Technetium-99m-MAG3 Scintigraphy in Acute Renal Failure after Transplantation: A Marker of Viability and Prognosis

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This study assessed ^{99m}Tc-mercaptoacetyltriglycine (MAG3) for determination of renal transplant prognosis for recovery in patients with early postoperative dysfunction. The postulate tested was that good tracer extraction may imply high likelihood of recovery, while poor extraction may confer a poor prognosis. **Methods:** A 2-min image acquired 1 min after MAG3 administration, named a cortical uptake phase (CUP) image, was visually analyzed according to standardized semiquantitative guidelines. Interpretation was expressed in tubular injury severity scores (TISS) that ranged from 1 (a normally functioning renal transplant) to 6 (a photopenic defect in place of renal transplant). **Results:** The study analyzed 64 patients (35 men, 29 women, age 45.9 ± 14 yr). All five patients with TISS of 6 or 5 lost the transplant. Only 1of 10 patients with TISS of 4 lost the transplant. All patients with TISS of less than 4 recovered renal transplant function. **Conclusion:** This study suggests that MAG3 scan (the CUP image specifically) is an accurate prognosticator in patients with early postoperative renal transplant dysfunction. Reproduction of these results in a larger population and other institutions is necessary before clinical implementation of this methodology.

Key Words: kidney transplantation; technetium-99m-mertiatide; radioisotope renography

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Renal scintigraphy has provided clinically important functional evaluation of renal transplants since the beginning of the transplantation era (*1*). The main role of this testing was to monitor the transplant function after surgery and to determine the etiology of transplant dysfunction, when such occurred. This was achieved by serial renal scintigraphy, using glomerular filtration and/or tubular uptake radiopharmaceuticals (*2*). Although the sensitivity of these tests for functional abnormality is rather high, the specificity reports have been variable (*2–8*). There is an ongoing debate regarding routine clinical utility of nuclear medicine tests for establishing the cause of renal transplant dysfunction, especially in view of suggested similar diagnostic accuracy of Doppler ultrasound in this setting (*9*).

Limited information is available regarding the prognostic utility of tests in patients with kidney transplants. While Doppler ultrasound has never been studied for that purpose, ^{131}I- or ^{123}I-labeled orthoiodohippurate (OIH) was found useful in predicting recovery in early transplant dysfunction (*10,11*). We investigated the utility of ^{99m}Tc-mercaptoacetyltriglycine (MAG3), a recently introduced renal tubular radiopharmaceutical (a functional analog of OIH), for determination of prognosis in patients with early postoperative renal transplant dysfunction. The hypothesis was that cortical uptake of MAG3 should parallel the amount of residual viable tubular mass, similar to what has been observed with OIH (*12,13*). Thus, poor uptake may indicate irreversible damage, while good uptake may predict improvement in renal function after transplantation, as the viable nephrons begin to recover.

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MATERIALS AND METHODS

We retrospectively reviewed studies of all patients who had renal nuclear medicine scans requested for suspected early post-transplantation kidney dysfunction at our institution from October of 1990 through September of 1994. The routine clinical protocol followed by our transplant service includes a standard quadruple therapy with Minnesota antilymphocyte globulin induction, azathioprine and prednisone, followed by maintenance therapy with cyclosporine, azathioprine and prednisone (*14*). In cases of post-operative oliguria, anuria or failure to clear the creatinine after surgery, a renal duplex ultrasound evaluation was obtained. The test technique and interpretation criteria at our institution recently have been reported (*14*). Only when duplex ultrasound did not adequately explain the clinical problem was a renal scintigraphy ordered. All patients were followed clinically, using medical records and phone contact, to determine transplant survival. The follow-up success rate was 100%. Whenever the kidney was removed or biopsy performed, we obtained a pathological diagnosis.

