Evaluation of dilated upper renal tracts by technetium-99m ethylenedicysteine F+0 diuresis renography in infants and children

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Aim: To evaluate the feasibility of modifying diuresis renography by the simultaneous administration of Tc-99m ethylenedicysteine and furosemide in the investigation of hydronephrosis and hydroureteronephrosis in infants and children. Parameters assessed were the diuretic response in normal kidneys and the ability of the F+0 study to differentiate between renal obstruction and nonobstruction. Methods: One hundred and thirty-three children (93 males, 40 females; mean age 35.2 months) with sonographic diagnoses of hydronephrosis or hydroureteronephrosis underwent F+0 diuresis renography. Tc-99m ethylenedicysteine (3.7 MBq/kg body weight) and furosemide at an appropriate dose were administered intravenously at the start of the study. Posterior imaging of the kidneys and bladder was performed for 20 min followed by imaging after voiding. All patients were followed-up for 12 months, and the results of the initial F+0 diuresis renography were compared with the final diagnoses. Final diagnosis was based on the pediatric urologist's decision of either surgery or conservative management. Results: A renal unit was defined as a kidney and its ureter. There were 262 renal units with 4 patients having a solitary kidney. 90 normal and 172 abnormal renal units on sonography were assessed by F+0 diuresis renography. The furosemide clearance half time for the 90 normal renal units was 5.8 ± 1.4 min. Of the 172 abnormal renal units. 100 were classified as nonobstructed and 72 as obstructed on diuresis renography. All 100 nonobstructed renal units were correctly classified with no false-negative studies; of the 72 renal units classified as obstructed, there were 43 true-positive studies and 29 false-positive studies. The sensitivity was 100%, specificity was 78% and accuracy was 83%. Conclusion: Tc-99m ethylenedicysteine F+0 diuresis renography is a valid method for the investigation of hydronephrosis and hydroureteronephrosis in infants and children.

Key words: Tc-99m EC, F+0, diuresis renography, pelviureteric junction obstruction

INTRODUCTION

Diuresis renography was introduced into clinical practice in 1978¹ and gained rapid acceptance amongst urologists and uroradiologists as the preferred investigation in evaluating upper urinary tract function and in assessing upper urinary tract dilatation or obstruction. Conventional diuresis renography involves an intravenous injection of the tracer followed by diuretic administration at 20 min

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(F+20); another method is to inject the diuretic 15 min before the radiopharmaceutical injection (F-15). A further modification of this technique that has been reported from mainly pediatric centers is the administration of diuretic soon after the radiopharmaceutical.² Administration of the diuretic along with the radiotracer was termed F+0 diuresis renography by O'Reilly et al.³ The duration of F+0 diuresis study is 25 min, which includes 20 min for the diuretic phase, followed by the 5 min post void image, while the traditional F+20 study takes approximately 45 min. The F+0 method therefore reduces the time required to undertake standard F+20 renography and is especially useful in pediatric patients. This technique requires a single intravenous injection thus

avoiding repeated venous punctures, which is difficult in infants with small veins and prominent subcutaneous fat. Diuresis renography using Technetium (Tc)-99m mercaptoacetyltriglycine (MAG3) and Tc-99m diethyltriaminepentaacetic and (DTPA) has been reported to be useful in the investigation of pelviureteric junction and vesicoureteric junction obstruction in neonates and children.^{4–9} Presently the radiopharmaceutical of choice for renography is Tc-99m MAG3.3 Tubular tracers like Tc-99m MAG3 and Tc-99m ethylenedicysteine (EC) are preferred over glomerular agents like Tc-99m DTPA especially in children because tubular function matures faster than glomerular function thus giving better images and sharper curves for interpretation. Tc-99m EC is a tubular agent like MAG3; it has been documented in the literature to have properties comparable or even superior to those of MAG3. 10 The image quality with Tc-99m EC (70% extraction fraction vs. 50% for MAG3) is better than with Tc-99m MAG3 because of lower background and liver activity. Moreover because of the faster clearance of EC than MAG3 the radiation dose is lower, which is an added advantage in pediatric patients. In India EC is more economical than MAG3 as the kits are readily available from Bhabha Atomic Research Centre (BARC), Mumbai, while the MAG3 kits have to be imported.

We undertook this study to prospectively evaluate the accuracy of F+0 diuresis renography with Tc-99m EC to differentiate renal obstruction from nonobstruction in hydronephrotic kidneys in children. Renogram parameters for Tc-99m EC in normal kidneys were also determined.

