



Dimercaptosuccinic Acid Scan as an Alternative Diagnostic Approach in Vesicoureteric Reflux Disease

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Abstract

Background: In vesicoureteral reflux urine passage from bladder into kidney and induce hydronephrosis. Current diagnostic methods are voiding cystourethrography and cystogram radionuclide. Dimercaptosuccinic acid scan is not routinely used in vesicoureteral reflux disease.

Objectives: So the aim of this study was evaluation diagnostic efficacy of dimercaptosuccinic acid scan as a alternative dignostic approach for vesicoureteral reflux diagnosis.

Methods: This is a case series study that was conducted on children who were under the age of 6 with varying degrees of vesicoureteral reflux or by vesicoureteral reflux indication review and referring to Amir Kabir hospital. Vesicoureteral reflux was diagnosed by voiding cystourethrograms and pediatrician confirmation, in following what dimercaptosuccinic acid scans has done for renal parenchyma evaluation. At the end, grade of vesicoureteral reflux in voiding cystourethrograms was compared to dimercaptosuccinic acid scan results.

Results: Dimercaptosuccinic acid scan and voiding cystourethrograms were correlated in high grades of vesicoureteral reflux ($P = 0.0001$). However, in low grade, there is no significant correlation between two tests ($P = 0.4$).

Conclusions: Dimercaptosuccinic acid scan is an appropriate dignostic approach with lower complications in the diagnosis of high graded vesicoureteral reflux, renal scar, and pyolonephrit.

Keywords: Vesicoureteral Reflux, Diagnosis, Dimercaptosuccinic Acid Scan

1. Background

Vesicourethral reflux (VUR) is defined as retrograde passage of urine from the bladder into kidney and upper urinary tract (1, 2). This condition can increase transporting bacteria from the bladder to the kidney and then predisposes patients to acute pyelonephritis (3, 4). Pyelonephritis as an acute and morbid event requires acute care in children and is a possible indication for hospitalization in infants. Also, loss of renal parenchyma (renal scarring) can occur by urinary tract infection (UTI) (5).

International classification of reflux study classified it I to V intensity grades of reflux nephropathy based on voiding cystourethrography (VCUG). Rating of reflux nephropathy mentioned below:

- Grade I: reflux limited to the ureter.
- Grade II: reflux up to the renal pelvis.

- Grade III: mild dilatation of ureter and pelvicalyceal system.

- Grade IV: tortuous ureter with moderate dilatation and blunting of fornices but preserved papillary impressions.

- Grade V: tortuous ureter with severe dilatation of ureter and pelvicalyceal system and loss of fornices and papillary impressions (6, 7).

In the diagnosis of this condition, VCUG is a method of choice. However, this is an invasive procedure that has irradiation risks on patients and their parents (8). For VUR diagnosis, it is very important to choose a procedure that is safe, noninvasive, and accepted by the patient and the parents. For urinary tract system evaluation, technetium 99 m-labeled dimercaptosuccinic acid scan (DMSA) are used for abnormalities urological system and renal parenchymal scars (9). Efficacy of DMSA scan was predicted in some

studies and ruled out by others (1, 10, 11).

For the DMSA scan, dimercaptosuccinic acid is injected intravenously and arrives to the kidney through the bloodstream (12). In addition, the kidneys are scanned by special cameras, that show the structure of the kidney (10). For this, test preparation is not necessary, eating and drinking for the individual is permitted. Except for infants who do not have necessary cooperation, sedation (sedative or hypnotic) or anesthesia have to be used (11, 13). The scan has 2 phases: injecting radioactive substances as a first step and taking scans of children as a second step. Between these two stages, there are about 2 to 4 hour intervals (3). Injected radioactive substance has been excreted through the kidneys. Hydration of children (getting enough fluids) can help fast disposal of radioactive materials. In addition, washing the urogenital area is an important act after urination (9, 14). Since VCUG can induce and increase children radiation, DMSA scan has suggested for evaluation of different grades of VUR.

2. Objectives

In our study, we consider the DMSA as an approach to evaluate prediction of VUR and its grade in children and to find a better diagnostic approach for VUR.

