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Ultrasound and ^{99m}*Tc-DMSA* Scan Versus Voiding Cystourethrography in Diagnosis of Vesicoureteral Reflux in Children

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Abstract

Background: Early detection of vesicoureteral reflux (VUR) is crucial to prevent potential complications such as recurrent urinary tract infections and kidney damage. Noninvasive diagnostic alternatives to voiding cystourethrography (VCUG), such as ultrasound (US) and 99mTc-DMSA scan, offer effective and safe methods for identifying VUR without exposing children to ionizing radiation. This investigation aimed to evaluate the efficacy of US and 99mTc-DMSA scan in detecting VUR compared with VCUG among children with urinary tract infection (UTI).

Methods: In this observational study, we included 540 hospitalized children with UTI in Aliasghar Children`s Hospital between April 2017 and May 2019. US and VCUG were performed on all patients, with 99mTc-DMSA administered to some to detect VUR. Sensitivity, specificity, positive and negative predictive values, overall accuracy, and kappa agreement were calculated to evaluate ultrasound efficacy in predicting VUR based on VCUG-confirmed existence or nonexistence of VUR.

Results: Out of 540 patients, VCUG identified VUR in 143 cases, with 90 (63%) classified as grades III to V. US results were abnormal in 97 of the 143 patients (67.8%) confirmed to have VUR via VCUG, while the 99mTc-DMSA scan showed abnormalities in 41 out of 69 (59%) cases detected by VCUG. The sensitivity and negative predictive value (NPV) of the 99mTc-DMSA scan for diagnosing VUR were recorded at 59.42% and 46.59%, respectively. For ultrasound, the overall accuracy was 61.30%, with sensitivity at 67.83%, specificity at 58.94%, NPV at 37.31%, and positive predictive value (PPV) at 83.57%. In children with high-grade VUR (grades III-V) as determined by VCUG, the sensitivity, specificity, and NPV for ultrasound were found to be 80%, 58.2%, and 93.60%, respectively. However, when both US and 99mTc-DMSA scan results were utilized for detecting high-grade VUR, the sensitivity, specificity, and NPV were calculated to be 92%, 42.30%, and 93.20%, respectively.

Conclusion: While both US and the 99mTcDMSA scan are not fully reliable in detecting all grades of VUR individually, integration of US and ^99mTc-DMSA scan demonstrates reliable sensitivity and NPV for effectively excluding high-grade VUR. These findings suggest that in children with normal results from both US and ^99mTc-DMSA scans, there may be no need for VCUG. This approach could significantly reduce unnecessary VCUG procedures, minimizing patient exposure to radiation and enhancing overall diagnostic efficiency in pediatric care.

Keywords: Vesicoureteral reflux, Technetium-99m-Dimercaptosuccinic acid, Ultrasound Urinary tract infection

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↑What is "already known" in this topic:
Voiding cystourethrography (VCUG) has been the gold standard for diagnosis of urinary tract infection (UTI), but it carries risks such as radiation exposure and discomfort from catheterization. This has led to increased interest in noninvasive alternatives for effective vesicoureteral reflux (VUR) screening. Previous studies indicate variable sensitivity and specificity for ultrasound and 99mTc-DMSA scans, with ultrasound being less reliable for low-grade reflux.

→What this article adds:
Our findings show that while both modalities have low sensitivity and negative predictive value individually, their combined use significantly enhances diagnostic performance for high-grade VUR (grades III-V), achieving a sensitivity of 92%. These results suggest that ultrasound and 99mTc-DMSA scans can serve as first-line screening tools, potentially reducing the need for invasive VCUG and minimizing patient exposure to radiation.

Introduction

Vesicoureteral reflux (VUR) is a common urinary tract disorder in children, defined by the abnormal flow of urine from the bladder back into the ureters and renal collecting systems, resulting from a malfunction of the ureterovesical valve (1). The incidence of VUR in healthy children is approximately 0.5% to 3%, but this increases to 30% to 40% in children who have UTIs (2). Identifying children with VUR at a young age allows for timely intervention, which can help avert instances of acute pyelonephritis and the resulting renal damage (3). Voiding cystourethrography (VCUG) is considered the preferred method for diagnosing and classifying the severity of VUR in patients (4). In the VCUG procedure, a catheter is placed into the child's bladder, allowing for the injection of radiocontrast material to fill it (5).

The procedure has several drawbacks, including discomfort from catheterization, potential complications, and significant radiation exposure, which is particularly concerning for children, who are more susceptible to the harmful effects of ionizing radiation. Furthermore, the likelihood of developing cancer is increased in children due to their longer life expectancy after the procedure compared to adults (6).