MATERIALS AND METHODS

One hundred and thirty-three consecutive children with a diagnosis of hydronephrosis (HDN) or hydroureteronephrosis (HDUN) on ultrasound (USG) examination were enrolled in the study. They had been referred by the pediatric urologist for evaluation of differential function and the status of the upper tracts. All children had undergone a detailed clinical examination and preliminary investigations like blood urea and serum creatinine determinations. Only those children with normal serum creatinine levels were included. None of the children had undergone any therapeutic intervention. There were 93 males and 40 females; age range was 25 days to 12 years; mean age was 35.2 months. Serum creatinine levels ranged from 0.4 to 1.4 mg/dl (reference range at our laboratory 0.2 to 0.8 in neonates, 0.5 to 1 in infants and 1 to 1.5 in children older than 1 year). Written instructions were given to each patient recommending liberal consumption of liquids throughout the day of attendance, and an additional 500 ml of liquids was advised on arrival to the department. Infants were asked to be breast-fed adequately from the morning of the test; intravenous hydration was not used. All children were asked to void just prior to the start of the test. Bladder catheterization was performed before the commencement of the study in children with suspected vesicoureteric junction obstruction (VUJO), when micturating cystourethrography showed greater than grade II reflux or where bladder abnormalities were documented.

All studies were performed on a single head SPX4 camera (Elscint-Haifa, Israel) with low energy all-purpose collimation. The patients were studied supine with the camera head positioned posteriorly. A xiphoid marker was used at the start of study to enable inclusion of the kidneys and bladder in the field of view. Tc-99m EC (3.7 MBq per kg body weight with a minimum total dose of 37 MBq) with diuretic, furosemide (1 mg/kg in infants and neonates and 0.5 mg/kg in children more than one year old) was injected intravenously at the start of the study. The dynamic perfusion sequence included 30 frames of 2 sec each followed by the parenchymal phase of 16 sec each frame for 20 minutes. The patients were then asked to void and return for a post void static image of 300 seconds. Delayed static images were acquired at 2 or 4 hrs in cases showing pelvicalyceal retention. Differential renal function was calculated using the integral method; region of interest included the entire kidney including the pelvis. A semilunar background ROI was positioned below and lateral to the kidney (at least two pixels away). Time to peak (Tmax) was calculated for each renal unit. Furosemide clearance half time (t1/2) 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. All studies were reported by a nuclear medicine physician with more than 10 years of experience in pediatric renal scintigraphy.

A renal unit was defined as a kidney and its ureter. Renal function was reported as preserved (differential function above 35%), impaired (differential function between 20 to 35%) or poor (differential function <20%). Scintigraphically obstruction was reported as at the pelviureteric junction (PUJO) or at the vesicoureteric junction (VUJO). Interpretation criteria for the diagnosis of obstruction in renal units with a differential function of above 20% were:

PUJO was diagnosed if (a) visual analysis showed progressive accumulation and no significant drainage of radiopharmaceutical from the renal pelvicalyceal system (PCS), (b) furosemide clearance t1/2 >20 min, and (c) visual comparison of post void and delayed images showed negligible clearance from the PCS.

VUJO was diagnosed if (a) visual analysis showed progressive accumulation and no significant drainage of radiopharmaceutical from the pelvis and ureter, (b) furosemide clearance t1/2 >20 min, and (c) visual comparison of post void and delayed images showed negligible clearance from the PCS and ureter.

A renal unit was also defined as obstructed if it had <20% differential function with progressive tracer accu-

Table 1 Results of the 172 abnormal units

F+0 diuresis renography		Final diagnosis	
Result	Number	Result	Number
1. Non-obstructed	100	Total non-obstructed	100
2. Total obstructed	72	Total PUJO/VUJO	42 (PUJO) + 1 (VUJO)
Non-functioning	5	Non-obstructed	29
Poor-function	3		
PUJO or VUJO	64		

Table 2 Results of the 72 obstructed units on diuresis renography

Obstructed units on initial F+0 study	Number	Treatment done	Final diagnosis
Non-functioning	5	nephrectomy	Hydronephrotic dysplastic kidneys
Impaired renal function	11	pyeloplasty	PUJO
Poor renal function	3	pyeloplasty including ureteric reimplantation in one case	PUJO = 2 PUJO + VUJO = 1
Good renal function	53	Anderson-Hynes pyeloplasty in 21 cases, pyeloplasty and ureteric reimplantation in 2 cases and ureteric reimplantation in 1 case	PUJO = 21 PUJO + VUJO = 2 VUJO = 1
		Conservative management = 29 cases	False positive for obstruction

mulation in the pelvis or ureter on delayed images, or no function in the presence of HDN or HDUN on USG.

