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Assessment of Differential Renal Function in Children with Hydronephrosis: Comparison of DMSA and MAG-3

Hidronefrozlu Çocuklarda Separe Renal Fonksiyonların DMSA ve MAG-3 Sintigrafisi ile Karşılaştırılması

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What's known on the subject? and What does the study add?

Of all publications in the field of urology, so far no study has demonstrated that mercaptoacetyltriglycine (MAG-3) scintigraphy is as effective as dimercaptosuccinic acid (DMSA) scintigraphy in detecting DRF. Our study demonstrates that, in the evaluation of differential renal function (DRF) in children with hydronephrosis, MAG-3 scintigraphy provides results similar to those obtained using DMSA scintigraphy and, therefore, that it can be used alone in determining DRF.

ABSTRACT

Objective

Nuclear imaging techniques such as 99mTc-dimercaptosuccinic acid (DMSA) and ^{99}mTc-mercaptoacetyltriglycine (MAG-3) are widely used for the diagnosis and follow-up of urinary tract obstructions. Both imaging techniques provide the differential renal function (DRF) in slightly different ways. The aim of this study was to assess the MAG-3 scan as an adjunct or alternative to DMSA for evaluating DRF in children with hydronephrosis.

Materials and Methods

Eighty-one patients with hydronephrosis were enrolled in this study. Patient age, sex, anteroposterior renal pelvis diameter (RPD) at the time of diagnosis, parenchymal thickness and the DRF percentage found by both DMSA and MAG-3 were recorded. DMSA scintigraphy was used for detecting renal scars and estimating DRF. MAG-3 scintigraphy was used for evaluation of renal clearance, the collecting system's outflow pattern and estimating DRF.

Results

A total of 102 renal units (38 left, 22 right and 21 bilateral) were evaluated. High correlation rates were found when we compared both tests' DRF values according to antero-posterior renal pelvic diameter and patient age (p>0.05). In all groups compared in the present study, both tests demonstrated very similar results and DRF values. Statistical analysis of cut-offs (45%, 40%, 10%) were also similar in both methods (p>0.05, kappa >0.7, r=0.926 Pearson).

ÖZET

Amaç

^{99}mTc-dimerkaprosüksinik asit (DMSA) sintigrafisi sepere renal fonksiyonların (SRF) hesaplanmasında altın standarttır. DMSA ve ^{99}mTc-Merkaptoasetilglisin-3 (MAG-3) böbrek sintigrafileri hidronefrozlu çocukların tanısında, izleminde ve operasyon endikasyonu belirlemede kullanılmaktadır. Her iki teknik kullanılarak SRF hesaplanabilir. Çalışmamızda hidronefrozlu çocuklarda MAG-3 sintigrafisinin DMSA sintigrafisine göre SRF'yi belirlemedeki etkinliği araştırıldı.

Gereç ve Yöntem

Ocak 2009 ile Ağustos 2013 tarihleri arasında çocuk ürolojisi kliniğimizde izlenen 81 hidronefrozlu çocuk çalışmaya dahil edildi. Çocukların tanı anındaki yaşı, cinsiyeti, renal pelvis anterior posterior (AP) çapı, parankim kalınlığı ve DMSA ile MAG-3 sintigrafisiyle belirlenen SRF'leri kaydedildi. Çocuklar SRF'ye göre %45, %40, %10; AP çaplarına göre 5-10 mm, 10-20 mm, 20-30 mm ve 30-40 mm ve yaşlarına gore 24 ay altı ve üstü olarak gruplandırıldı. Gruplar her iki nükleer görüntüleme yönteminin SRF değerleri açısından karşılaştırıldı.

Bulgular

Seksen bir çocuğun (54 kız, 27 erkek) ortalama yaşı 25,9±39,7 aydı. Toplam 102 hidronefrozlu böbreğin (38 sol, 22 sağ ve 21 çift taraflı) tanı anındaki ortalama AP çapları 22,0 mm idi (min:7, max:62). AP çapa ve yaşa göre ayrılan gruplar arası SRF değerleri her iki görüntüleme tekniği içinde benzerdi (p>0,05). Grupların SRF %45, %40, %10'a göre aralarında istatistiki anlamlı fark saptanmadı (p>0,05, kappa >0,7, r=0,926 Pearson).