Renal scintigraphy was performed on an urgent basis, usually within a few hours of receiving the request from a transplant service. Imaging was obtained on a General Electric integrated gamma camera and computer system. The camera detector was fitted with an all-purpose, parallel-hole collimator with an acquisition window set at 20%, centered on 140 keV. All images were obtained after intravenous injection of 370 MBq (±10%) of MAG3. Patients were studied at their baseline hydration status without forcing fluids. They were positioned supine on an imaging table. The camera detector was positioned anteriorly over the pelvis with the symphysis pubis projected at the bottom edge of field of view.

The computer was set to acquire a two-phase dynamic study. The first phase was obtained at a rate of 1 sec/frame for a total of 60 frames. The second phase was acquired at a rate of 15 sec/frame for 120 frames. The imaging matrix was 128 × 128 pixels at 16 bit. For visual assessment of the flow, the first phase was reformatted into 3-sec images and photographed in a 16-on-1 format. Transplant perfusion was assessed by comparison of renal flow to the aortic flow (K/A ratio), as previously described (*15*).

The second phase was reformatted into 2-min images and photographed in a format in which 15 images are displayed on one film. A single static image of the foley bag was obtained for 2 min

TABLE 1
Description of Image Features for Tubular Injury Severity Scores (TISS)

TISS	Image features
1	No significant background or vascular activity (i.e., normal).
2	Faint vascular activity; no background.
3	Mild/moderate background activity; renal uptake significantly greater than iliac vascular activity.
4	Moderate background activity; renal uptake about that or slightly greater than that of iliac vessels.
5	Marked background activity; renal uptake less than vascular but greater than background.
6	Marked background activity; renal uptake less than background activity (i.e., photopenic defect).

at the end of the study. It has been our empiric observation that the first five frames of the second phase (total time of 75 sec, acquired from minute 1 through minute 2.15) invariably depicts the cortical phase of tracer dynamics when all the radiopharmaceutical is concentrated in the renal cortical parenchyma. These frames were added together to generate an image that was referred to as a "cortical uptake phase" (CUP) image. This image was visually assessed for the amount of MAG3 extraction by the transplant using a qualitative six-level grading system (Table 1 and Fig. 1). This schema rendered a tubular injury severity score (TISS); the higher the TISS, the lower the residual tubular viability. There is an important theoretical limitation of TISS that should be recognized in patients with residual native renal function. It is conceivable that background activity in these patients may be somewhat lower than in patients without residual native renal function, rendering a lower TISS.

Statistical analysis was performed using Data Desk® version 4.2 (Data Description Inc., Ithaca, NY). Interval data were compared between groups by using Student's t-test. Ordinal data were tested using chi-square analysis.

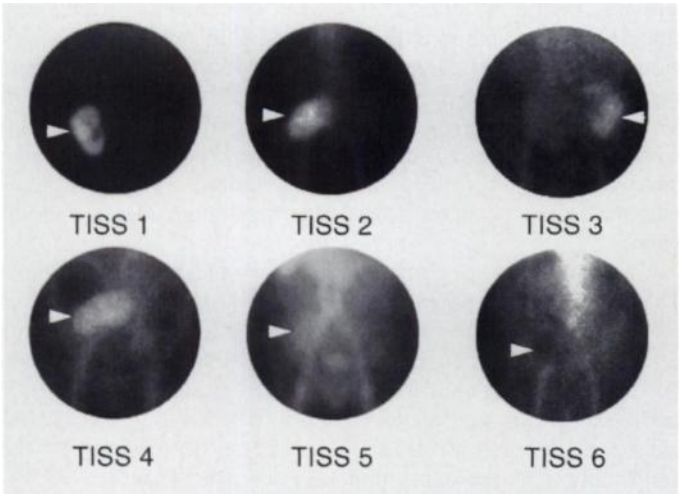

FIGURE 1. Representative images illustrate corresponding tubular injury severity scores (TISS). These images are summations of frames acquired for 75 sec, starting from the end of the first minute after injection.