A nonobstructed renal unit was diagnosed if (a) visual analysis showed good drainage from the renal pelvicalyceal system, (b) furosemide clearance half time (t1/2) <20-min, and (c) visual comparison of post void and delayed images showed further drainage. The t1/2 as assessed from the renogram curves was not independently considered for decision making. Renal units showing an obstructive curve pattern (t1/2 >20 minutes) but showing good clearance of tracer from the PCS on delayed images were equivocal for obstruction but were considered unlikely to need surgical intervention.

All patients had a clinical follow-up at 3-monthly intervals, with USG and diuresis renography performed at intervals of 3 months especially in children less than two years (including antenatally detected HDN). They were followed up for at least 12 months, and the results of the initial F+0 diuresis renography were compared with the final diagnosis. The final diagnosis was based on either the surgical findings or conservative management with repeated sonography and Tc-99m EC examinations at the end of 12 months. The decision for surgical intervention

or conservative management was made by the pediatric urologist, who considered the results of diuresis renography, including differential function of the kidney, the childs clinical findings and serial USG appearance before making the management decision.

Statistical analysis: A 2×2 matrix was used to tabulate test results from which information content of the test was derived by calculation of sensitivity, specificity and test accuracy. Fischer's exact test was applied to assess the significance of the association between the disease and scan findings.

RESULTS

A total of 262 renal units were analyzed because four patients had a solitary kidney. There were no side effects associated with the injection of furosemide with the radio-tracer in any case.

There were 90 normal nondilated renal units on sonographic examination. On F+0 diuresis renography these units had a mean Tmax of 2.7 ± 0.69 min (range from 1.5 to 4.25 min) and all showed rapid tracer clearance with mean furosemide clearance halftime (t1/2) of

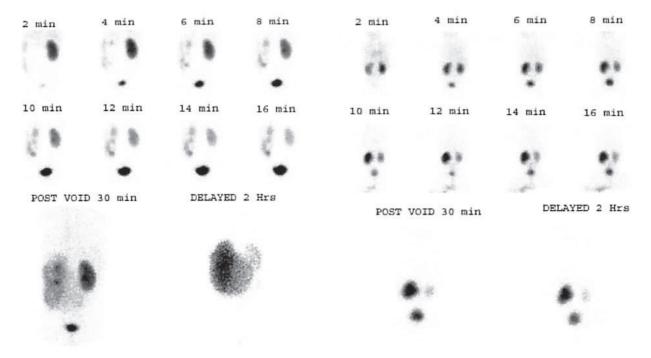


Fig. 1 Diuresis renography in a patient with impaired renal function and left PUJO. Two minute posterior views show parenchymal thinning of left kidney with progressive tracer accumulation in the dilated PCS, whereas the right kidney appears normal. The delayed images show progressive tracer retention in the PCS up to 4 hrs. Tight PUJO was diagnosed at surgery.

Fig. 2 Diuresis renography in a patient with good renal function and left PUJO. One minute posterior views show symmetrical parenchymal radiotracer uptake by both kidneys followed by progressive tracer accumulation in the dilated PCS of left kidney. The delayed images show progressive tracer retention in the PCS of left kidney up to 4 hrs. Tight PUJO was diagnosed at surgery.

$5.8 \pm 1.4 \text{ min (range from 2.5 to 7.75 min)}.$

172 renal units had HDN or HDUN on USG and were investigated using F+0 diuresis renography. After the F+0 study, 100 renal units were classified as nonobstructed and 72 were classified as obstructed, scintigraphically. Final results of these 172 abnormal units are given in Table 1.