3. Methods

3.1. Study Setting

It was a hospital-based study that was conducted in the pediatric clinic of Amir-Kabir hospital.

3.2. Study Population

Study populations were all male and female children lower than 6 years of age by indication for VCUG (first UTI) and pediatrician confirmation of VUR in six months in 2016. With these criteria, others in following, samples (101 patients) were randomly chosen and enrolled in the study for study group.

3.3. Measurements

A VCUG and then DMSA renal scan were done for all patients. VUR has detected by VCUG and approved by pediatric nephrologists and were divided into I and VI, according to the VCUG test and based on the international reflux study classification. Medical, demographic, and epidemiological information was taken from the patients by questionnaire.

In order to evaluate renal parenchymal, we carry out the DMSA scan for children. The scan was done 3 - 4 hours after injection of technetium-99m and renal parenchymal is evaluated based on the technetium uptake.

3.4. Ethical Considerations

Ethical issues were completely observed by the authors. The study group adheres to the principles of medical ethics introduced by the health ministry and the declaration of Helsinki and legislation in the Medical ethics committee of Arak University of Medical Sciences. In addition, the ethical committee of Arak University of Medical Sciences approved the protocol of the study.

3.5. Statistical Analysis

The data were analyzed by the SPSS program and $P < 0.05$ was considered as a significant value. We consider the t-test for quantitative variables and X2 test for qualitative variables.

3.6. Inclusion and Exclusion Criteria

Each child that was under the age of 6, by diagnosis of VUR, were recruited based on the Nelson book and medical supervision of pediatrics nephrologists. The children should not have any mental and physical illness. Parents and children who did not cooperate in entering to study, presence of any chronic kidney disease or other urinary tract problems, and chronic use of any drug were considered as the exclusion criteria.

4. Results

In total, 101 patients were examined, 88 cases were male (87.1%) and 13 cases were female (12.9%). In addition, children under the age of 6 and other characteristics of children with VUR have been presented as No. (%) (Table 1).

As shown in Table 2, the mean of VUR in the renal scaring ($P = 0.0001$) and pyelonephritis in the DMSA scan ($P = 0.0001$) were significantly different between the two groups. In addition, the age ($P = 0.24$) and gender ($P = 0.4$) of children have no significant difference in the two groups (Table 3).

5. Discussion

Our results showed that DMSA scan in pyelonephritis and renal scar is a diagnostic approach, and according to DMSA scan, high graded VUR can be predicted.

In a study by Tseng et al., specificity and sensitivity of DMSA scan for prediction of VUR, respectively, were 71%, 58%, 44%, and 88% (15). Camacho et al., reported PPV and NPV respectively as 88% and 48% for prediction of VUR by DMSA scan and concluded that DMSA scan is normal during acute UTI and renal damage risk is low (16). In Alshamsam and Mahant studies, sensitivity, specificity, PPV, and NVP of ultrasonography was reported respectively as 40%,

Table 1. Characteristics of Children with Vesicoureteric Reflux (N = 101)^a

Variables	Children with Vesicoureteral Reflux
Gender	
Male	13 (12.9)
Female	88 (87.1)
Age, y^b	
1 and lower	44 (43.6)
1 - 5	42 (41.6)
5 and higher	15 (14.9)
Birth weight^c	
VLBW	18 (17.8)
LBW	69 (68.4)
NBW	8 (7.9)
HBW	6 (5.9)
Household incomes^d	
Low	32 (31.6)
Moderate	65 (64.3)
High	2 (2)
Paternal education	
University	13 (12.9)
High school	85 (84.2)
Elementary school	3 (2.9)
Maternal education	
University	31 (30.8)
High school	70 (69.2)
Elementary school	0 (0)
Consanguineous marriage	
Yes	10 (9.9)
No	91 (90.1)
Gestational age, week	
Full term (= 37)	98 (97.1)
Premature (< 37)	3 (2.9)
Post-term (> 40)	0 (0)
Patient with siblings	
Yes	73 (72.3)
No	28 (27.7)
Location	
City	37 (36.6)
Village	64 (63.4)
Maternal age, y	
< 20	62 (61.4)
20 - 30	36 (35.6)
> 31	3 (3)
Paternal age, y	
< 20	0 (0)
20 - 30	81 (80.2)
> 31	20 (19.8)