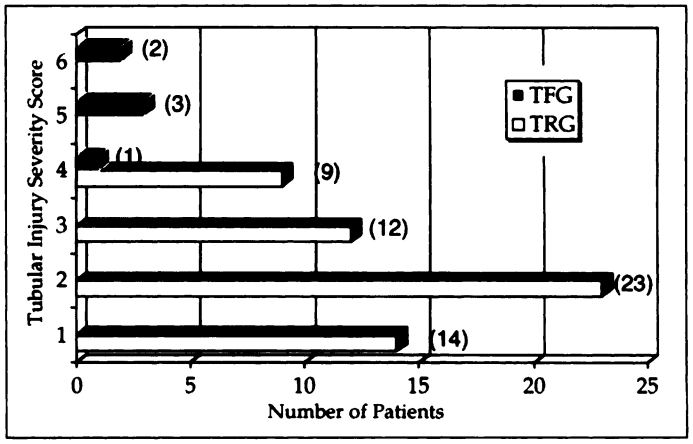

FIGURE 2. Occurrence and distribution of TISS in transplant recovery group (TRG) and transplant failure group (TFG) is represented by white and black bars, respectively.

RESULTS

The mean age of the study population was 45.9 ± 14 yr (35 men, 29 women). The reasons for obtaining renal scan were as follows:

1. Early postoperative failure to make urine and/or rising serum creatinine (52 patients).
2. Suspected postrenal obstruction (five patients).
3. Post-transplant hypertension (five patients).
4. Suspected urinary leak (two patients).

There were six patients comprising the transplant failure group (TFG) who sustained irreversible renal failure that necessitated transplant removal within 1 mo after surgery. There were 58 patients in the transplant recovery group (TRG) in which patient's renal function improved sufficiently to sustain dialysis-free living for 1 yr after transplantation. The age of the patients in the TFG and TRG was not statistically different (46.7 ± 10.9 versus 45.8 ± 14.3 yr; $p = 0.2$). The gender ratio (men:women) was 1:2 in the TFG versus 1:0.76 in TRG, but it was not statistically significant.

In the TFG, two patients had a photopenic defect in the area of the transplant (TISS = 6), three had severe reduction of uptake (TISS = 5) and one had moderately reduced uptake (TISS = 4). The distribution of TISS in patients who regained renal function and those who lost the transplant is shown in Figure 2. The difference in scores between these groups was highly significant (chi-square of 53.41 and $p < 0.0001$). A score of 5 and 6 clearly indicates irreversible transplant failure. Only 1 of 10 patients with a score of 4 lost the kidney. None of the patients with scores less than 4 had an early loss of the transplant.

The renogram curves were also assessed for patterns seen in our clinical cases. We identified nine patterns that could be grouped into three general categories (Fig. 3), recognizing the fact that in reality they probably represent a continuum. The curve pattern A1 is a normal tracing, seen only once in this patient population. We have seen it frequently in uncomplicated transplant cases imaged in other clinical studies. The curve pattern A2 was seen in patients with relatively normal cortical uptake, resulting in normal time-to-peak activity but yet a mildly reduced washout. Residual activity at 20 min to peak activity ratio (RA20/P) was between 0.2 and 0.5. The curve pattern A3 was different from A2 in that the RA20/P was greater than 0.5. Both A2 and A3 curves were seen mostly in patients who were either in the late stages of recovering from acute tubular necrosis (ATN) or early after sustaining only a mild ATN. Only one patient with A3 pattern had a biopsy which confirmed mild rejection. The curve pattern B1-B3 was seen in patients with ATN who were either oliguric (B1) or anuric (B2 and B3). The