Details of the 72 units classified as obstructed on F+0 renography are given in Table 2. Mean age of these children was 62.8 months. The ratio of right to left obstructions was 26:38; four patients (8 units) had bilateral (B/L) PUJO. All five patients with nonfunctioning units on renography underwent nephrectomy for hydronephrotic dysplastic kidneys. The 3 renal units with poor renal function underwent PCN followed by pyeloplasty on >5% improvement of differential function. One of these cases had a narrow PUJ along with VUJ obstruction and pyeloplasty was combined with ureteric reimplantation. All cases with impaired renal function (differential function less than 35%) underwent pyeloplasties for tight PUJO's (Fig. 1). Of the remaining 53 units classified as obstructed with a differential function of greater than 35%, there were 52 units with PUJO (Fig. 2) and one unit with VUJO. Anderson Hynes reduction pyeloplasty was undertaken in 23 units, PUJO was confirmed at surgery in each case; in addition there were two PUJO's associated with VUJO. The one case of VUJO was operated upon for VUJ obstruction associated with a ureterocele, and ureteric reimplantation was performed.

In the remaining 26 patients with unilateral (U/L) obstruction (PUJO) and well preserved differential function no intervention was undertaken up to the end of the 12 month follow up period. Mean age of these children was 3.8 months and all had antenatally detected hydronephrosis on USG. These patients were clinically asymptomatic with no evidence of worsening hydronephrosis on USG or fall in differential function on renography. Since no intervention was undertaken in these 26 units they were considered false positive for PUJO.

At the end of 12 months there were another 3 false positive studies for PUJO with all three renal units showing nonobstructive outflow tracts in the subsequent follow up studies. Two of these units were the contralateral kidneys of the cases with B/L PUJO who had undergone pyeloplasty. These patients remained clinically well in the 12 month follow-up period with improving appearance on sonography and Tc-99m EC studies. One case showed reducing dilatation on USG though the drainage pattern

remained obstructive with the delayed images showing good clearance from the PCS. These children were aged 3 months, 6 months and 4 weeks respectively.

A total of 100 renal units were classified as nonobstructed with no renal unit showing obstruction on the subsequent 12-month follow-up. All patients had nonobstructive renogram curves and the delayed images showed good clearance of tracer from the PCS. Furosemide clearance half time was <20 min in all patients.

On the basis of the final diagnosis (based on the pediatric urologist's decision of either surgery or conservative management with follow up USG and Tc-99m EC studies), there were 43 true-positive, 100 true-negative, 29 false-positive and no false-negative studies for PUJO. The sensitivity of F+0 diuresis renography for differentiating obstructive (PUJO/VUJO) versus nonobstructive dilatation was 100%, specificity was 78% and accuracy was 83%. Fischer's exact test gave a p < 0.00001, χ^2 = 76.48), suggesting a strong association between the disease and scan findings.

The results of the level of obstruction were determined by visual analysis of the dynamic and static images of diuresis renography. PUJO with associated vesicoureteric junction abnormalities was not identified on the scintigraphic study.

DISCUSSION

Accepted protocols for furosemide injection during renography are the F+20 and F-15 methods described by O'Reilly et al.³; these procedures are time consuming with the child having to lie relatively still for at least 45 minutes in the F+20 protocol. The recommended well tempered diuretic renogram⁹ and procedure guidelines for diuretic renography in children¹¹ are cumbersome to apply in neonates and young infants because of the need for venous access and bladder catheterization. Sfakiankis et al.² were the first to propose another diuretic protocol; early injection of furosemide following the radiotracer (F+3). Administration of radiopharmaceutical and furosemide together was termed F+0 diuresis renography by O'Reilly et al.³ This method is easy, shorter and avoids repeated venous punctures. It is thus convenient for children particularly in neonates and young infants where establishing venous access can be difficult. F+0 diuresis renography has been validated in adults by Adeyoju et al., 12 who showed that the timing of furosemide injection did not have a significant effect on calculation of relative function, and urodynamic data from the F+0 test were similar to data obtained from F+20 or F-15 studies with little influence on management decisions. Recently Wong et al.¹³ and Boubaker et al.¹⁴ published encouraging results for the use of the F+0 protocol during Tc-99m MAG3 and I-123 renography respectively, in children. Tc-99m EC is a tubular agent like MAG3, and comparable results have been demonstrated with the use of both agents in various renal disorders.¹⁰ In India, MAG3 kits have to be imported while EC kits are available at an economical price from BARC, Mumbai. Therefore we evaluated the accuracy of Tc-99m EC renography using the F+0 diuresis protocol in the evaluation of dilated upper tracts in children

Except for the group that underwent pyeloplasty we lacked a gold standard to compare the results of the F+0 method. However, like Wong et al. ¹³ we considered the 12 month follow up data to be a satisfactory predictor for distinguishing children who could be managed conservatively from those undergoing surgery.

