F+0 Diuresis Renography in Infants and Children

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The purpose of this study was to evaluate the feasibility of modifying diuresis renography by the simultaneous administration of ^{99m}Tc-mercaptoacetyltriglycine (MAG3) and furosemide in the investigation of hydronephrosis and hydroureteronephrosis in infants and children. Two parameters were assessed: the diuretic response in normal kidneys and the ability of the F+0 study to differentiate between renal obstruction and nonobstruction and to identify the level of obstruction in cases of renal obstruction. Methods: Seventy-two patients (48 males, 24 females; age 2 d to 7 y; median age 6 wk) with sonographic diagnoses of hydronephrosis or hydroureteronephrosis were reviewed prospectively over a 3-y period. All patients had prior sonographic studies and micturating cystourethrography. Bladder catheterization was not routinely performed and was undertaken only if the child had suspected vesicoureteric junction (VUJ) obstruction or grade II or more vesicoureteric reflux. A weight-adjusted dose of 99mTc-MAG3 (maximum 200 MBg, minimum 20 MBq) and 1 mg/kg of furosemide (maximum 40 mg) were administered intravenously at the same time. Posterior imaging of the kidneys and bladder was performed for 20 min and followed by gravity-assisted drainage or imaging after voiding. All patients were followed-up for 6-12 mo, and the final diagnoses were based on either surgery or conservative management with repeated sonography or follow-up ^{99m}Tc-MAG3 studies (or both). The results of the F+0 diuresis renography were then compared with the final diagnoses. Results: A renal unit was defined as a kidney and its ureter. There were 151 renal units with 1 patient having bilateral duplex kidneys, 6 patients having unilateral duplex kidneys and 1 patient having a solitary kidney. Fifty-five normal renal units and 96 abnormal renal units on the basis of sonographic findings were assessed. The furosemide clearance half-time for the 55 normal renal units was 1.3-6.3 min (mean 3.8 min). Of the 96 abnormal renal units, 53 were classified as nonobstructed and 43 were classified as obstructed. Of the 53 renal units classified as nonobstructed, there were 48 true-negative studies and 5 false-negative studies; of the 43 renal units classified as obstructed, there were 40 true-positive studies and 3 falsepositive studies. The sensitivity was 88.9%, specificity was 94.1% and accuracy was 91.7%. The level of obstruction, either pelviureteric junction or VUJ, was also correctly identified. Conclusion: F+0 diuresis renography shows excellent diuretic responses in normal kidneys and is a valid method for the investigation of hydronephrosis and hydroureteronephrosis in infants and children.

Key Words: diuresis renography; ^{99m}Tc-mercaptoacetyltriglycine; furosemide; infants

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With the widespread use of antenatal sonography during pregnancy, there has been a marked increase in the early detection of hydronephrosis and hydroureteronephrosis. This early detection has resulted in the investigation of many infants with these abnormalities (1,2). Urinary tract obstruction can be located anywhere from the renal pelvis to the urethra, and, in pediatric patients, the most common site is at the pelviureteric junction (PUJ). Less commonly, the vesicoureteric junction (VUJ) or ureterocele is the site of obstruction (3,4). Diuresis renography in the investigation of hydronephrosis has been shown to be reliable in the neonatal period (5,6). Diuresis renography using 99mTc-mercaptoacetyltriglycine (MAG3) and diethylenetriamine pentaacetic acid has also been reported to be useful in the investigation of PUJ and VUJ obstruction in neonates and children (6-10). However, establishing venous access in infants is often difficult because the veins are small and subcutaneous fat may be prominent. In addition, some young children cannot lie relatively still for the 45 min required for a traditional F+20 diuresis renogram. The F+20 diuresis renography requires an interval of 20 min between the injections of the radiopharmaceutical and the diuretic (9-11), and intravenous access has to be maintained for 20 min. The maximal effect of furosemide is 15-18 min after intravenous injection, justifying the alternative method of giving the diuretic 15 min before the radiopharmaceutical (F-15). The F-15 timing is recommended when F+20 results are equivocal or when renography under a state of maximal diuresis is required (11,12). Again, this method involves an interval between the injections of the diuretic and radiopharmaceutical. Other investigators suggest injection of furosemide 3 min after the radiopharmaceutical (13,14). Some administer the radiopharmaceutical and furosemide together. This procedure was termed F+0 diuresis renography by O'Reilly et al. (11). However, there is a paucity of literature validating this F+0 method (12). We decided to prospectively investigate modified diuresis renography in which the radiopharmaceutical and diuretic are administered together. Two parameters require validation: whether there is an adequate response in kidneys that appear normal on sonographic examination and whether renal obstruction can be differenti-

