Comparison of Ultrasound and ^{99m}Tc -DMSA Scan Findings with Voiding Cystourethrography in Detecting Vesicoureteral Reflux in Children

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Research article

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Abstract

Background: Vesicoureteral reflux (VUR) is a common urinary tract disorder in pediatrics and could increase the risk of severe complications. The aim of this study is to assess the efficacy of ultrasound (US) and ^{99m}Tc -DMSA scan in detecting VUR in comparison with voiding cystourethrography (VCUG) among children hospitalized with urinary tract infection (UTI).

Methods: In this cross-sectional study, the total numbers of 540 children with UTI referred to Ali-Asghar children's hospital were enrolled, from April 2017 to May 2019. All patients underwent US and VCUG, ^{99m}Tc -DMSA performed for some of them to detect VUR. Accuracy, sensitivity, specificity, negative predicted value (NPV), positive predicted value (PPV) and Kappa agreement coefficient was used to compare the US and ^{99m}Tc -DMSA with VCUG results.

Results: Among 540 patients, VUR was detected in 143 children on VCUG including 90 (63 %) with grades III – V. US was abnormal in 97 of 143 patients (67.8 %) with confirmed VUR on VCUG and ^{99m}Tc -DMSA scan was abnormal in 41 of 69 (59 %) with VUR detected by VCUG. The overall accuracy, sensitivity, specificity, NPV and PPV for US were 61.30%, 67.83%, 58.94%, 37.31 and 83.57%, respectively. Among children with high grade VUR (grade III – V) on VCUG, the sensitivity, specificity and NPV of US were 80%, 58.2% and 93.60 respectively. However, when using both US and ^{99m}Tc -DMSA scan results for detecting the high grade VUR, the sensitivity, specificity and NPV were 92%, 42.30% and 93.20% respectively.

Conclusion: Although neither the US nor the ^{99m}Tc -DMSA scan can alone be sufficiently accurate to detect all grades of VUR, US, especially when combined with ^{99m}Tc -DMSA scan has enough sensitivity and NPV for ruling out high-grade VUR. These results indicate that there is no need to do VCUG in children with normal US and ^{99m}Tc -DMSA scans.

Background

Vesicoureteral Reflux (VUR) is a common urinary tract disorder among pediatric population and defined as the retrograde flow of urine from the bladder into the ureters and renal collecting systems due to a failure in the ureterovesical valve function (1). Identifying children with VUR at an early age provides an opportunity to prevent episodes of acute pyelonephritis and the consequent renal scarring (2). Voiding cystourethrography (VCUG) is the modality of choice for diagnosis and grading of VUR (3). In VCUG, the child is catheterized and radiocontrast material is injected through the catheter to fill the bladder (4).

Disadvantages of this procedure are catheterization discomfort, complications and considerable radiation exposure of the children who are relatively more vulnerable to the adverse effects of ionizing radiation. In addition, the risk of carcinogenesis is higher in children as they have a longer life expectancy following the procedure than adults (5).

Considering the mentioned disadvantages of VCUG, many attempts have been made to find a non-invasive alternative modality with adequate accuracy to detect VUR. Ultrasound (US) is a proper modality for evaluation pediatric urinary tract system due to its accuracy, accessibility and non-invasiveness (6, 7). However, there is controversy among clinicians regarding the accuracy of US for diagnosis of VUR. Some authors demonstrated that normal ^{99m}Tc -DMSA scan appears to be useful for ruling out high grade VUR. Therefore, another alternative for VCUG is performing prompt ^{99m}Tc -DMSA renal scan within two weeks of the onset of urinary tract infection (UTI) (8).

VCUG allows grading of VUR using the five-level International Reflux Scale (IRS) (9). Grade of VUR is strongly associated with the outcomes such as spontaneous resolution, recurrence of UTI and renal scarring (10). Recent guidelines recommend clinical decision-making based on the grade of VUR on VCUG, including observation (without medical therapy) for selected children with grade I or II VUR (11). But higher grades of VUR need medical or surgical interventions.(10) The diagnostic accuracy of VCUG for diagnosing reflux is very high and nearly 100% for high-grades of reflux (grade III -V) (12).

