 (table-II).

Considering UTI episodes, children had 2-5 episodes of UTI. Out of total 140 kidneys, maximum number ($n=58$) had 3 episodes of UTI whereas only 6 kidneys had 5 episodes of UTI. It was observed that episodes of UTI were more in patients with high grade of reflux. Although only six kidneys had 5 episodes of UTI but five (83.3%) out of these had grade-V VUR. As compared to this only 3 out of 34 kidneys (8.8%) with 2 episodes of UTI had grade-V VUR. p -value by spear-

man rank correlation coefficient between number of UTI episodes and VUR severity was <0.001 . Similarly, percentage of renal scarring increased progressively with increased episodes of recurrent UTIs (table-III). So renal scar was found in 26.5% of kidneys with 2 episodes UTI which increased to 66.7% in kidneys having 5 episodes of UTI. A p -value by spearman rank correlation coefficient between UTI episodes and renal scar was 0.085 (table-III).

DISCUSSION

One of the most common congenital abnormalities of urinary tract is VUR. Although its prevalence is reported to be 1%, some believe it is higher than described⁴. VUR is the most common predisposing factor for UTIs and UTI in turn leads to scarring of kidneys called renal scar². According to severity, VUR can be graded from grade-I to grade-V⁵. In the present study, we wanted to find out a correlation if present between VUR severity and renal scarring in patients having recurrent UTI episodes.

We took 70 patients (and thus 140 kidney units as each patient had one left and one right kidney) with recurrent UTIs and diagnosed to have VUR. The patients having vesicoureteral reflux of grade-I and grade-II were excluded from the study because we don't routinely do DMSA renal scan of patients with these VUR grades. This is because most of these patients resolve without any permanent damage to kidneys. In kidneys having VUR of grades III to V, it was observed that the frequency of kidneys having scarring on DMSA scan increased with increase in the grade of VUR. Renal scarring was present in total 36.4% of kidneys out of which grade-III VUR kidneys were 7.8% and grade-V VUR kidneys contributed 15%. Also when we applied spearman rank correlation coefficient test, the severity of VUR and presence of renal scar was found to be positively correlated with coefficient of +0.279 and significance value of 0.001. Both these were the same results found in the study by Supavekin *et al*¹² and RIVUR trial by Mattoo *et al*⁴. Another recent study by Yilmaz *et al* showed that renal scarring was not only significantly associated with presence of VUR but also more renal damage was seen in VUR with higher grades¹⁵. Snodgrass *et al* found higher risk of renal scar in UTI patients having VUR irrespective of its grades but the risk was even higher with grades IV and V¹⁶.

Comparing right and left kidneys, we found that the frequency of presence of renal scarring increased with increase in severity of VUR both in left and right kidneys. Using spearman rank test showed that corre-

lation between VUR severity and renal scar was significant ($p=0.002$) in left sided kidneys and insignificant in right kidneys ($p=0.111$). These findings were a bit different from the studies which were previously performed by Supavekin *et al*¹² and Rahman *et al*². These studies showed significant correlation between VUR severity and renal scarring in both sided kidneys.

Regarding number of UTI episodes that each patient and thus each kidney unit had, it was found that with increasing number of UTI episodes, percentage of kidneys who were having higher degrees of VUR increased. Applying spearman rank test revealed a significant positive correlation between VUR severity and number of UTI episodes the kidney units had ($p<0.001$). This showed that higher VUR severity lead to increased number of recurrent UTI episodes. Although study by keren *et al*³ showed that children having VUR had more UTI episodes than those who had no VUR but they didn't study the correlation of VUR severity with the number of UTI episodes which we did in this study.

It was also seen in the present study that chances of developing renal scarring increased with increasing number of UTI episodes. So renal scar was present in only 26.5% of the kidney units having two UTI episodes which increased to 66.7% of those having five episodes of UTI. Although not significant, there was a positive correlation between number of UTI episodes and the presence of renal scarring (p -value=0.085, Spearman's rho coefficient=0.146). A study by Rodríguez Azor *et al*¹⁷ observed that recurrence of UTI was significantly associated with renal scarring on DMSA scan but they did not comment on any relationship between the number of episodes of UTI and renal scar. The study by Goldman *et al*¹⁸, contrary to our study, showed no correlation between number of UTI episodes and presence of renal scarring. In contrast, RIVUR trial by Mattoo *et al*⁴ showed that renal scar occurred in children who had at least two episodes of UTI although they didn't study the correlation between these two. Also the study by Supavekin *et al*¹² revealed a significant correlation between number of UTI episodes and presence of renal scar in left kidneys ($p=0.017$) but insignificant correlation in the right kidneys ($p=0.081$). So this is a domain where further studies are still needed.

We didn't include grade-I and grade-II VUR patients in our study because DMSA scan of these patients is not routinely done. Also these patients have a tendency towards spontaneous resolution.

CONCLUSION

There was a significant positive correlation between degree of VUR severity and presence of renal scarring on DMSA scan in children with recurrent urinary tract infections. Moreover, there was a significant positive correlation between VUR severity and number of UTI episodes a kidney unit suffered from.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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