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50 Bilat HN 6.5 5.1 47:53 No obs bilat	49	LHN	12.9	3.4		51:49	No obs L	
	50	Bilat HN	6.5	5.1		47:53	No obs bilat	

TABLE	1 (Continu	ed)
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Patient	Sonography	Scan half-time (min)		Poor drainage	Differential		Final diagnosis (if different
no.		L	R	with GAD	L/R (%)	Scan result	from scan)
51	L HN	8	3.4	L	54:46	L PUJO	
52	Bilat HN	15.6	5.3		47:53	No obs bilat	
53	L HN	11.5	5.8		47:53	No obs L	L PUJO
54	R HN	1.3	– Rum		65:35	No function R um	
			2.0 R Im			No obs R Im	
55	L HN	9.8	5.1		47:53	No obs L	
56	L HN	8.2	6.3		47:53	No obs L	
57	L HN	7.7	_		100:0	No obs L	
58	Bilat HN	œ	80	Bilat	51:49	Bilat PUJO	
59	L HN	4.0	1.8		43:57	No obs L	
60	L HN	1.3	1.3		52:48	No obs L	
61	L HN		4.2		0:100	No function L	
62	R HU	2.9	8	R	64:36	R VUJO	
63	R HN	6.2	25.1	R	50:50	R PUJO	
64	L HN	9.4	6.0		48:52	No obs L	L PUJO
65	R HN	2.8	_		0:100	No function R	
66	L HN	14.8	6.6	L	54:46	No obs L	L PUJO
67	Bilat HU	œ	œ	Bilat	56:44	Bilat VUJO	
68	R HN	4.8	œ	R		R PUJO	
69	Bilat HN	3.5	6.2		48:52	No obs bilat	
70	R HN	1.3	_		100:0	No function R	
71	LHN	7.4	5.1		44:56	No obs L	
72	R HN	5.3	œ	R	42:58	R PUJO	

GAD = gravity-assisted drainage; HN = hydronephrosis; ∞ = infinity; um = upper moiety of duplex system; Im = lower moiety of duplex system; No obs = no obstruction; HU = hydroureteronephrosis; VUJO = vesicoureteric junction obstruction; PUJO = pelviureteric junction obstruction; Bilat = bilateral.

ated from nonobstruction and the level of obstruction identified using this modified technique.

MATERIALS AND METHODS

Seventy-two patients (48 males, 24 females; age 2 d to 7 y; median age 6 wk)with a diagnosis of hydronephrosis or hydroureteronephrosis detected on sonographic examination and who had difficulty either with venous access or with remaining still for a standard F+20 diuretic renogram were enrolled prospectively over a 3-y period. The serum creatinine level ranged from 0.02 to 0.17 mmol/L with a mean of 0.04 mmol/L (normal \leq 0.05 mmol/L). Nine patients had creatinine levels > 0.05 mmol/L.

All patients had prior evaluation for vesicoureteric reflux with micturating cystourethrograms. At this institution, bladder catheterization was performed before the commencement of the study only if the child had suspected VUJ obstruction or grade II or more vesicoureteric reflux on the micturating cystourethrogram. If catheterization was required, amoxicillin or gentamicin was given because of a risk of introducing infection with the catheter. The children were orally hydrated before commencement of the study, and no volume expansion was undertaken intravenously. The degree of oral hydration was not strictly defined; infants were usually breast-fed before the study and the quantitation of milk in this situation could not be undertaken. All studies were performed on either a model 400 AC or a model 300 gamma camera attached to a Starcam computer (General Electric Medical Systems, Milwaukee, WI) with low-energy, all-purpose collimation. The patients were studied supine and positioned so that the heart, kidneys and bladder were in the field of view. Images were obtained posteriorly. A weight-adjusted dose of 99mTc-MAG3 (using Gilday's graph [15]), with a maximum dose of 200 MBq and minimum dose of 20 MBq, was administered intravenously, followed immediately by 1 mg/kg of furosemide (maximum dose 40 mg). Tissue extravasation of MAG3 or diuretic was detected either clinically with swelling at the injection site or imaging the injection site (or both). Initial dynamic images were acquired at forty 1-s frames followed by sixty-two 20-s frames. The patients were then held upright for about 5 min to allow gravity-assisted drainage. Alternatively, a static image was acquired after voiding. Differential renal function was calculated using the total counts of the renogram curve for each kidney minus background counts during the interval between 1.5 and 2.5 min after the injection of the radiopharmaceutical. The renogram included the entire kidney and the renal pelvis. The furosemide clearance half-time was generated from the exponential fit of the maximal slope of the washout component of the renogram curve, starting at the peak of the renogram curve. Visual analysis was performed for the purpose of this study; quantitation of the counts in the regions of interest of the kidneys before and after gravity-assisted drainage will be addressed elsewhere.

