Validation of IAEA Software Package for the Analysis of Scintigraphic Renal Dynamic Studies

Parameters of Renal Transit in Children With Renal Pelvic Dilatation

Slobodanka Lj. Beatovic, MD, PhD,† Dragana P. Sobic-Saranovic, MD, PhD,† Emilija D. Jaksic, MD, PhD,† Milica M. Jankovic, MSc,† Jelena Marinkovic, PhD,† and Vladimir B. Obradovic, MD, PhD†

Purpose: The objectives of the study were to use the International Atomic Energy Agency (IAEA) software package for the analysis of scintigraphic renal dynamic studies to obtain values of curve parameters and excretory parameters in children with hydronephrosis and to validate the reliability of these numerical outputs by comparing with values established by consensus reports.

Patients and Methods: Fifty children with hydronephrosis (median age, 16 months; 30 boys, 20 girls; 99 kidneys) underwent 99mTc-MAG3 diuresis renography. Studies were analyzed by 2 observers, and according to the assessment of images, renograms, and differential function, kidneys were classified as normal (42, kidneys contralateral to hydrourephrotic kidney), hypotonic unobstructed (49), and obstructed (8). The IAEA software was applied to each renogram. The parameters analyzed were as follows: normalized residual activity at 20 minutes (NORA 20) and on postmicturition (PM) acquisition, output efficiency at 20 minute (OE 20), PM to maximum renal count ratio (PM/max), and mean transit time (MTT).

Results: Mean values for normal, hypotonic unobstructed, and obstructed kidneys were as follows: NORA 20: 0.25, 0.57, and 2.16; OE 20 (%): 94.5, 87, and 57; normalized residual activity on PM acquisition: 0.02, 0.03, and 0.27; PM/max: 0.01, 0.02, and 0.13; and MTT (minutes): 1.9, 3.5, and 8.9, respectively. Difference between obstruction/dilatation and normal/dilatation was significant ($P < 0.0001$), as well as the correlation between NORA 20/OE 20 ($R = -0.982$). Cutoff values to predict obstruction were as follows: NORA 20: 1.6; OE 20: 73%; NORA PM, 0.11; PM/max, 0.06; and MTT, 8.23 minutes.

Conclusions: The IAEA software package gives reliable values of numerical parameters of renal excretion. The use of the software improves diagnostic accuracy of diuresis renography in children.

Key Words: children, antenatal hydronephrosis, diuresis renography, normalized residual activity, output efficiency, IAEA software package

The patients selected were children presented with antenatally detected HN attributed to pelvireteric junction (PUJ) stenosis. They had undergone 99mTc-MAG3 renography with furosemide stimulation over a 14-month period between June 2012 and July 2013. Children with a history of urinary tract infection and abnormal finding on voiding cystourethrography were excluded, as were those with prior renal or ureteric surgery. In total, 50 patients were selected on the basis of these criteria.

PATIENTS AND METHODS

The patients and methods section would detail the specifics of the study, including patient selection criteria, study design, and data collection methods. The data acquisition section would describe the technical details of the renography procedure, including imaging protocols and specific parameters measured.

Data Acquisition

A 22-minute acquisition protocol with 132 ten-second images in $128 \times 128$ matrix size was applied. The dose of 99mTc-MAG3 was adjusted for body weight, with minimum of 19 MBq (0.5 mCi) and maximum of 70 MBq (1.9 mCi), according to the guidelines published by the Society of Nuclear Medicine and Molecular Imaging and the European Association of Nuclear Medicine.10 Furosemide was administered at the end of the second minute during the 12th frame (F+2 test). The postvoid static image of 1-minute duration was acquired not before 60 minutes after tracer injection.

Received for publication December 27, 2013; revision accepted March 19, 2014.
From the *University of Belgrade - Faculty of Medicine; †Center for Nuclear Medicine, Clinical Center of Serbia; ‡University of Belgrade - Faculty of Electrical Engineering, Belgrade, Serbia.
Conflicts of interest and sources of funding: none declared.
Reprints: Slobodanka Lj. Beatovic, MD, PhD, Center for Nuclear Medicine, Clinical Center of Serbia, Visegradska 26 St, 11000 Belgrade, Serbia. E-mail: boba.beatovic@sbb.rs, slobodanka.beatovic@jces.ac.rs.
Copyright © 2014 by Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.
Data Reconstruction and Image Analysis

The study files were imported to The IAEA software package as the wild type files. Several composite images were generated; these are as follows: cardiac image, cortical image, parametric image, and amplitude image of maximum pixel values. For drawing renal regions of interest (ROIs), the parametric image was used. The renal ROI included the cortex and the kidney pelvis. For background correction, the perirenal area was used. Differential renal function (DRF) was determined using both integral method and the Rutland-Patlak plot method.