Considering the noted drawbacks of VCUG, numerous efforts have been made to identify a noninvasive alternative that offers sufficient accuracy for detecting VUR. Ultrasound (US) serves as a suitable imaging modality for evaluating the pediatric urinary tract system due to its accuracy, availability, and noninvasive nature. Unlike VCUG, US does not involve ionizing radiation, making it a safer option for children. However, while US can provide valuable insights into kidney and bladder conditions, its sensitivity and specificity for detecting VUR may vary, often requiring supplementary methods for comprehensive assessment (7, 8). There is ongoing debate among clinicians regarding the effectiveness of US in diagnosing VUR. Some studies suggest that a normal 99mTc-DMSA scan can effectively rule out high-grade VUR. Consequently, performing a 99mTc-DMSA renal scan shortly after the onset of a urinary tract infection (UTI) has emerged as an alternative to VCUG. This approach allows for timely diagnosis while minimizing the risks associated with more invasive procedures (9).

VCUG facilitates the grading of VUR according to the 5-grade International Reflux Scale (10).

The VUR grade is closely linked to various outcomes, including the likelihood of spontaneous resolution, recurrence of UTIs, and the potential for renal scarring. This grading system plays a crucial role in guiding treatment decisions and predicting long-term renal health in affected children (11).

Recent guidelines emphasize that clinical decisions regarding the management of VUR should be based on the grade of VUR as determined by VCUG. For children diagnosed with grade I or II VUR, observation without medical treatment may be appropriate (12). In contrast, advanced grades of VUR require medical or surgical treatments (11). VCUG boasts a diagnostic accuracy that is nearly 100% for high-grade reflux (grades III-V) (13). Conversely, children presenting with UTIs alongside high-grade VUR seldom exhibit normal findings on 99mTc-DMSA renal scans or US. Therefore, performing VCUG is warranted in specific cases to ensure accurate diagnosis and appropriate management (14).

In our study, we assessed the effectiveness of US and 99mTc-DMSA renal scans in detecting VUR compared with VCUG in children diagnosed with UTI.

Methods

Design & Setting

The study was conducted as a cross-sectional investigation at Aliasghar Children's Hospital—a university hospital affiliated with Iran University of Medical Sciences in Tehran, Iran. The study protocol received approval from the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.FMD.REC.1397.257).

Participants

A total of 540 eligible patients <8 years who were diagnosed with UTIs were enrolled in the study from April 2017 to May 2019. All patients underwent US and VCUG to evaluate VUR. Additionally, a 99mTc-DMSA scan was performed for some patients to assess complications such as a renal scar. The exclusion criteria were children with chronic kidney disease (CKD) and obstructive nephropathy.

CKD is defined as either kidney damage or a decreased glomerular filtration rate (GFR) of <60 mL/min/1.73 m2 for at least 3 months. Obstructive nephropathy is renal dysfunction (renal insufficiency, renal failure, or tubulointerstitial damage) resulting from urinary tract obstruction.

Variables, Data Sources, & Management

For boys, urine samples were gathered with either a urine bag or midstream clean catch technique, while girls underwent catheterization for sample collection. Febrile UTI was characterized as a temperature exceeding 38.5°C along with significant bacteriuria, indicated by $>10^5$ colony-forming units per mL in urine cultures obtained through the aforementioned methods. US was performed immediately after diagnosis, while VCUG and 99mTc-DMSA scans were conducted after the resolution of fever and confirmation of a negative urine culture. US was carried out by a single radiologist using a Philips Affiniti 50 ultrasound machine equipped with 4–7 MHz convex and 7–10 MHz linear transducers, both with a full and empty bladder. Key ultrasonographic findings associated with VUR included dilation of the renal pelvis or ureter. Additional observations noted changes in kidney size and cortical echogenicity, reduced thickness of renal parenchyma, irregular kidney margins, and increased urothelial thickening. The renal cortical scan utilizing 99mTc-DMSA was performed approximately 2 hours after intravenous injection of 2-3 mCi of the radiopharmaceutical, capturing multiple static anterior, posterior, and right and left posterior oblique views. Abnormal findings were characterized as focal or diffuse cortical hypoactivity with an intact outline (indicative of cortical

damage) and single or multiple cortical defects (denoting cortical scarring). A differential renal function (DRF) of 45% to 55% was regarded as normal. The VUR classification system via VCUG follows the International Reflux Study Committee guidelines:

- Grade I: Reflux into the ureter
- Grade II: Reflux into the ureter and renal pelvis without dilation
- Grade III: Reflux with mild dilation
- Grade IV: Reflux with moderate dilation and rounded fornices
- Grade V: Gross dilation of the ureter, ureteral tortuosity, and papillary obliteration

Reflux is considered low-grade in grades I and II, while grades III, IV, and V are classified as high-grade reflux (15).

Study Size

All hospitalized children diagnosed with UTI who were referred to Aliasghar Children's Hospital were enrolled in the study from April 2017 to May 2019 using a consecutive sampling method.