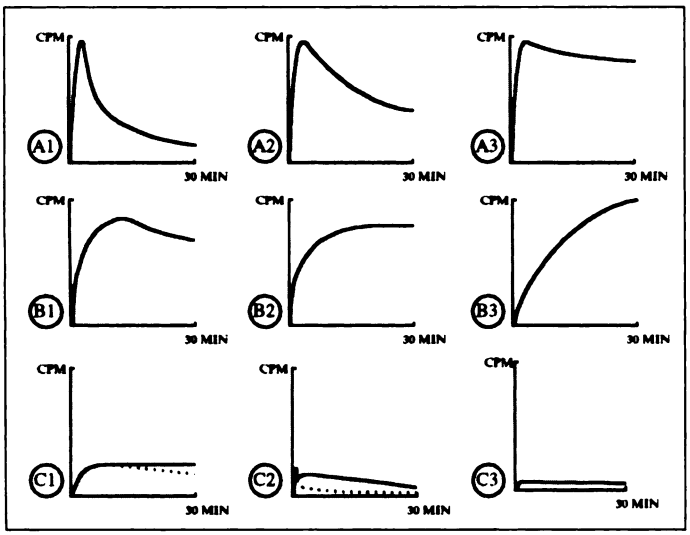

FIGURE 3. Prototypical curves are presented to exemplify each pattern. Radioactivity is plotted on the vertical axis in counts per minute (CPM), which is scaled to the height of an average normal curve peak. The horizontal axis spans 30 min of scanning time.

group C curves were seen in patients with severe functional loss, and all study patients with transplant failure had a type C curve. In fact, the only patient with a TISS of 4 who lost the transplant had a curve pattern C2, while the patients with a TISS of 4 who recovered had curve patterns B2 (four patients) or B3 (five patients).

The K/A ratio was significantly ($p < 0.0001$) lower in the failure group (0.26 ± 0.27) than in the recovery group (0.51 ± 0.24). In the failure group, patients with photopenic defect on the CUP image (TISS 6), the ratio was below 0.1, while in three patients with TISS of 5, the K/A ratios were 0.1, 0.32 and 0.49. The final patient in this group who had TISS of 4 had a K/A ratio of 0.63. There was a significant overlap in K/A values between the two groups, rendering this index not quite as useful as TISS.

DISCUSSION

One of the most critical clinical questions in patients with dysfunctioning renal transplant during the early postoperative period is a likelihood of functional recovery. This is important because a patient who has no hope of transplant recovery could potentially benefit from early termination of immunosuppression and transplant removal. For example, early termination of immunosuppression should reduce the likelihood of infections (*16*). Reducing the number of hospitalization days could result in a very significant cost saving.

Several reports have suggested that the absence of perfusion or tracer uptake on renal scintigraphy correlates with conditions that confer a grave prognosis for survival of the renal transplant (*17–22*). Clinical experience with ^{131}I-labeled orthoiodohippurate (OIH) furnishes significant proof of the scan's predictive power in renal transplants (*10,11,23–25*). Visual analysis of the renogram curve was used in these studies; poor uptake of OIH by the transplant was depicted by a lower height of the renogram curve and was strongly associated with early transplant failure in all studies, while good uptake (even in patients with severe tracer retention) was associated with recovery. This relationship is probably based on preserved viability of temporarily dysfunctional nephrons in the latter group. Importantly, it was tubular extraction function that allowed prognostication, since OIH is taken up nearly exclusively by that mechanism (*26–28*). Furthermore, uptake of OIH is proportional to renal viability and is well correlated to the kidney's ability to regain normal function after ischemic damage, as demonstrated in an animal model (*12,13,29,30*). However, there are significant limitations associated with clinical use of OIH:

1. Poor quality images and significant radiation exposure due to ^{131}I label.
2. Impracticality of repeating the study within 24–48 hr because of the long half-life.
3. The ^{123}I label makes the test significantly more expensive.

There is some evidence in patients with native kidneys who develop acute renal failure, which suggests that MAG3 can predict recovery (*31*).

This study population was a selected group of patients because the clinical service referred only complicated cases for renal scintigraphy. Patients with diagnoses that were obvious on Duplex ultrasound and who subsequently lost the transplant were not referred to nuclear medicine. Therefore, our reported incidence of early renal transplant loss of 9.4% should be viewed cautiously in view of the patient selection bias. The CUP image provided the most useful information with respect to prognosis of the dysfunctional transplant. Patients with TISS of 6 and 5 invariably lost the transplant, while TISS of 4 implied some risk (10%). There were no lost renal transplants in those with TISS of less than 4, which encompassed the majority of patients (77%). Importantly, it takes only a few minutes after initiation of renal scintigraphy to obtain this critical information, allowing a prompt decision regarding further patient management. The renogram curve also appeared useful in evaluating prognosis.