For each renogram, the following parameters were calculated: time to peak height (T<sub>max</sub>), the half-time (T<sub>1/2</sub>, defined as the delay time from a peak time to reduce activity by 50%), washout index (A<sub>20</sub>/A<sub>max</sub>, 20 minutes to maximum count ratio), normalized residual activity at 20 minutes (NORA 20), output efficiency at 20 minutes (OE 20), elimination index (EI, 3–20 minutes count ratio), normalized residual activity on the postmicturition acquisition (NORA PM), PM to maximum renal count ratio (PM/max), and whole kidney mean transit time (MTT) (Fig. 1).

The consensus of 2 experienced observers analyzed each study and classified the kidneys into 3 categories. Control group (group 1) consisted of 42 kidneys contralateral to the hydronephrotic kidney without any structural abnormality on previous diagnostics. Group 2 consisted of 49 hypotonic nonsignificantly obstructed kidneys, referred to as unobstructed. Those kidneys showed good drainage of the pelviureteric system and significant further drainage on PM images. They were also diagnosed if the visual analysis showed no significant drainage, as long as the PM images showed significant further drainage. The sonograms of these kidneys showed mild to moderate pelvic dilatation. Group 3 consisted of 8 obstructed kidneys, which were characterized by slow transit or progressive accumulation of radiopharmaceutical in the collecting system and significant retention of tracer on PM image. The sonographic examination revealed significant dilatation of the pelvicalyceal system.

Statistical Analysis

For testing the hypothesis, we used the paired <i>t</i> test to compare the values between group 1 (control group) and group 2 and between group 2 and 3. The 1-way analysis of variance was used for evaluating the differences between all 3 groups. The relationship between OE 20 and NORA 20 was assessed by Pearson correlation coefficient and linear regression analysis. To determine how well the NORA 20, OE 20, NORA PM, PM/max, and MTT could distinguish between obstruction and dilatation as well as between dilatation and the normal kidneys, receiver operating characteristic (ROC) curve analysis was performed. The sensitivity, specificity, the area under the curve

![Standard display of IAEA software package review screen. Eleven 1-minute images followed by PM image of kidneys; parametric image with ROIs for whole kidney, renal parenchyma, and background; PM image; renogram curves; patient values for time to peak height of the renogram, split function, MTT, NORA 20, NORA PM, PM/max, and OE 20.](image-url)
(AUC) with 95% confidence interval, and cutoff values were analyzed.

The results were presented as mean (SD). The statistical significance has been put at 0.05 level. SPSS version 21 and MedCalc software packages were used.

RESULTS

Population Selected
Fifty patients, 30 boys and 20 girls aged 2 months to 10 years (median, 16 months; mean, 35 months), were selected on the basis of the abovementioned criteria. Forty-two children presented with unilateral HN (28 left side; 14 right side) and 8 with bilateral HN. There was 1 nonfunctioning kidney, which was excluded from the study for statistical analysis. Neither of the kidneys had undergone a pyeloplasty before our investigation. In total, 99 kidneys were analyzed.

Numerical Outputs of IAEA Software in Control Group
There were 42 normal renal units (14 on the left side and 28 on the right side); all showing good drainage in the diuretic phase. In 39 of 42 kidneys, the DRF was between 45% and 54%. The remaining 3 kidneys had differential function of 82%, 75%, and 64%, respectively.

Table 1 shows the mean (SD) as well as the minimum and maximum values for $T_{\text{max}}$, $T_{1/2}$, $A_{20}/A_{\text{max}}$, NORA 20, OE 20, EI, NORA PM, PM/max, and MTT. The results were shown for the left kidney, right kidney, and for all normal kidneys together. A t test evaluating the differences between the left and right kidney showed no significant difference for $T_{\text{max}}$, $T_{1/2}$, $A_{20}/A_{\text{max}}$, EI, NORA 20, OE 20, and MTT ($P > 0.05$), whereas the values of NORA PM and PM/max were significantly higher for the right kidney ($P < 0.05$). As expected, the values for $A_{20}/A_{\text{max}}$ and NORA 20 were low whereas the OE 20 and EI were high. Values for both NORA PM and PM/max were very low.