Statistical Methods

Data analysis was conducted using Stata software Version 12 (StataCorp, TX), with $P < 0.05$ considered as statistically significant. Descriptive statistics of quantitative variables were presented as means and standard deviations, while qualitative variables were expressed as percentages. To compare qualitative variables, we used the chi-square test and 1-way analysis of variance to evaluate the differences in the means of quantitative variables. To evaluate the efficacy of US in predicting VUR, we calculated sensitivity, specificity, positive predictive value, negative predictive value, overall accuracy, and the kappa agreement coefficient based on the confirmed presence or the absence of VUR as determined by VCUG.

Results

From the 572 patients evaluated for VUR, 540 were included in our study. Among these participants, 269 (49.8%) were boys and 271 (50.2%) were girls. All patients underwent VCUG and US, with 177 children additionally receiving a 99mTc-DMSA scan. VUR was identified through VCUG in 143 cases, accounting for 26.5% of the total. The mean age of the children diagnosed with VUR was 2.5 years, with 53 cases (37%) classified as low-grade VUR and 90 cases (63%) as high-grade VUR. Abnormal US results were noted in 97 out of the 143 patients (67.8%) who had confirmed VUR, while 163 out of 397 cases (41%) without VUR also showed abnormal findings. The 99mTc-DMSA scan indicated abnormalities in 41 of the 69 patients (59%) with VUR detected by VCUG and in 47 of the 108 patients (43.5%) without VUR. The overall sensitivity and negative predictive value (NPV) of ultrasound for detecting VUR were found to be 67.83% and 37.31%, respectively, while for the 99mTc-DMSA scan, these figures were recorded at 59.42% and 46.59% (Table 1). Among the 136 children who had US findings suggestive of VUR but negative VCUG results, a significant majority (84.5%) exhibited fullness or mild distension of the renal pelvises. High-grade reflux cases showed more severe hydronephrosis, with only 31 instances of high-grade VUR (9.4%) displaying no hydronephrosis on US (Table 2). The anteroposterior diameter (AP diameter) of the renal pelvis was greater in

Table 1. Comparison of US[e] 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 finding		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

Variable	Reflux grading				*P* value
	No VUR (Mean± SD)	Low grade VUR (Mean± SD)	High grade VUR (Mean± SD)	Total	
AP diameter	3.51 ± 3.13[a*]	3.35 ± 4.13[a]	6.82 ± 6.47[b]	4.05 ± 4.16	<0.001

*Dissimilar values (a, b) of each row are significantly different in LSD post hoc analysis.

Table 4. Comparison 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%0	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%)

Table 5. Comparison of diagnostic values in US[e] and ^{99m}Tc-DMSA scan with VCUG in high grade VUR.

Variable		High grade VUR[e]	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	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]			54.00	76.40	80.80	47.40	70.05	
	Abnormal	27 (54%)						0.29
	Normal	23 (46%)						
	Total	50(100%)						
US or DMSA scan[b]			92.00	43.30	93.20	39.00	57.06	
	Abnormal	46 (92%)						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

high-grade reflux cases compared to those without VUR or with low-grade reflux, as detailed in Table 3. Of the 90 children with high-grade VUR (grades III–V) identified on VCUG, 72 (80%) showed abnormal US findings, leading to a sensitivity of 80% and an NPV of 93.6% for this group. All grade V cases and 83.9% of grade IV VURs exhibited abnormal ultrasound findings, while both grade V and IV VURs showed abnormal results on the 99mTc-DMSA scan in 80% and 62.5% of cases, respectively (Table 4). In a subgroup of 50 children with high-grade VUR on VCUG who had positive findings on both US and the 99mTc-DMSA scan, an impressive 46 patients (92%) exhibited abnormal findings on either imaging modality, resulting in a sensitivity of 92% and an NPV of 93.2% (Table 5).

Discussion

There is considerable interest in the timely and early identification of VUR because of its links to recurrent UTIs, renal scarring, hypertension, and renal insufficiency. Early identification is crucial, particularly for high-grade VUR (grades III-V), as these patients face a greater risk of developing serious complications such as renal scarring and hypertension compared to those with low-grade VUR (16, 17). VCUG is considered the gold standard for diagnosing VUR (18). However, due to the disadvantages associated with VCUG, such as bladder catheterization and radiation exposure in pediatric patients, there is increasing interest in identifying alternative, less invasive methods for detecting VUR that maintain acceptable accuracy.