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ABSTRACT

Conclusion

DMSA and MAG-3 are tests that are of assistance in the evaluation of hydronephrosis. Compared to DMSA, MAG-3 also provides valuable information to evaluate DRF values in hydronephrotic renal unit (RU). Avoiding unnecessary DMSA imaging will save time and cost and prevent over-radiation of the pediatric population.

Key Words

Kidney, hydronephrosis, MAG-3, DMSA, differential function, children

ÖZET

Sonuç

MAG-3 sintigrafisi SRF değerlendirmesinde DMSA sintigrafisi kadar etkili bir testtir. Hidronefroz ile takip edilen çocukların SRF acısından değerlendirilmesinde ve izleminde tek test olarak kullanılabilir.

Anahtar Kelimeler

Böbrek, hidronefroz, MAG-3, DMSA, separe fonksiyon, çocuk hastalar

Introduction

Hydronephrosis is a common problem in pediatric urology. There is no absolute criterion used for determining urinary system obstructios. The most widely accepted definition of late refers to hydronephrosis generated by obstruction of the urinary system, which subsequently causes progressive renal injury (1). Nuclear imaging techniques such as ^{99}mTc-dimercaptosuccinic acid (DMSA) and ^{99}mTc-mercaptoacetyltriglycine (MAG-3) are widely used for the diagnosis and follow-up of urinary tract obstructions (2). DMSA scan, specifically, is the reference imaging procedure for determining renal cortical integrity and differential renal functions (DRFs) and this feature makes it the most reliable method for detection of cortical scarring (DRF) (3,4). DMSA scan is considered to be the most effective method in this regard (5). However, MAG-3 scan is also good at determining renal tubular functions such as renal uptake, excretion and consequent drainage (6). Consequently, both methods can calculate the contribution of each kidney to total renal function and contribute to estimating the DRF percentage. Parenchymal features of the kidney are best calculated with DMSA (2). Although MAG-3 allows for obtaining information about the collecting system and the dynamics of the kidney, its percentage of DRF estimation with sensitivity and specificity is 88-89% and 88-100%, respectively (2,7). A difference between DRF values of more than 10% or a sole DRF value below 45% is accepted as abnormal (8). 40% and 10% values are often definitive for deciding on the form of treatment and on the timing of surgical interventions (8). Particularly in such cases described above, using both methods together is costly and leads to more radiation exposure.

In this study, we aimed to evaluate the effectiveness of MAG-3 as an alternative imaging method. The goal was investigate whether it can replace DMSA imaging in evaluating DRF and to evaluate the accuracy of decision-making for surgery indication as the stand-alone imaging method.

Materials and Methods

The medical data of 81 patients with hydronephrosis, who attended our pediatric urology department, were analyzed retrospectively. Sonographically measured anteroposterior renal pelvis diameter (RPD), parenchymal thickness and kidney dimensions were evaluated and calculated by the radiology department at our hospital. The Society for Fetal Urology guidelines for ultrasound grading of hydronephrosis were used as a reference in this study (9).

Management and Follow-Up

For detailed evaluation, each patient underwent a physical examination. A detailed medical history was obtained and urine analysis, culture, urinary ultrasound and nuclear imaging were also performed.

Urinary Ultrasound

Since transitory neonatal dehydration lasts about 1 week after birth, all neonatal first urinary ultrasounds (US) are obtained after this period. Ultrasound should assess the anteroposterior diameter of the renal pelvis, calyceal dilatation, kidney size, thickness of the parenchyma, cortical echogenicity, ureters, bladder wall and residual urine volume.

Voiding Cystourethrogram

Children, who suffered from recurrent urinary tract infections (UTIs) and had bilateral hydronephrosis, underwent voiding-cystouretrogram (VCUG), enabling us to evaluate the uretral valves, and detect the presence of ureteroceles, diverticula and vesicoureteral reflux.

Nuclear Imaging

DMSA and MAG-3 were performed together in all patients who were enrolled in this study. DMSA scintigraphy was used for detecting renal scars and estimating DRF. MAG-3 scintigraphy was used for evaluation of renal clearance, the collecting system outflow pattern and estimating DRF. All MAG-3 scintigraphies were performed under standardized circumstances (hydration, transurethral catheter) between the fourt and sixth weeks of life or after detection of hydronephrosis by the nuclear medicine department at our hospital.