Numerical Outputs of IAEA Software in Kidneys With HN
In group 2, there were 49 renal units, 29 on the left side and 20 on the right side. The sonographic examination revealed renal pelvic diameter between 7 and 25 mm. Of 49 kidneys, 44 had the DRF between 45% and 54%. One kidney had lower differential function (36%), and 4 kidneys had “supranormal” differential function (58% and 57%). Group 3 consisted of 8 renal units, 6 on the left side and 2 on the right side. Six kidneys had relative function between 45% and 54%, and the remaining 2 kidneys had poor relative function (18% and 25%, respectively). The concomitant sonograms showed high-grade HN with anteroposterior renal pelvic diameter between 18 and 50 mm.

The results for NORA 20, OE 20, NORA PM, PM/max, and MTT are shown in Table 2. The values obtained for $T_{\text{max}}$, $T_{1/2}$, $A_{20}/A_{\text{max}}$, and EI were excluded from the statistical analysis. In group 2, the values of NORA 20, NORA PM, PM/max, and MTT were higher in comparison with the control group, whereas OE 20 was lower than in the control group. The NORA 20 and OE 20 values out of range observed in the control group were found in 65% of the kidneys. After micturition, the NORA PM and PM/max values out of range observed in the control group were found in 27% and 10% of the kidneys, respectively. A highly significant difference was obtained between this group and the control group for the values of all parameters ($P < 0.0001$).

In group 3, low OE 20 values were observed, whereas the values of NORA 20, NORA PM, PM/max, and MTT were high. The values for each patient were out of range observed in group 2. The significant difference is obtained between this group and the control group for the values of all parameters ($P < 0.0001$).
differences between group 2 and 3 for the values of all parameters were seen, indeed ($P < 0.001$).

The 1-way analysis of variance comparison was made between all 3 groups, taking group 1 as a reference one, for the NORA 20, OE 20, NORA PM, PM/max, and MTT. Highly significant difference was obtained (Fig. 2).

Linear regression analysis showed significant inverse linear correlation between NORA 20 and OE 20 ($R = 0.982$; years $= 99.6 - 21.1 	imes$) at 0.01 level. The dispersion of the values along the line of regression increased when the quality of drainage decreased (Fig. 3).

### Receiver Operating Characteristic Curve Analysis

The performance of the NORA 20, OE 20, NORA PM, PM/max, and MTT to distinguish between obstruction and dilatation, as well as between dilatation and the normal kidneys, were analyzed by ROC curve analysis. The AUC with 95% confidence interval (CI), optimal cutoff values, sensitivity, and specificity are summarized in Table 3. Receiver operating characteristic analysis revealed cutoff values of the best predicting significant obstruction at 1.62, 71%, 0.11, 0.06, and 8.23 minutes for NORA 20, OE 20, NORA PM/2, PM/max, and MTT, respectively. The sensitivity and specificity were almost 100% for all 5 indices. The respective cutoff values for the 5 indices to discriminate between dilatation and normal kidneys were 0.37, 91%, 0.03, 0.01, and 2.12 minutes. Figure 4 shows the examples of ROC curves for the identification of dilatation.

### TABLE 2. The Parameters of Renal Washout for Hydronephrotic Kidneys

<table>
<thead>
<tr>
<th>Kidney</th>
<th>Renal Transit</th>
<th>Renal Transit</th>
<th>Renal Transit</th>
<th>Renal Transit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NORA 20</td>
<td>OE 20, %</td>
<td>NORA PM</td>
<td>PM/max</td>
</tr>
<tr>
<td>Unobstructed</td>
<td>n</td>
<td>48</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>0.57</td>
<td>87</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.19</td>
<td>7.8</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>0.08</td>
<td>56</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>1.62</td>
<td>98</td>
<td>0.12</td>
</tr>
<tr>
<td>Obstructed</td>
<td>n</td>
<td>7</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>2.16</td>
<td>56.6</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.33</td>
<td>9.6</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>1.84</td>
<td>44</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>2.63</td>
<td>71</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>$P^*$</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

The NORA 20, OE 20, NORA PM, PM/max, and MTT are displayed for unobstructed and obstructed kidneys. NORA and PM/max are given in units, OE in percentage, and MTT in minutes.

$^*$Paired $t$ test.

n, number of single kidneys.
DISCUSSION

This study examined the performances of the IAEA software package in evaluating renal emptying in children with antenatally detected renal pelvic dilatation. The overall results provided evidence of excellent agreement with previously reported values of the quantitative parameters of renal washout. The normal kidneys presented with NORA 20 values less than 0.5, OE 20 values higher than 90%, and NORA PM less than 0.05. In kidneys with significant PUJ obstruction, NORA 20 was higher than 1.5, OE 20 less than 75%, and NORA PM higher than 0.1.