An important limitation to this investigation is that patients with absent flow and no parenchymal uptake (TISS 5 and 6) were not referred for angiography, probably because of the belief that renal transplant loss is inevitable regardless of any intervention (*32*). However, recent evidence indicates that transplant function in those patients can be saved by prompt restoration of blood flow (*33*). Another limitation is a small number of patients in the TFG. However, chi-square analysis indicates that our findings are highly significant. Hence, our experience strongly suggests that poor MAG3 uptake observed on a cortical uptake phase image represents a grave prognosis and that transplant loss is unavoidable. Early recognition of irreversible functional loss allows early management, possibly saving on unnecessary hospitalization. Even more importantly, however, patients who are unnecessarily continued on immunosuppression can develop serious complications. Early removal of an irreversibly damaged kidney would allow termination of immunosuppression, decreasing the likelihood of these complications. However, before this method can be adopted into routine clinical practice, it must be replicated at other institutions and possibly with a greater number of patients recruited prospectively.

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MAG3 SPECT: A Rapid Procedure to Evaluate the Renal Parenchyma

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Renal parenchymal (cortical) scintigraphy (planar or SPECT) is indicated for the diagnosis and follow-up of focal functional disorders, such as acute pyelonephritis, and for accurate quantitation of split renal function, especially in cases of atypical location of the kidney(s). This static imaging procedure is currently performed 3–5 hr after the injection of a cortical fixation agent, ^{99m}Tc-DMSA or ^{99m}Tc-GH, and requires effective immobilization of the patient for 30 min. **Methods:** In five healthy adult volunteers and five children with various clinical indications, SPECT renal parenchymal scintigraphy was performed with a three-detector camera in 1-min per revolution sequential intervals for a total acquisition time of 4 min, beginning immediately after an intravenous injection of a graduated dose of 20 mCi (minimum 2 mCi) of the dynamic renal agent ^{99m}Tc-MAG3. **Results:** Tomograms of the renal parenchyma reconstructed in three projections and volume-rendered reprojection of the SPECT-volume data indicated normal or abnormal renal parenchyma. Comparisons were made with planar MAG3 and SPECT-GH and favored MAG3-SPECT. However, comparisons with DMSA indicated certain disadvantages of MAG3 SPECT. For most organs, the radiation dose estimates from 20 mCi MAG3 were lower than those from DMSA (6 mCi) or GH (20 mCi). Simultaneous injection of MAG3 and a diuretic (2–40 mg furosemide) resulted in lower than usually reported radiation dose estimates for the urinary bladder (target organ) and the gonads, and allowed subsequent evaluation of the drainage system. **Conclusion:** MAG3 SPECT is feasible, clinically useful and may be offered as a rapid (4 min) renal parenchymal imaging procedure, or it may precede planar dynamic (diuretic) MAG3 scintigraphy.

Key Words: renal parenchymal scintigraphy; SPECT; technetium-99m-MAG3; acute pyelonephritis; ectopic kidney; growth-arrested kidney; split renal function

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High-resolution renal parenchymal (cortical) scintigraphy is indicated for the diagnosis and follow-up of focal (functional or anatomical) disorders of the kidneys, primarily acute pyelonephritis and scars, especially in children (*1–9*). It is also useful in evaluating the split renal function, particularly in cases of renal ectopia, in certain renal axis deviations, and in ptotic or wandering kidneys (*10–14*). Currently, the technique of choice for renal parenchymal scintigraphy is static late imaging 3–6 hr after an intravenous injection of a cortical fixation agent, ^{99m}Tc-glucoheptonate (GH) or ^{99m}Tc-dimercaptosuccinic acid (DMSA). Imaging is usually performed in planar mode and

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