^aThe values are presented as No. (%)^bBased on the years.^cVLBW, > 1500; LBW, 1500 - 2500; NBW, 2500 - 4000; HBW, > 4000; based on the gr scale.^dLow, family monthly income < 5 million Rials; Moderate, family monthly income of 5 million to 10 million Rials; High, family monthly income > 10 million Rials.**Table 2.** Relationship Between Renal Scarring, Pyelonephrit and Mean of Vesicoureteric Reflux Grades (N = 101)^a

Variables	Mean of Vesicoureteric Reflux Grade		P Value
	LK	RK	
Renal scar			0.0001
Yes	2.7 ± 1.06	1.9 ± 1.52	
No	1.78 ± 1.34	1.6 ± 1.3	
Pyelonephriti			0.0001
Yes	2 ± 1.7	2.6 ± 0.57	
No	1.9 ± 1.34	1.58 ± 1.3	

Abbreviations: LK, Left Kidney; RK, Right Kidney.

^aThe Values are presented mean ± SD

76%, 32%, and 82%, for prediction of VUR (17). Moorthy et al., in a study, reported that 16% of children with VUR had a abnormal kidney. In addition, they concluded that ultrasonography examination for predication of VUR is not recommended and VCUG is preferred to ultrasonography (18). Kass et al., mentioned that the ability of DMSA or ultrasonography for prediction of VUR is not recommended (19). Based on our study, accuracy of DMSA scan in high graded VUR was approved. In a study by Ajdinovic et al., the specificity and sensitivity of ultrasonography for prediction of high grade VUR (III and higher) were 84% (20). Sorkhi et al., evaluated prediction of VUR and DMSA scan and concluded that DMSA scan or ultrasonography cannot predict VUR (especially low grade VUR), however, based on NPV, absence of VUR can be predicted with these tests (8). However, with the reasons that few clinical studies have been carried out in regards to this test, further studies are needed before the verification accuracy of DMSA scan as a better diagnostic approach.

The limitation was parental noncompliance due to the use of the DMSA scan as a non-routine diagnostic approach for VUR. However, when we explained to parents that DMSA scan is a cheap and safe test in compare to VCUG scan, they were convinced. In addition, Due to a low number of clinical studies, we recommend further studies with larger sample sizes.

5.1. Conclusion

Our funding showed that DMSA scan, as an alternative dignostic approach, can be used in the diagnosis of high graded VUR, renal scar, and pyolonephrit, however, not in low garded VUR. Since VCUG is golden standard in VUR, DMSA scan is better in a high grade of VUR due to the fact that VCUG is invasive, which causes anxiety in patients and their parents. In addition, DMSA has lower complications and is better for children.

Table 3. Comparison Between Age groups, Gender, and Grades of Vesicoureteric Reflux in the Study Groups (N = 101)^a

Variables	Grade of Vesicoureteric Reflux												P Value
	0		1		2		3		4		5		
	LK	RK	LK	RK	LK	RK	LK	RK	LK	RK	LK	RK	
Age^b, y													0.24
1 and lower	12 (11.8)	9 (8.9)	1 (0.9)	2 (1.9)	11 (10.9)	18 (17.7)	15 (14.8)	10 (9.9)	2 (1.9)	5 (4.9)	3 (2.8)	0 (0)	
1 - 5	9 (8.9)	17 (16.8)	1 (0.9)	3 (2.9)	18 (17.7)	10 (9.9)	11 (10.9)	10 (9.9)	3 (2.9)	2 (1.9)	0 (0)	0 (0)	
5 and higher	4 (3.9)	7 (6.9)	3 (2.9)	1 (0.9)	4 (3.9)	4 (3.9)	4 (3.9)	3 (2.9)	0 (0)	0 (0)	0 (0)	0 (0)	
Gender													0.4
Male	4 (3.9)	2 (1.9)	1 (0.9)	2 (1.9)	2 (1.9)	3 (2.9)	2 (1.9)	2 (1.9)	1 (0.9)	3 (2.9)	2 (1.9)	0 (0)	
Female	21 (20.5)	26 (25.4)	4 (3.9)	4 (3.9)	27 (26.4)	26 (25.4)	21 (20.5)	18 (17.6)	3 (2.9)	2 (1.9)	0 (0)	0 (0)	

Abbreviations: LK, Left Kidney; RK, Right Kidney.