To differentiate between obstruction and nonobstruction, the diagnoses were determined on the following criteria:

Significant PUJ obstruction was diagnosed if (a) visual analysis showed no significant drainage or progressive accumulation of radiopharmaceutical in the renal pelvicalyceal system, or furosemide clearance half-time > 20 min, and (b) visual comparison of before and after gravity-assisted drainage images showed no significant change.

Significant VUJ obstruction was diagnosed if (a) visual analysis showed no significant drainage or progressive accumulation of radiopharmaceutical in the ureter, or furosemide clearance halftime > 20 min, and (b) visual comparison of before and after gravity-assisted drainage images showed no significant change.

An obstructed renal unit (defined as a kidney and its ureter) was also diagnosed if there was poor, i.e., <20%, relative function or no function in the renal unit in the presence of hydronephrosis or hydroureteronephrosis on sonographic examination.

A not significantly obstructed (referred to as nonobstructed) renal unit was diagnosed if (a) visual analysis showed good drainage of the renal pelviureteric system, or furosemide clearance half-time < 20 min, and (b) visual comparison of before and after gravity-assisted drainage images showed significant further drainage.

A not significantly obstructed (referred to as nonobstructed) renal unit was also diagnosed even if the visual analysis showed no significant drainage or progressive accumulation of radiopharmaceutical in the renal pelvicalyceal system or ureter, or furosemide clearance half-time > 20 min, as long as the visual comparison of the before and after gravity-assisted drainage images showed significant further drainage.

All patients were followed-up for 6–12 mo, and the results of the F+0 diuresis renography were compared with the final diagnoses. All patients had clinical follow-up at 3-mo intervals with sonographic examinations performed at intervals of 3–6 mo. Repeated diuresis renography was performed if there was increasing dilatation found on the sonographic study. The final diagnoses were based on either surgical findings or conservative management with repeated sonography and ^{99m}Tc-MAG3 examinations. The decision for surgical intervention or conservative management was determined by the pediatric urologist, who considered the results of the diuresis renography, including the relative function of the kidney, the child's clinical findings and serial sonographic examination appearances before making the management decision.

RESULTS

The patients' data and results are shown in Table 1. A renal unit was defined as a kidney and its ureter. Of the 72 patients, there were 151 renal units for data analysis because 1 patient (patient 23) had bilateral duplex kidneys, 6 patients (patients 1, 26, 31, 35, 42 and 54) had unilateral duplex kidneys and 1 patient (patient 57) had a solitary kidney. One patient (patient 41) had a horseshoe kidney.

There were 53 normal nondilated renal units on sonographic examination, all showing good diuretic responses on F+0 diuresis renography with furosemide clearance halftimes of 1.3-6.3 min (mean 3.8 min). In addition, 9 patients (patients 5, 10, 11, 17, 22, 24, 31, 40 and 58) had creatinine levels of 0.06-0.17 mmol/L, and differentiation of renal obstruction from nonobstruction was achieved in this group except for patient 11. The nondilated renal units in this group with elevated creatinine levels had a furosemide clearance half-time of 2.3-5.3 min (mean 4.1 min).

Except for the renal units with no or poor function, the level of obstruction was determined by visual analysis of the

TABLE 2 Results of 96 Abnormal Renal Units

F+0 diuresis stud	Final diagnosis (if different from scan)		
Result	No.	Result	No
Nonobstruction	53	Obstruction	5
Total nonobstruction	53		
Obstruction	27	Nonobstruction	3
Poor function	4		
No function	12		
Total abote stice	43		

diuresis renography studies as outlined in Table 1. The results of the abnormal renal units are summarized in Table 2. Ninety-six renal units had hydronephrosis or hydroureteronephrosis on sonography and were investigated for renal obstruction using F+0 diuresis renography. After the F+0 study, 53 of these renal units were further classified as nonobstructed and 43 were classified as obstructed.