On the other hand, children with UTI and accompanying high-grade VUR rarely show normal results on ^{99m}Tc -DMSA renal scan or US, therefore, the VCUG has to be done in selected cases (13).

The objective of our study was to determine the accuracy of US and ^{99m}Tc -DMSA renal scan for detecting VUR in comparison with VCUG in children with UTI.

Methods

In this cross-sectional study, the total numbers of 540 children younger than the age of 8 with UTI referred to Ali-Asghar children's hospital, a pediatric center in Tehran, Iran were enrolled, from April 2017 to May 2019. All patients underwent US and VCUG to detect VUR. ^{99m}Tc -DMSA scan was performed for some of them to detect complications such as renal scar.

All patients with Chronic Kidney Disease (CKD) and obstructive nephropathy were excluded from the study. Urine samples were collected either with a urine bag or by midstream clean catch in boys and by catheter in girls. Febrile UTI was defined as a temperature higher than 38.5 °C with significant bacteriuria and > 10⁵ colony forming units (CFUs) per mL on urine cultures from samples obtained through aforementioned methods. US was performed immediately after diagnosis, and VCUg and ^{99m}Tc-DMSA scan were performed after the resolution of fever and confirmation of a negative urine culture.

US was performed by a single radiologist using a Philips Affiniti 50 ultrasound machine with 4–7 MHz convex and 7–10 MHz linear transducers with the bladder being both full and empty. The most important ultrasonographic findings related to VUR, were dilatation of the renal pelvis or the ureter. Additionally, changes in kidneys size and cortical echogenicity, reduction in the thickness of renal parenchyma, irregularity of the kidneys margin, and increase of urothelial thickening were also noted.

Renal cortical scan by ^{99m}Tc-DMSA was performed in multiple static anterior and posterior, and right and left posterior oblique views about 2 hours after IV injection of 2–3 mCi of radiopharmaceutical. Abnormal findings were described as focal or diffuse cortical hypoactivity with intact outline (defined as cortical damage) and single or multiple cortical defects (defined as cortical scar. Differential Renal Function (DRF) of 45–55% was considered normal.

Grading system for VUR on VCUg is according to the International Reflux Study Committee:

- Grade I: reflux into the ureter;
- Grade II: reflux into the ureter and renal pelvis without dilatation;
- Grade III: reflux with mild dilatation;
- Grade IV: reflux with moderate dilatation, rounded fornices;
- Grade V: gross dilatation of the ureter, ureter tortuosity, papillary obliteration.

Grades I and II were classified as low grade and grades III, IV, and V as high grade reflux (14).

Statistical analysis

We used the mean and standard deviation and percent for reporting the descriptive statistics of quantitative and qualitative variables, respectively. Qualitative variables were compared using the Chi square test and one way analysis of variance (One-way ANOVA) was used to compare the mean of quantitative variables. We used the sensitivity, specificity, positive predictive value, negative predictive value, overall accuracy and kappa agreement coefficient to investigate the efficacy of US for prediction of VUR based on the actual presence or absence of VUR confirmed by VCUg. Data was analyzed using Stata software, version 12 (StataCorp, TX) and p-value < 0.05 was considered as the level of significant.

Results

Among 572 patients evaluated for VUR, 540 patients entered our study. A total of 269 (49.8%) were boys and 271 (50.2%) were girls. All patients underwent VCUg and US. Children also underwent ^{99m}Tc-DMSA scan were 177. Among 540 patients, VUR was diagnosed by VCUg in 143 (26.5%) cases. Mean age of children who had VUR was 2.5 years old. Fifty three cases (37%) had low-grades and 90 cases (63%) had high-grades of VUR. US was abnormal in 97 of 143 patients (67.8%) with confirmed VUR on VCUg and in 163 of 397 cases (41%) without VUR on VCUg.