Up to now, no studies had been published that assessed the accuracy of the numerical outputs of the IAEA software package, neither in adult population nor in children. We began the validation of the software with diuresis renography in children because of the lower reproducibility, greater interobserver variability, and more indeterminate findings in comparison with renography in adults.11,12

The analysis of the numerical outputs of the IAEA software package was made in a control group of normal kidneys and in 2 groups of kidneys with renal pelvic dilatation (hypotonic, referred to as unobstructed, and obstructed kidneys). The division into these 2 categories was made by the consensus opinion of 2 experienced observers. It was done on the basis of sonographic findings, the analysis of the pattern of excretion after furosemide, and comparison of before and after gravity-assisted drainage.

The Tmax and T1/2 were analyzed only in the group of normal kidneys. These parameters are readily estimated and recommended in guidelines for reporting of diuresis renography, although they are not accurate enough in the case of impaired drainage.13,14,15,16

The washout index (A20/Amax) for normal kidneys in our study was clearly smaller than those reported previously on basic renograms in adults because of the younger age of our patients and the acceleration of the radiopharmaceutical transit after furosemide.17 The values of EI were compared with results reported by Boubaker et al18,21,27 who proposed EI greater than or equal to 3 as normal and EI less than or equal to 1 as definitely abnormal. We observed that the values are greater than or equal to 3.4 in normal kidneys and less than or equal to 0.8 in obstructed kidneys, which were in accordance with proposed values.

Results obtained in the present study for normal values of both NORA 20 and OE 20 were highly comparable with previously reported values.19,28,29 The values of NORA PM and PM/max for

| TABLE 3. Receiver Operating Characteristic Analysis for NORA 20, OE 20, NORA PM, PM/max, and MTT to Predict Significant Obstruction and to Predict Dilatation |
|---|---|---|---|---|---|---|
| Predictor Variables | n | AUC | 95% CI | P | Optimal Cutoff Value | Sensitivity, % | Specificity, % |
| Dilatation vs obstruction |  |  |  |  |  |  |
| NORA 20 | 55 | 1.00 | 0.935–1.000 | 0.0001 | 1.62 | 100 | 100 |
| OE 20 | 53 | 0.991 | 0.915–1.000 | 0.0001 | 71 | 100 | 95.65 |
| NORA PM | 55 | 0.999 | 0.933–1.000 | 0.0001 | 0.11 | 100 | 97.87 |
| PM/max | 55 | 1.00 | 0.935–1.000 | 0.0001 | 0.06 | 100 | 100 |
| MTT | 54 | 1.00 | 0.934–1.000 | 0.0001 | 8.23 | 100 | 100 |
| Control vs dilatation |  |  |  |  |  |  |
| NORA 20 | 86 | 0.870 | 0.781–0.933 | 0.0001 | 0.37 | 70.83 | 97.37 |
| OE 20 | 83 | 0.872 | 0.780–0.935 | 0.0001 | 0.91 | 73.91 | 94.59 |
| NORA PM | 88 | 0.709 | 0.602–0.801 | 0.0001 | 0.03 | 92.79 | 100 |
| PM/max | 88 | 0.660 | 0.551–0.757 | 0.0012 | 0.01 | 51.06 | 75.61 |
| MTT | 86 | 0.879 | 0.791–0.940 | 0.0001 | 2.12 | 80.85 | 87.18 |

The AUC with 95% CI, optimal cutoff values, sensitivity, and specificity are given for each parameter. NORA and PM/max are given in units, OE in percentage, and MTT in minutes.

P, significance level.
normal kidneys in the present study were very low and reflected the complete washout from the collecting system. They were even lower than the normal values in children reported by Piepsz et al28 (G0.1; after F+20 diuretic renography) and by Nogare`de et al19 (G0.2; after F+0 diuretic renography). We could not find the exact explanation for the lower values in our study, except that the longer time interval between the tracer injection and PM acquisition was more than 60 minutes.

We were unable to find any published article regarding the measurement of kidney transit times in children during an early diuretic stimulation. In the report by Carlsen et al,30 a measurement of kidney transit times was performed in normal children during baseline renography with 123I-hippuran. The obtained value for MTT of 4.2 minutes was longer than the values observed in the present study.