Indications for surgical intervention are an impaired DRF due to obstruction or a decrease in DRF in subsequent studies and increased anteroposterior diameter on ultrasound, and kidney detoriaration-grade IV dilatation as defined by the Society for Fetal Urology. %10, 40%, 45% are important cut-off values to make surgical decisions. More than 10% difference between the two renal units (<45% DRF) is considered abnormal (8,10,11). In the case of serial renogram results, less than 40% is the cut-off value to make the surgical decision for pyeloplasty and 10% is the cut-off value to make the surgical decision for a simple nephrectomy. The DMSA and MAG-3 DRF results of the patients were categorized according to cut-off values (10%, 40%, 45%) and were later compared.

Since the kidneys complete their development during the first years of postnatal life and reach their full functional maturity in adolescence, the postnatal age criteria became important when DRF are compared

regarding to DMSA and MAG-3 results. Thus, both tests predictive for DRF according to age were also compared. Patients with urinary system anatomical abnormalities (solitary and horse shoe kidneys, duplicated system, agenetic or nephrectomize) were excluded from the study.

Statistical Analysis

Statistical analysis was performed using original SPSS software, version 20.0 (IBM Corp, NY, USA). Each test was classified as <10%, <40% and <45% according to DRF values. Inter-method analyses were carried out by means of Kappa statistics. The McNemar and Mann-Whitney U tests were also applied in the statistical analysis of the study where necessary. A p value of less than 0.05 was considered statistically significant.

Results

A total of 183 patients with hydronephrosis attended our pediatric urology outpatient clinic. Data of 81 of these patients were available. Fifty-four patients were male (66.7%) and 27 were female (33.3%). A total of 102-38 left, 22 right and 21 bilateral-hydronephrotic renal units were detected. The mean age of the patients at the time of diagnosis was 25.9±39.7 months. Estimated mean anteroposterior RPD was 22 mm (min:7, max:62). Thirty-six ureteropelvic junction-plasty (UPJ-plasty), 3 ureteroneocystostomy (UNC), 3 posterior ureteral valve (PUV) ablation and 5 diagnostic cystoscopy operations were performed. Thirty-four of the patients included in this study were diagnosed with transient hydronephrosis and did not require any surgical intervention. These patients were followed using periodic ultrasound screening (Table 1). Comparison of anteroposterior RPD values measured during the follow-up by DMSA and MAG-3 RF is also presented in Table 1. In all groups compared in the present study, both tests demonstrated very similar results and DRF values. No statistically significant difference was determined between the results.

The present study also analyzed DRF within 3 groups (≤45%, ≤40% and ≤10%) for more accurate timing of surgical intervention or follow-up. From those patients who were evaluated using DMSA, 20 renal units were detected at ≤45%, 14 renal units at ≤40% and 2 renal units at ≤10%. MAG-3 also showed similar results: 27 renal units were detected at ≤45%, 12 renal units at ≤40% and 3 renal unit ≤10%. The results in each group were compared using the McNemar test and no significant differences were found. A close correlation was determined between the DRF values obtained by these two tests (Kappa values: 0.673, 0.725 and 0.794, respectively (substantial agreement)) (Table 2).

More detailed anteroposterior (AP) RPD statistics are summarized in Table 3. We used 5 cut-offs and assessed DRF values within 5 groups: 5-10 mm: 11 patients, 10-20 mm: 31 patients, 20-30 mm: 21 patients, 30-40 mm: 13 patients and ≤40 mm: 5 patients. After classification of AP RPD based on the cut offs, DRF values were assessed and DMSA-MAG-3 results were found N to be not statistically different (p≥0.05) (Table 3).

Sixty-six of the 81 patients were younger than 24 months at the time of diagnosis (mean: 40.4±34.2 SD). The remaining 15 patients were older than 24 months (mean: 407.2±184.4 SD weeks). MAG-3 demonstrated similar results to those of DMSA and no statistically significant difference was found (Table 4). The scintigraphic results as obtained by MAG-3 scan were very close to those by DMSA with statistically significant correlations of DRF values (r=0.926) (Figure 1).