The ^{99m}Tc-DMSA scan was abnormal in 41 of 69 (59%) patients with VUR detected by VCUg and in 47 of 108 (43.5%) patients without VUR on VCUg.

The overall sensitivity and NPV of US for detecting VUR were 67.83% and 37.31%, respectively. Sensitivity and NPV of ^{99m}Tc-DMSA scan for diagnosis of VUR were 59.42% and 46.59%, respectively (Table 1). Most of the 136 children with findings suggestive of VUR on US but negative VCUg findings, showed fullness or mild distension of the renal pelvises (84.5%). In addition, the severity of hydronephrosis was higher in cases with high-grade reflux. Only 31 cases of high-grade VUR (9.4%) had no hydronephrosis on US (Table 2). The anteroposterior diameter (AP diameter) of renal pelvis was shown in Table 3. It seems that mean AP diameter in high-grades of reflux is larger than no-VUR cases or low-grades of reflux.

Among 90 children with high-grade VUR (grade III–V) on VCUg, 72 (80%) had abnormal findings on US (Table 4) and sensitivity and NPV of US among these cases, were 80% and 93.6% respectively (Table 5). All cases of grade V and 83.9% of grade IV VURs had abnormal US findings. Also 80% of grade V and 62.5% of grade IV VURs had abnormal ^{99m}Tc-DMSA scan (Table 4). In 50 children with high-grade VUR on VCUg, who

had findings of US and ^{99m}Tc -DMSA scan present, 46(92%) patients had abnormal findings on US or ^{99m}Tc -DMSA scan with 92% sensitivity and 93.2% NPV, respectively (Table 5).

Discussion

There is considerable interest in prompt and early detection of VUR as it is linked to recurrent UTIs, renal scarring, hypertension, and renal insufficiency. VCUG is the modality of choice for detecting VUR (15). However, owing to some disadvantages such as bladder catheterization and pediatric radiation exposure, there is a growing interest in finding alternative and less invasive methods with acceptable accuracy to detect VUR (16). In this study, we evaluated the accuracy of US and ^{99m}Tc -DMSA renal scan in predicting VUR among children hospitalized with UTI.

Several studies have evaluated the efficacy of US in diagnosis of VUR and their results have been conflicting with some reporting unreliability of ultrasound in evaluation of VUR. Mehnat and colleagues showed that the sensitivity and specificity of US for detecting VUR were 40% and 76%, respectively and demonstrated that renal US was neither sensitive nor specific for detection of VUR in children with a first-time UTI (17). In another investigation, Adibi and colleagues demonstrated the sensitivity, specificity; NPV and PPV of US in diagnosis of VUR were 70.9%, 51.4%, 69.6% and 52.9% respectively. They suggested that US is a sensitive but not specific method in diagnosis of VUR (18).

In a review article in 2016, Shaikh N. and colleagues concluded that US could not replace VCUG in detecting VUR. In addition, ^{99m}Tc -DMSA scan could not replace VCUG in detection of VUR or high-grade VUR (4). On the other hand, some studies reported that US is a reliable modality for evaluation of VUR. Rosenberg and associates stated that invasive VCUG is not an essential test for children showing normal results on US and ^{99m}Tc -DMSA renal scan (19).

Hey-young Lee and colleagues demonstrated that 95.3% of high grade VUR cases could be detected by US and ^{99m}Tc -DMSA renal scan. However, they also stated that the diagnosis of VUR by US and ^{99m}Tc -DMSA renal scan had some limitations in cases of low-grad VUR and detection ratio of these cases was only 62.5% (20).

In our study the sensitivity and specificity of US (67.83% and 58.94%) and ^{99m}Tc -DMSA scan (59.42% and 56.48%) were low if either done alone. However, combining both methods the sensitivity rose to 82.61% with an accuracy of 58.76% in detection of VUR.