^aThe values are presented as No. (%)^bBased on the years

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Footnote

Conflict of Interests: The authors declared no competing interests.

References

- Wongbencharat K, Tongpenyai Y, Na-Rungsri K. Renal bladder ultrasonography and late 6-month DMSA scan screening for high-grade vesicoureteral reflux after first febrile urinary tract infection in infants aged < 1 year. *Pediatrics*. 2015;135(Supplement 1).
- Ki HC, Kim SO, Yoo DH, Hwang IS, Hwang EC, Oh KJ, et al. Abnormal dimercaptosuccinic Acid scan may be related to persistence of vesicoureteral reflux in children with febrile urinary tract infection. *Korean J Urol*. 2012;53(10):716-20. doi: 10.4111/kju.2012.53.10.716. [PubMed: 23136633]. [PubMed Central: PMC3490093].
- Lee MD, Lin CC, Huang FY, Tsai TC, Huang CT, Tsai JD. Screening young children with a first febrile urinary tract infection for high-grade vesicoureteral reflux with renal ultrasound scanning and technetium-99m-labeled dimercaptosuccinic acid scanning. *J Pediatr*. 2009;154(6):797-802. doi: 10.1016/j.jpeds.2008.12.045. [PubMed: 19230904].
- Mattoo TK, Chesney RW, Greenfield SP, Hoberman A, Keren R, Mathews R, et al. Renal Scarring in the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) Trial. *Clin J Am Soc Nephrol*. 2016;11(1):54-61. doi: 10.2215/CJN.05210515. [PubMed: 26555605]. [PubMed Central: PMC4702233].
- Cyrus A, Dorreh F, Sharafkhah M, Safi F, Naziri M, Taherahmadi H. Correlation of sacral ratio and reflux-related renal injury in children with vesicoureteral reflux with and without nephropathy. *J Pediatr Nephrol*. 2014;2(3):116-8.
- Massanyi EZ, Preece J, Gupta A, Lin SM, Wang MH. Utility of screening ultrasound after first febrile UTI among patients with clinically significant vesicoureteral reflux. *Urology*. 2013;82(4):905-9. doi: 10.1016/j.urology.2013.04.026. [PubMed: 23768525].
- Kocherov S, Arafah WA, Zeldin A, Ostrovsky IA, Ioscovich A, Farkas A, et al. Downgrading of high-grade vesicoureteral reflux is a reliable option in the treatment of children with grade IVV reflux accompanied by breakthrough infections. *J Pediatr Urol*. 2013;9(2):212-6. doi: 10.1016/j.jpuro.2012.02.006. [PubMed: 22391110].
- Sorkhi H, Nooreddini HG, Amiri M, Osia S, Farhadi-Niake S. Prediction of vesicoureteral reflux in children with first urinary tract infection by dimercaptosuccinic Acid and ultrasonography. *Iran J Pediatr*. 2012;22(1):57-62. [PubMed: 23056860]. [PubMed Central: PMC3448216].
- Kwatra N, Shalaby-Rana E, Majd M. Scintigraphic features of duplex kidneys on DMSA renal cortical scans. *Pediatr Radiol*. 2013;43(9):1204-12. doi: 10.1007/s00247-013-2619-z. [PubMed: 23385361].
- Zhang X, Xu H, Zhou L, Cao Q, Shen Q, Sun L, et al. Accuracy of early DMSA scan for VUR in young children with febrile UTI. *Pediatrics*. 2014;133(1):e30-8. doi: 10.1542/peds.2012-2650. [PubMed: 24366989].
- Lee J, Woo BW, Kim HS. Prognostic factors of renal scarring on follow-up DMSA scan in children with acute pyelonephritis. *Child Kidney Dis*. 2016;20(2):74-8. doi: 10.3339/jkspn.2016.20.2.74.
- Surucu E, Demir Y, Torun Bayram M, Kavukcu S, Durak H. Is Imaging Time Between two Tc 99m DMSA Scans Sufficient for Reporting as Renal Parenchymal Scarring? Healed Parenchymal Renal Defect After 6 Years. *Mol Imaging Radionucl Ther*. 2013;22(1):14-7. doi: 10.4274/Mirt.22. [PubMed: 23610726]. [PubMed Central: PMC3629786].
- Berger C, Becker T, Koen M, Zeino M, Fitz F, Beheshti M, et al. Positioning irrigation of contrast cystography for diagnosis of occult vesicoureteric reflux: association with technetium-99m dimercaptosuccinic acid scans. *J Pediatr Urol*. 2013;9(6 Pt A):846-50. doi: 10.1016/j.jpuro.2012.11.010. [PubMed: 23219319].
- Moon EH, Kim MW, Kim YJ, Sun IO. Crossed Fused Renal Ectopia: Presentations on 99mTc-MAG3 Scan, 99mTc-DMSA SPECT, and Multidetector CT. *Clin Nucl Med*. 2015;40(10):835-7. doi: 10.1097/RLU.0000000000000937. [PubMed: 26252333].
- Tseng MH, Lin WJ, Lo WT, Wang SR, Chu ML, Wang CC. Does a normal DMSA obviate the performance of voiding cystourethrography in evaluation of young children after their first urinary tract infection? *J Pediatr*. 2007;150(1):96-9. doi: 10.1016/j.jpeds.2006.09.028. [PubMed: 17188624].