Table 1. Comparison between 99mTc-DMSA and 99mTc-MAG-3 DRF results according to hydronephrosis etiology

		n	Right kidney DRF (%)	Left kidney DRF (%)	Hydronephrotic kidney APD (mm)	p value
Follow-up	DMSA	34	49.1 (±11.4)	50.8 (±11.4)	16.2 (±9.2)	<0.408
	MAG-3	34	48.5 (±12.8)	51.4 (±12.8)		
UPJ-plasty	DMSA	36	52.6 (±12.0)	47.6 (±12.7)	28.6 (±12.5)	<0.216
	MAG-3	36	50.8 (±14.3)	49.2 (±12.6)		
UNC	DMSA	3	61.6 (±11.5)	38.3 (±11.5)	14.5 (±2.1)	<0.260
	MAG-3	3	56.6 (±6.0)	43.3 (±6.0)		
PUV ablation	DMSA	3	20.3 (±24.8)	79.6 (±24.8)	22.0 (±9.8)	<0.697
	MAG-3	3	21.6 (±22.5)	78.3 (±22.5)		
Diagnostic cystoscopy	DMSA	5	41.6 (±27.0)	58.4 (±27.0)	17.0 (±9.1)	<0.794
	MAG-3	5	41.2 (±26.1)	58.8 (±26.1)		
Total	DMSA	81	49.6 (±14.7)	50.5 (±15.0)	22.0 (±12.2)	<0.316
	MAG-3	81	49.2 (±15.5)	50.8 (±15.0)		

MAG-3: Mercaptoacetyltriglycine, DMSA: Dimercaptosuccinic acid, UNC: Ureteroneocystostomy, PUV: Posterior ureteral valve, UPJ-plasty: Ureteropelvic junction-plasty, APD: Anterior-posterior diameter, DRF: Differential renal function

Table 2. DMSA and MAG-3 comparison with regard to specific DRF results (≤45%, ≤40% and ≤10%)

DRF/Total	DMSA DRF %	MAG-3 DRF %	p value (McNemar test)	Kappa value
<45% / Total	20/81 (24.6%)	27/81 (33.3%)	p=0.065	0.673 (very good)
<40% / Total	14/81 (17.3%)	12/81 (14.8%)	p=0.687	0.725 (very good)
<10% / Total	2/81 (2.4%)	3/81 (3.7%)	p>0.05	0.794 (very good)

MAG-3: Mercaptoacetyltriglycine, DMSA: Dimercaptosuccinic acid, DRF: Differential renal function, RPD: Renal pelvis diameter

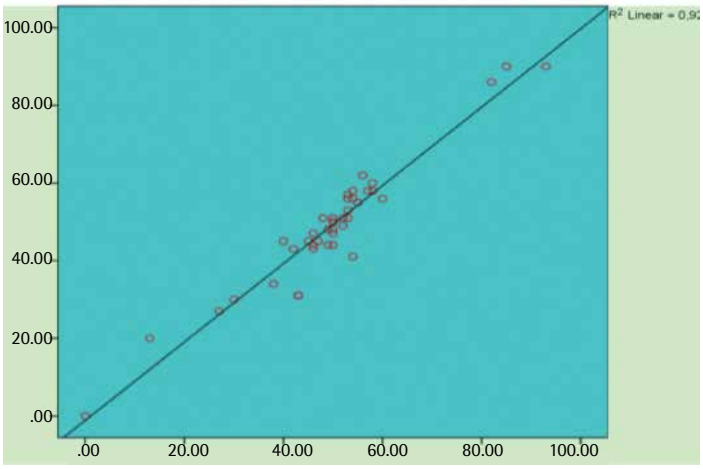

Figure 1. Kaplan meier analyses of cancer spesific survival between the groups

Tablo 3. Comparison DMSA and MAG-3 according to AP RPD and DRF

Anteroposterior RPD (mean)		n	DRF (%)		p value
			(right kidney)	(left kidney)	
5-10 mm	DMSA	11	48.5	51.5	0.929
	MAG-3		48.6	51.4	
10-20 mm	DMSA	31	50.1	50.1	0.752
	MAG-3		50.3	49.6	
20-30 mm	DMSA	21	51.3	49.6	0.050
	MAG-3		53.5	48.3	
30-40 mm	DMSA	13	49.6	50.3	0.399
	MAG-3		48.3	51.6	
40 mm	DMSA	5	52.4	47.6	0.522
	MAG-3		56.2	43.8	