As in other reports, the diagnosis of VUR by US and ^{99m}Tc -DMSA scan had several limitations in the cases of low-grade reflux (20, 21). In our study, the detection rate of low-grade reflux was only 47.2% for US and 47.4% for ^{99m}Tc -DMSA scan.

However, for high-grade VURs, the sensitivity (80%) and NPV (93.6%) of US are acceptable and with combination of US and ^{99m}Tc -DMSA scan findings, the sensitivity and NPV would even be higher (92% and 93.2%).

Similar to other investigations, we found that sensitivity and NPV of US and ^{99m}Tc -DMSA scan to detect low-grade VURs are low. However, regarding high frequency of spontaneous resolution of low grade VUR while children grow up, it can be recommended that VCUG be performed only in children with abnormal findings on US and ^{99m}Tc -DMSA scans, avoiding many unnecessary VCUG procedures.

Conclusion

Although neither the US nor the ^{99m}Tc -DMSA scan alone is sufficiently accurate to detect all acceptable grades of VUR, US especially associated with ^{99m}Tc -DMSA scan has enough sensitivity and NPV for ruling out high-grade VUR.

So there is no need to VCUG in children with normal US and ^{99m}Tc -DMSA scan.

Abbreviations

VUR: Vesicoureteral reflux

US: Ultrasound

VCUG: Voiding cystourethrography

UTI: Urinary tract infection

CKD: Chronic Kidney Disease

Declarations

Ethic approval and consent to participate

The informed consent was verbally confirmed by all participants and the Ethics committee of Iran University of Medical Sciences confirmed all procedures of this study (IR.IUMS.FMD.REC.1397.257).

Since this study was solely based on routine medical records and there was no medical interventions, the Ethics committee was of the opinion that verbal consent suffice and written consent is not necessary.

For children under 18 years old the consents were obtained from their parents.

Consent to publish

The authors declare that they consent to publish

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest

No competing interest

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Author's Contributions

EZ (study conception & design and Critical revision), AR and MK and JA (Acquisition of data, Analysis and interpretation of data & Drafting of manuscript), SH (Critical revision & Analysis and interpretation of data). All authors have read and approved the manuscript.

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Tables

Table 1
Correlation of US and ^{99m}Tc-DMSA scan findings with VCUG.

Variables		VCUG ^e		Total	Sensitivity	Specificity	NPV ^c	PPV ^d	Overall accuracy	KAPPA agreement coefficient
		Abnormal	Normal							
US	Abnormal	97 (37.3%)	163 (62.7%)	260 (100%)	67.83	58.94	37.31	83.57	61.30	0.21
	Normal	46 (16.4%)	234 (83.6%)	280 (100%)						
	Total	143 (26.5%)	397 (73.5%)	540 (100%)						
DMSA scan ^e	Abnormal	41 (46.6%)	47 (53.4%)	88 (100%)	59.42	56.48	46.59	68.54	57.63	0.15
	Normal	28 (31.5%)	61 (68.5%)	89 (100%)						
	Total	69 (39%)	108 (61%)	177 (100%)						
US & DMSA scan ^a	Abnormal	33 (57.9%)	24 (42.1%)	57 (100%)	47.83	77.78	57.89	70.00	66.10	0.26
	Normal	36 (30%)	84(70%)	120(100%)						
	Total	69(39%)	108(61%)	177(100%)						
US or DMSA scan ^b	Abnormal	57 (48.3%)	61 (51.7%)	118 (100%)	82.61	43.52	48.31	79.66	58.76	0.23
	Normal	12 (20.3%)	47 (79.7%)	59 (100%)						
	Total	69(39%)	108(61%)	177(100%)						
a. abnormal means positive findings in both US and DMSA scan										
b. abnormal means positive findings in US or DMSA scan										
c. Negative predictive value										
d. Positive predictive value										
e.US: ultrasound study; VCUG: voiding cystourethrography ;DMSA: dimercaptosuccinic acid scan										