16. Camacho V, Estorch M, Fraga G, Mena E, Fuertes J, Hernandez MA, et al. DMSA study performed during febrile urinary tract infection: a predictor of patient outcome? *Eur J Nucl Med Mol Imaging*. 2004;**31**(6):862-6. doi: [10.1007/s00259-003-1410-z](https://doi.org/10.1007/s00259-003-1410-z). [PubMed: [14758509](https://pubmed.ncbi.nlm.nih.gov/14758509/)].
17. Alshamsam L, Al Harbi A, Fakeeh K, Al Banyan E. The value of renal ultrasound in children with a first episode of urinary tract infection. *Ann Saudi Med*. 2009;**29**(1):46-9. doi: [10.4103/0256-4947.51817](https://doi.org/10.4103/0256-4947.51817). [PubMed: [19139618](https://pubmed.ncbi.nlm.nih.gov/19139618/)]. [PubMed Central: [PMC2813611](https://pubmed.ncbi.nlm.nih.gov/PMC2813611/)].
18. Moorthy I, Easty M, McHugh K, Ridout D, Biassoni L, Gordon I. The presence of vesicoureteric reflux does not identify a population at risk for renal scarring following a first urinary tract infection. *Arch Dis Child*. 2005;**90**(7):733-6. doi: [10.1136/adc.2004.057604](https://doi.org/10.1136/adc.2004.057604). [PubMed: [15970618](https://pubmed.ncbi.nlm.nih.gov/15970618/)]. [PubMed Central: [PMC1720473](https://pubmed.ncbi.nlm.nih.gov/PMC1720473/)].
19. Kass EJ, Kernan KM, Carey JM. Paediatric urinary tract infection and the necessity of complete urological imaging. *BJU Int*. 2000;**86**(1):94-6. doi: [10.1046/j.1464-410x.2000.00728.x](https://doi.org/10.1046/j.1464-410x.2000.00728.x). [PubMed: [10886091](https://pubmed.ncbi.nlm.nih.gov/10886091/)].
20. Ajdinovic B, Jaukovic L, Krstic Z, Dopuda M. Technetium-99m-dimercaptosuccinic acid renal scintigraphy in children with urinary tract infections. *Hell J Nucl Med*. 2006;**9**(1):27-30. [PubMed: [16617390](https://pubmed.ncbi.nlm.nih.gov/16617390/)].