MAG-3: Mercaptoacetyltriglycine, DMSA: Dimercaptosuccinic acid,
DRF: Differential renal function, RPD: Renal pelvis diameter, AP: Anteroposterior

Table 4. Patients age at the time of diagnosis and comparison of results

Age		Mean	n	Std. deviation	p value
<24 month	DMSA	47.6	66	34	
	MAG-3	47.5	66	34	0.923
>24 month	DMSA	53.3	15	184	
	MAG-3	51.4	15	184	0.193

MAG-3: Mercaptoacetyltriglycine, DMSA: Dimercaptosuccinic acid

Discussion

DMSA and MAG-3 are tests that are of assistance in the evaluation of hydronephrosis and that are often employed together during the clinical decision making process (8). Although the pharmacokinetic properties of the nuclear agents employed in the two tests differ, both tests predict the separated renal functions (12,13). In the present study, it was concluded that in the case of patients for which DMSA and MAG-3 are utilized regardless of the etiology of hydronephrosis, considering separated renal functions and variables such as patient age, the degree of hydronephrosis and etiology is believed to separate the two tests; in the clinical setting, MAG-3 can be employed in place of DMSA. A statistically significant difference was not detected between the two tests when they were compared based on hydronephrosis degree and etiology and patient age. The two tests were also found to be highly similar and compatible when compared in terms of clinical applicability.

The subject of the present study arose from a desire to minimize radionuclide evaluation in the pediatric patient population. In this study, the aim was to compare the results obtained using DMSA and MAG-3 and contrast management in the different conditions of hydronephroticrenal units such as transient hydronephrosis, ureteropelvic junction obstruction (UPJO), vesicoureteric reflux (VUR), posterior urethral valve (PUV), ectopic ureter based on DRF values.

DMSA is a radionuclide molecule that enters the proximal and distal tubules of the kidney. For this reason, it is a method of choice for cortical assessment. MAG-3 is mostly excreted by the proximal tubules; it enters the collecting systems and leaves the kidneys very fast. DMSA scan is usually performed 2-3 hours after the DMSA injection. But MAG-3 images are obtained immediately after the injection of MAG-3. Both techniques, therefore, estimate the kidneys` contribution to total renal function in slightly different ways.

In the evaluation of hydronephrosis, assessment of DRF is essential to provide a prognosis or to determine whether to perform surgery. Although DMSA scan is the most reliable method in measuring DRF (4), the long residence time in the renal cortex results in over-radiation of the children who have to attend nuclear medicine clinic twice for later scanning. In addition, evaluation by means of DMSA is limited to only cortical assessment, not the collecting system outflow pattern (3,4,14). Other agents, such as MAG-3, also measure DRF and are employed in the evaluation of renal clearance. MAG-3 is cleared from the blood by the renal tubules and excreted into the collecting system (15,16). Therefore, it is possible to evaluate renal perfusion, tubular function, tubular secretion to the collecting system and the urodynamics of the collecting system by means of MAG-3. Thity minutes after injection, most tracer activity leaves the kidney, which is an important advantage of this technique as it makes the radiation dose received by the patient less than that received by a patient undergoing a DMSA scan. It should also be noted that MAG-3 takes less time and requires less follow-up visits. The radiation exposure for a DMSA study is approximately ten times higher than that for a MAG-3 study, thus, eliminating the need for the DMSA study will reduce radiation exposure. This change in practice would, therefore, result in considerable savings in time, cost and radiation burden (13).

When previously published studies on this topic are reviewed, one comes to see that there have been many studies comparing the correlation between these two techniques. However, to our knowledge, all such similar studies have been published in nuclear medicine or radiology journals. None of them include clinical prognosis of the disease (13,17,18,19). In addition, worldwide, no such article has been published by a pediatric urology clinic.