Fifty-three renal units classified as nonobstructed, with 48 renal units showing no obstruction on the subsequent 12-mo follow-up. There were five false-negative studies with surgery revealing typical PUJ obstruction on 4 renal units (patients 36, 45, 53 and 66). Two patients (patients 36 and 45) had increasing pelvicalyceal dilatation on follow-up sonographic examinations; 2 other patients (patients 53 and 66) had worsening sonographic appearances, and subsequent F+20 diuresis renography studies revealed PUJ obstruction. Intermittent left loin pain developed in patient 64 and he was found to have anomalous lower pole vessels at surgery, most likely causing intermittent ureteric obstruction. The ages of the 5 patients with false-negative studies varied, ranging from 8 wk to 5.5 y.

Of the renal units classified as obstructed, there were 4 renal units (patients 1, 31, 42 and 43) with poor renal function, 12 renal units (patients 5, 7, 9, 10, 26, 35, 38, 41, 54, 61, 65 and 70) with no renal function, and 27 renal units with obstruction. Of the 4 renal units with poor function, patient 1 had a right upper pole nephrectomy for a VUJ obstruction associated with a large ureterocele at the right side of the trigone, and patient 42 had a left lower pole pyeloplasty for a grossly dilated lower pole component with a tight PUJ obstruction. Patients 31 and 43 had pyeloplasties for tight PUJ obstruction.

For 5 of the 12 obstructed renal units with no function, patients 5, 7, 61, 65 and 70 (5 renal units) had nephrectomies for hydronephrotic dysplastic kidneys with features associated with a tight PUJ obstruction. Patient 54 (one renal unit) had upper pole partial nephrectomy for a nonfunctioning obstructed right upper pole moiety. Patients 9 and 35 (two renal units) had left nephrectomy, left ureterectomy and excision of associated ureterocele and left upper pole nephrectomy, left ureterectomy and excision of ureterocele, respectively, for VUJ obstruction. Patients 10, 26 and 38 (three renal units) had left nephrectomy, left lower pole partial nephrectomy and right nephrectomy, respectively, for nonfunction associated with renal dysplasia, which was diagnosed histologically after resection. Patient 41 (one renal unit) had a nonfunctioning component of a horseshoe kidney. Figure 1 shows a nonfunctioning lower pole moiety of the duplex left kidney associated with a severe PUJ obstruction confirmed surgically.

The remaining 27 renal units classified as obstructed had 19 renal units (patients 8, 12, 14, 19, 21, 22, 25, 27, 30, 41, 51, 58, 63, 68 and 72) with PUJ obstruction and 8 renal units (patients 2, 6, 11, 29, 37, 62 and 67) with VUJ obstruction. Figure 2 illustrates a case of unilateral PUJ obstruction, and Figure 3 shows a case of bilateral VUJ obstruction. At surgery, obstruction of 24 of these renal units (patients 2, 6, 12, 14, 19, 22, 25, 27, 29, 30, 37, 41, 51, 58, 63, 67, 68 and 72) was confirmed with either pyeloplasties or reduction ureteroplasties and ureteric reimplantation performed. All 18 renal units (patients 8, 12, 14, 19, 22, 25, 27, 30, 41, 51, 58, 63, 68 and 72) with PUJ obstruction and 6 renal units (patients 2, 6, 37, 62 and 67) with VUJ obstruction were correctly identified as to the level of obstruction on diuresis renography compared with the results of the surgery.

There were 3 false-positive studies with 3 renal units (patients 11, 21 and 29) showing no obstruction on follow-up sonography and 99m Tc-MAG3 examinations. Two of these renal units (patients 11 and 29) were diagnosed on the F+0 diuresis renography study as having VUJ obstruction, and 1 renal unit (patient 21) was diagnosed as having PUJ obstruction. These 3 patients remained clinically well in the 12-mo follow-up period with improving appearances on sonography and 99m Tc-MAG3 studies. Two of these patients (patients 21 and 29) were 6 wk old and the other (patient 11) was 9 mo old.

On the basis of the F+0 diversis renography study and the final diagnoses based on either surgery or conservative management with follow-up sonography and ^{99m}Tc-MAG3

studies, the sensitivity of the study was 88.9%, specificity was 94.1% and accuracy was 91.7%.

DISCUSSION

F+0 diuresis renography is a term recently used by O'Reilly et al. (11). Some departments use the F+0 diuresis renography method (11), but there is a paucity of literature validating this method (12).

It is difficult to provide a gold standard for the F+0 diuresis renography study. However, we believe that follow-up data of up to 12 mo to ascertain whether the patients require surgery with the subsequent operative findings or conservative management is a valid way of justifying the feasibility of the F+0 diuresis renography study. A 3- to 6-mo observation period for neonates with hydronephrosis associated with PUJ anomalies when definite obstruction cannot be confirmed by diuresis renography has been recommended (2,16). The pediatric urologist takes into account not only diuresis renography studies but also other parameters such as the relative function of the kidney, the child's clinical presentation and sonographic examination findings before embarking on surgical intervention.