Numerous studies have assessed the effectiveness of US in diagnosing VUR, and their results have been conflicting. Some research indicates that the US may not be reliable for this purpose. For instance, Mehnat et al reported that the sensitivity and specificity of US for detecting VUR were 40% and 76%, respectively, demonstrating that renal US was neither sensitive nor specific in evaluating VUR among children with a first-time UTI (19). In another investigation, Adibi et al demonstrated that the sensitivity, specificity, NPV, and PPV of US in the diagnosis of VUR were 70.9%, 51.4%, 69.6%, and 52.9%, respectively. They suggested that while US is a sensitive method for detecting VUR, it lacks specificity, indicating that it may produce false positives in certain cases. This highlights the need for caution when relying solely on US for VUR diagnosis, as its limitations necessitate further confirmatory testing, such as VCUG, to ensure accurate assessment and management of the condition (20).

In a review published in 2016, Shaikh et al concluded that US cannot replace VCUG for detecting VUR. Additionally, they found that the 99mTc-DMSA scan is not a substitute for VCUG in identifying VUR or high-grade VUR (5). Conversely, some studies have suggested that US is a reliable method for evaluating VUR. Rosenberg et al argued that invasive VCUG may not be necessary for children with normal findings on US and 99mTc-DMSA renal scans (21).

Hey-young Lee et al found that US and 99mTc-DMSA renal scans could detect 95.3% of high-grade VUR cases. However, they noted limitations in diagnosing low-grade VUR, with a detection rate of only 62.5% (22).

In our study, the sensitivity and specificity for US were 67.83% and 58.94%, respectively, while for the 99mTc-DMSA scan, they were 59.42% and 56.48%. When both methods were combined, the sensitivity increased to 82.61%, with an accuracy of 58.76% for VUR detection.

Similar to other reports, our findings indicated limitations in diagnosing low-grade reflux using US and the 99mTc-DMSA scan, with detection rates of just 47.2% and 47.4%, respectively (22, 23).

For high-grade VURs, however, US demonstrated acceptable sensitivity (80%) and an NPV of 93.6%. Moreover, when combining the findings from both US and the 99mTc-DMSA scan, the sensitivity and NPV improved further to 92% and 93.2%, respectively.

The relatively low sensitivity and NPV of US and 99mTc-DMSA scans in detecting low grade of VUR can be attributed to several factors. Operator dependence is a significant issue, as the accuracy of both imaging techniques can vary based on the skill and experience of the practitioner performing the examination. Additionally, technical limitations, such as suboptimal imaging conditions, patient movement during scans, and the inherent challenges in visualizing lower grades of VUR, contribute to reduced sensitivity. For instance, the long acquisition time required for 99mTc-DMSA scans can lead to motion artifacts, particularly in pediatric patients who may struggle to remain still during the procedure (24, 25). Furthermore, while 99mTc-DMSA is more sensitive than US for detecting renal cortical defects, its ability to identify low-grade VUR remains limited due to nonspecific findings that can complicate interpretation (26). These factors collectively hinder the effectiveness of US and 99mTc-DMSA scans in reliably diagnosing low-grade VUR. On the other hand, according to our study, the combination of US and 99mTc-DMSA scans has good sensitivity in diagnostic high-grade VUR and especially in cases where early detection is crucial for preventing complications such as renal scarring and hypertension.

Consistent with other studies, we observed that the sensitivity and NPV of US and 99mTc-DMSA scans for detecting low-grade VUR are low. Given the high rate of spontaneous resolution of low-grade VUR as children develop, we recommend that VCUG be conducted only in cases where US and 99mTc-DMSA scans reveal abnormal findings, thereby reducing the number of unnecessary VCUG procedures.

Limitations

Our study has several limitations due to its retrospective design, which affected data collection. Many patients included in our study did not undergo a DMSA scan because of hardware constraints and economic factors. Additionally, the lack of regular follow-up visits for many patients resulted in incomplete information in their files, leading to their inevitable exclusion from the study.

Future research should focus on conducting prospective studies to validate our findings regarding VUR and enhance data collection while reducing selection bias. Exploring alternative noninvasive modalities, such as contrast-enhanced US, could provide valuable insights into VUR detection while minimizing patient exposure to ionizing radiation. Ensuring access to DMSA scans for all eligible patients and encouraging regular follow-up visits will contribute to a more comprehensive assessment. In addition, including a larger and more diverse patient population can enhance the generalizability of the findings.

Conclusion

Although neither 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. Thus, there is no need for VCUG in children with normal US and 99mTc-DMSA scan. Also, our findings suggest

that a US and ^99m^Tc-DMSA scan can be used as a first-line screening approach to identify children who do not require invasive VCUG, thereby reducing unnecessary radiation exposure and discomfort.

Authors' Contributions

E.Z.: study conception & design and Critical revision; A.R., M.K., and J.A.: acquisition of data, analysis and interpretation of data, & drafting of the manuscript; S.H.: critical revision & analysis and interpretation of data. All authors have read and approved the manuscript.

Ethical Considerations

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).

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Conflict of Interests

The authors declare that they have no competing interests.

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