The first published articles comparing the two techniques, DMSA and MAG-3, included only a few patients. Piepszet et al.(12) performed and evaluated both test on healthy volunteers. As a result, they found similar results.

Aktaş et al. (17) compared MAG-3 and DMSA RRF estimations and assessed the reproducibility of these estimations in children with unilateral hydronephrosis. Their results showed that DMSA and MAG 3 were correlated for both time intervals and for observers. DRF estimation can be a problem in infants and in patients with higher grades of hydronephrotic kidney. Only comparison with 45% was slightly different in each test (17). Consequently, it is determined that both screening techniques gave us similar results for follow-up and for timing of operations. Therefore, we support that both techniques can be used alone for further evaluations.

Ritchie et al. (13) compared DRF values calculated using ^{99}mTc-DMSA and those calculated using ^{99}mTc-MAG-3 in pediatric patients and again found good correlation between DMSA and MAG-3.

In the present study, the mean DRF of the left unit with ^{99}mTc-DMSA was 48.9% (SD 16.4) and was 49.6% (SD 15.6%) using ^{99}mTc-MAG-3. Thus, both tests showed a significant correlation with each other. There was a lack of consistency between DRF estimations or supranormal functions only in a limited number of cases (Tables 1, 4). The measurement of DRF can be overestimated by ^{99}mTc-MAG-3 in the affected kidneys (5).

Although many decisions regarding surgery are based on the functional changes detected by serial diuretic renography evaluations, the ability of MAG-3 in estimating DRF has been questioned. In follow-up, DRF values of 10%, 40%, 45% are important cut-off values to make surgical decisions. More than 10% difference between the two renal units (<45% DRF) is considered an abnormal test result (8,10,11). According to serial renogram, less than 40% is the cut-off value to make a surgical decision for ureteroplasty and 10% is the cut-off value to make a surgical decision for simple nephrectomy. In the present study, there were no statistically significant differences in prognosis and management based on the values presented by the two nuclear imaging methods. Only 2 patients presented dissimilar results according to DRF 40% (DMSA: 39% and 39% vs MAG-3: 43% and 45%, respectively) and 1 patient according to 10% (DMSA: 4% vs MAG-3: 15%). Renal cortical thickness, pelvic anterior-posterior diameter (APD), urine and blood tests do not contribute to follow-up results.

In the calculation of clearance adjusted according to the body mass index during childhood, those kidneys that demonstrated progressive maturation until the third week, drew a plateau until year 1, appeared to grow 1.5 times in size by year 2 and later appeared to become fixed (20). In the present study, values obtained in 24 months were compared and there were similar test results in each test. Regardless of whether the kidney completes maturation or not, their power is unchanging in determining separated renal functions.

Study Limitations

Our study included a small number of patients with low renal function (at ≤40% and at ≤10%).

Conclusion

The results suggest that in routine clinical management and follow up, MAG-3 scan will provide accurate DRF, similar to that with DMSA. MAG-3 provides additional information on the urodynamics of the urinary tract avoiding unnecessary radiation exposure besides being timesaving. The results of MAG-3 do not change the clinical decision on the management of the condiditon and patient follow-up. Therefore, it is possible to regard the ^{99}mTc-MAG-3 as adequate in evaluating DRF as an initial screening test in children with various renal disorders. The ^{99}mTc DMSA scan is the only suitable in doubtful cases such as those involving small cortical focal defects.

Ethics Committee Approval: The study were approved by the Marmara University of Local Ethics Committee, **Informed Consent:** Consent form was filled out by all participants, **Concept:** Cem Akbal, Tufan Tarcan, Ferruh Şimşek, **Design:** Cem Akbal, Tufan Tarcan, Ferruh Şimşek, **Data Collection or Processing:** Ahmet Şahan, Asgar Garayev, Çağrı Akın Şekerci, Harika Alpay, **Analysis or Interpretation:** Ahmet Sahan, Cem Akbal, **Literature Search:** Ahmet Sahan, Asgar Garayev, **Writing:** Cem Akbal, Ahmet Şahan, **Peer-review:** Internal peer-reviewed, **Conflict of Interest:** No conflict of interest was declared by the authors, **Financial Disclosure:** The authors declared that this study has received no financial support.

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