All normal nondilated renal units on sonography showed rapid tracer clearance from the PCS with the furosemide clearance half time well below 10 min, which is similar to the normal range of MAG3. These units served as controls for establishing the normal range of renogram parameters for EC which are comparable to those of MAG3. ¹⁵

All patients with obstructed units on renography had diuretic clearance half times of greater than 20 minutes as has been reported for MAG3.¹³ The delayed images in all cases showed progressive tracer accumulation in the PCS with negligible clearance on the 4 hr delayed image. Factors, which may effect drainage, were taken care of and all patients had a post micturition image. The uncertainty regarding curve patterns and t1/2 in renal units with impaired function was taken care of by visual analysis revealing progressive retention of tracer in the pelvicalyceal system up to 4 hours. Twenty-nine renal units were considered false positive at the end of 12 months. In two cases following contralateral pyeloplasty the drainage pattern of these units improved within an interval of six months and these patients are being followed up at regular intervals. In another, possibly progressive maturation resulted in resolution of the obstruction and can explain the improvement in drainage with decreasing dilatation on USG. 26 renal units with preserved renal function, t1/2 > 20 min and progressive tracer accumulation in PCS up to 4 hours were taken as false positive. They were on conservative follow-up at the end of the 12 month followup period and the surgeon did not feel the need for intervention in any of these cases. None of the 100 units classified as nonobstructed on the basis of curve pattern and t1/2 <20 minutes showed obstruction on the subsequent 12 month follow-up. Thus there were no false negative results. The F+0 diuresis protocol with Tc-99m EC had a sensitivity of 100%, specificity of 78% and accuracy of 83%. In the study of Wong et al. 13 the sensitivity, specificity and accuracy of MAG3 F+0 diuresis renography for identification of obstruction were 88.9%, 94.1% and 91.7% respectively. They had five false negatives, which resulted in a drop in sensitivity while the number of false positives was only 3. The low specificity in our study was due to the fact that the 26 cases which were classified as obstruction on the basis of the scintigraphic criteria were taken as false positive as they

did not undergo any intervention and were kept on conservative follow-up.

Previously, symptomatic children and adults were diagnosed as having PUJO, from findings of poor drainage on diuretic renography. Poor drainage was defined either from the shape of the renogram or if the t1/2 was >20 min. However this definition and an obstructive curve pattern have become controversial in the subgroup of patients with antenatally detected hydronephrosis. Surgical intervention is no longer undertaken even though diuresis renography shows an obstructive curve pattern. There is thus a controversy among pediatric urologists and nuclearmedicine physicians regarding the interpretation of results of impaired drainage on diuretic renography in this group. 16 All twenty-six patients with U/L PUJO and obstruction on renography had antenatally detected hydronephrosis. Preservation of renal parenchymal function was demonstrated in all up to the 12 month follow-up though the drainage pattern remained obstructive. Serial ultrasonography did not show progressive dilatation, and the children are presently asymptomatic. This group is being closely followed up with serial USG and diuresis renography studies to identify signs of obstructive injury so that treatment can be promptly instituted. It remains to be seen how many of these patients will show a spontaneous resolution of obstruction with improvement in the drainage pattern and decreasing dilatation on USG. Conservative management of antenatal hydronephrosis is an important protocol being followed by many pediatric urologists. Preliminary results regarding their experience with this protocol have been published. 17,18 In the case of B/L hydronephrosis only 12.5% cases and in the case of U/L HDN 22% of children (<2 yrs) followed up conservatively required pyeloplasty. In both these groups the decision for surgical intervention was based entirely on serial measurements of differential function irrespective of obstructive patterns and depended on subsequent change rather than the initial degree of function or dilatation of each kidney.

Thus though the ability of renography to predict future behavior of hydronephrosis in infants is questionable it still retains an important place in the management of cases with antenatal obstructive hydronephrosis. The overall results of this study indicate excellent sensitivity and relatively low specificity of F+0 diuresis renography, suggesting its usefulness in excluding patients without functional obstruction from the careful follow-up group. The relatively low specificity may be, at least in part, due to the limitations of standards for the final diagnosis, a general problem in studying the diagnostic ability of diuresis renography.

CONCLUSION

Tc-99m ethylenedicysteine F+0 diuresis renography with its more convenient intravenous regimen and shorter

duration is a suitable test in routine pediatric urology clinical practice and is an excellent method for evaluating dilated upper tracts in children.

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