In the neonatal group, the operative findings that cause the obstruction vary. Some children have classic fibromuscular hyperplasia at the PUJ. Other children appear to have proximal ureters with a corkscrew appearance that may result in obstruction at the PUJ caused by kinking of the ureter at the site of tortuosity. Another group has lower pole vessels that compress the renal pelvis and result in intermittent PUJ obstruction. Causes of VUJ obstruction include adynamic nonperistaltic tonically contracted distal ureteral segments and ureteroceles.

Another justification of the F+0 diuresis renography method is that the 53 normal nondilated renal units all had a furosemide clearance half-time of <10 min, which is the normal or nonobstructed range reported in the literature (17,18). In addition, 9 patients had creatinine levels between 0.06 and 0.17 mmol/L, and results of the F+0 study were still interpretable with the nondilated renal units all having a



FIGURE 1. Nonfunctioning renal unit. Posterior views show no radiopharmaceutical uptake in lower pole moiety of left duplex kidney. (Furosemide [Lasix; Hoechst-Roussel Pharmaceuticals, Inc., Somerville, NJ] was given with mercaptoacetyltriglycine [MAG3].) Good drainage was seen in upper pole moiety of left kidney and right kidney. Furosemide clearance half-time was 2.8 min for upper pole moiety of left kidney and 4.1 min for right kidney. Severe PUJ obstruction was found in nonfunctioning lower pole moiety of left duplex kidney at surgery. Post-GAD = after gravity-assisted drainage.



FIGURE 2. Left PUJ obstruction. Posterior views show radiopharmaceutical in dilated left pelvicalyceal system, which drained poorly and remained essentially unchanged after gravity-assisted drainage (Post-GAD). (Furosemide [Lasix; Hoechst-Roussel Pharmaceuticals, Inc., Somerville, NJ] was given with mercaptoacetyltriglycine [MAG3].) Furosemide clearance half-time was infinity for left kidney and 3.4 min for right kidney. Tight PUJ obstruction was found at surgery.

normal furosemide clearance half-time of <10 min. However, the number of patients is small, and caution should be undertaken when interpreting renography results in patients with severe renal impairment.

Five renal units were considered false-negative studies for the purpose of this investigation; on follow-up, the patients underwent surgical exploration and were found to have PUJ obstruction. The phenomenon of transitional hydronephrosis has been postulated, in which progressive maturation may result in either progression or resolution of the obstruction (16, 19-21) or intermittent hydronephrosis, which can be disabling (22). False-negative studies may also be associated with partial obstruction (23). Follow-up is recommended for patients with a nonobstructed appearance because falsenegative studies and obstruction may also develop with time (16, 21, 22-24).

Three renal units were considered false-positive studies for the purpose of this investigation; the patients were classified as having significant obstruction but were managed expectantly because of good relative renal function and improving sonographic and ^{99m}Tc-MAG3 findings. In this subgroup of patients, spontaneous improvement in drainage occurred on follow-up assessment. False-positive diuretic renography studies have included patients with a poorly functioning kidney and patients in whom there is a very large dilated collecting system.

The duration of the F+0 diuresis renography study is 25 min, i.e., 20 min for the diuretic phase, followed by the 5-min gravity-assisted drainage or imaging after voiding. The need for an additional view after gravity-assisted drainage in diuresis renography has been emphasized (25). The traditional F+20 diuresis renography study takes approximately 45 min to acquire (9–11). Therefore, the F+0 study is a shorter study.

Because the radiopharmaceutical and diuretic are administered together in a single intravenous injection, the F+0 diuresis renography study is also less invasive compared with the F+20 study, which requires two separate injections within 20 min (9-11).

All normal nondilated renal units on sonographic examinations showed a good diuretic response with a furosemide clearance half-time well below 10 min, which is the accepted normal range (17). Together with the sensitivity, specificity and accuracy obtained for the F+0 diuresis renography study, we believe that this is a valid method for the investigation of hydronephrosis and hydroureteronephrosis in infants and children.



CONCLUSION

In the F+0 diuresis renography study of infants and children, good diuretic responses are shown in normal kidneys; the data and results justify the usefulness of this method in the investigation of hydronephrosis and hydroure-teronephrosis to differentiate between renal obstruction and nonobstruction. The level of the obstruction is also correctly identified in cases in which there is good renal function. In addition, the F+0 diuresis renography study has a shorter imaging time and is less invasive compared with the traditional F+20 study.

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