We found somewhat lower values of OE and higher values of NORA 20 in kidneys with obstruction and in dilated unobstructed kidneys in comparison to the previous reports.5,29,19 These findings are probably due to slightly shorter interval between furosemide injection and the point for calculation of NORA and OE, which was 18 minutes instead of 20 minutes. In addition, the selection of kidneys into the group of obstruction was stricter, and only those with significant retention of tracer on PM image were classified as obstructed, whereas in the study by Nogare`de et al,19 the criteria for the selection into the group with HN was the anteroposterior pelvic diameter greater than 15 mm.

The NORA PM values in our study were remarkably lower in comparison with previously observed values, not only in kidneys with pelvic dilatation, but also in normal kidneys. This has to be clarified further but could be partly explained by the time interval between dynamic and PM acquisition, which was longer than 60 minutes.

In our study, the correlation between OE and NORA was better than previously reported by Piepsz et al28,31 (R = −0.982 vs R = −0.926 and R = −0.936 at 20 minutes and on PM acquisition).

We have determined the optimal cutoff value to distinguish between obstruction and dilatation as well as between dilatation and the normal kidneys. Of course, the challenge in clinical practice is primary to differentiate the drainage characteristics of a dilated

**FIGURE 4.** Examples of ROC curves corresponding to the NORA 20, OE 20, NORA PM, and MTT used to discriminate between dilatation and normal kidneys. A, The optimal NORA 20 cutoff value to predict dilatation was 0.37 (AUC, 0.870; 95% CI, 0.781–0.933). B, The optimal OE 20 cutoff was 91% (AUC, 0.872; 95% CI, 0.780–0.935). C, The optimal NORA PM cutoff value was 0.03 (AUC, 0.709; 95% CI, 0.602–0.801). D, The optimal MTT cutoff value was 2.12 minutes (AUC, 0.879; 95% CI, 0.791–0.940).
nonobstructed kidney from the one with high suspicion of obstruction.2 The previously reported cutoff values for obstruction were 1.5 and 78% for NORA 20 and OE 20, respectively.19,20 The cutoff values to predict significant obstruction obtained in our study were similar and yielded a sensitivity and specificity of almost 100%. Our hypothesis affirmed the high sensitivity and specificity of numerical outputs of IAEA software for detecting significant PUJ obstruction.

Study Limitations

This study has some limitations. The main limitation refers to the absence of a criterion standard to evaluate our results. The long-term prospective evaluation through either conservative management or after a surgery was missing. The patients were followed-up for less than 12 months, which was not satisfactory to confirm the diagnosis of obstruction or nonobstruction. At the time of completion of the study, the final diagnosis of obstruction was available for only 3 units from the group 3 in whom a pyeloplasty was performed due to the deterioration of differential function. For the remaining 5 units of this group, the final diagnosis was missing due to the lack of feedback information from the pediatric urology unit. In group 2, a follow-up ultrasound finding of decreasing pelvicalyceal size was available in 23 units and a repeat MAG3 result of nonobstruction in another 3 units. In 26 of 49 units, a follow-up ultrasonography was missing. So, we were not able to validate parameters obtained by IAEA software against surgical finding or follow-up data as the criterion standard. The present study was restricted to the comparison of the numerical outputs of IAEA software with previously established values for diuresis renography in children.

Another limitation of the study is the uneven distribution of kidneys between groups, with just 8 renal units in group 3, which decreased the quality of statistical analysis. This drawback is caused by the limited time during which the trial was conducted and the fact that the children were sent from only 1 pediatric department.

The third limitation is the nonstandardized time at which the late PM image is acquired. In our patients, the late image was performed at a time interval of 60 to 120 minutes after tracer injection, which would have explained the lower values of PM parameters when compared with established values. In the upcoming work, the time at which the late image should be performed has to be standardized to facilitate the comparison between reports.

CONCLUSIONS

This study demonstrates that the use of The IAEA software package provides a reliable quantitative analysis of the 99mTc-MAG3 diuresis renography in children. The implementation of the software will facilitate the standardization and harmonization in the reporting on the diuresis renography. It will give the opportunity to compare the results between physicians and departments. The nuclear medicine section of the IAEA should be encouraged to produce the final version of the software and to distribute it among nuclear medicine departments, primarily in developing countries. The validation of the software should be continued in the various age groups of patients. The children with antenatal HN should be evaluated prospectively for several years. The upcoming work should also be focused on the validation of the IAEA software concerning the observer reproducibility of drainage assessment and DRF estimation.

REFERENCES