Table 2
Prevalence of hydronephrosis in various grades of VUR

US findings		No VUR	Low grade VUR	High grade VUR	Total
Hydronephrosis	No hydronephrosis	261(79.3%)	37(11.2%)	31(9.4%)	329(100%)
	fullness	62(75.6%)	7(8.5%)	13(15.9%)	82(100%)
	Mild hydronephrosis	53(72.6%)	3(4.1%)	17(23.3%)	73(100%)
	Moderate hydronephrosis	15(45.5%)	3(9.1%)	15(45.5%)	33(100%)
	Severe hydronephrosis	6(26.1%)	3(13%)	14(60.9%)	23(100%)
Total		397(73.5%)	53(9.8%)	90(16.7%)	540(100%)

Table 3
The result of one-way analysis of variance (ANOVA) to compare the mean of AP diameter in reflux grading groups

Variables	Reflux grading				P value
	No VUR (Mean $\pm$ SD)	Low grade VUR (Mean $\pm$ SD)	High grade VUR (Mean $\pm$ SD)	Total	
AP diameter	3.51 $\pm$ 3.13 ^{a*}	3.35 $\pm$ 4.13 ^a	6.82 $\pm$ 6.47 ^b	4.05 $\pm$ 4.16	< 0.001
*Dissimilar values (a, b) of each row are significantly different in LSD post hoc analysis.					

Table 4
Correlation of us and ^{99m}Tc-DMSA scan findings with various grades of VUR detected by VCUG

VUR grading	US		DMSA scan		US +	DMSA scan	US /	DMSA scan
	abnormal	normal	abnormal	normal	+	-	+	-
I	6(31.4%)	13(68.4%)	2(40%)	3(60%)	1(20%)	4(80%)	3(60%)	2(40%)
II	19(55.9%)	15(44.1%)	7(50%)	7(50%)	5(35%)	9(64%)	8(57%)	6(43%)
Low grade	25(47.2%)	28(52.8%)	9(47.4%)	10(52.6%)	6(31%)	13(69%)	11(57%)	8(43%)
III	25(65.8%)	13(34.2%)	14(58.3%)	10(41.7%)	10(41%)	14(59%)	21(87%)	3(13%)
IV	26(83.9%)	5(16.1%)	10(62.5%)	6(37.5%)	9(56%)	7(44%)	15(93%)	1(7%)
V	21(100%)	0	8(80%)	2(20%)	8(80%)	2(20%)	10(100%)	0
High grade	72(80%)	18(20%)	32(64%)	18(36%)	27(54%)	23(46%)	46(92%)	4(8%)

Table5. Correlation of findings in US and ^{99m}Tc-DMSA scan with VCUG.

Variables		High grade VUR ^a	Sensitivity	Specificity	NPV ^c	PPV ^d	Overall accuracy	KAPPA agreement coefficient
US	Abnormal	72 (80%)	80.00	58.2	93.60	27.70	61.85	0.21
	Normal	18 (20%)						
	Total	90 (100%)						
DMSA scan ^e	Abnormal	32 (64%)	64.00	55.90	79.80	36.40	58.19	0.16
	Normal	18(36%)						
	Total	50 (100%)						
US & DMSA scan ^a	Abnormal	27 (54%)	54.00	76.40	80.80	47.40	70.05	0.29
	Normal	23(46%)						
	Total	50(100%)						
US or DMSA scan ^b	Abnormal	46(92%)	92.00	43.30	93.20	39.00	57.06	0.25
	Normal	4 (8%)						
	Total	50(100%)						
a. abnormal means positive findings in both US and DMSA scan								
b. abnormal means positive findings in US or DMSA scan								
c. Negative predictive value								
d. Positive predictive value								
e. US:ultrasound study; VUR: Vesico ureteral reflux; DMSA: Dimercaptosuccinic acids scan								