

## Miscellaneous

### Ethylenedicysteine Versus Diethylenetriamine Pentaacetic Acid as the Carrier of Technetium Tc 99m in Diuretic Renography for Patients with Upper Urinary Tract Obstruction

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#### ABSTRACT

**Introduction:** L,L-ethylenedicysteine (EC) is a new carrier of technetium Tc 99m ( $^{99m}\text{Tc}$ ) with a lower affinity to plasma albumin in comparison with diethylenetriamine pentaacetic acid (DTPA). We compared  $^{99m}\text{Tc}$ -EC scan with  $^{99m}\text{Tc}$ -DTPA scan in diuretic renography for patients with obstructive uropathy.

**Materials and Methods:** Thirty-three patients with upper urinary tract obstruction were randomly selected and underwent diuretic renographies by  $^{99m}\text{Tc}$ -EC and  $^{99m}\text{Tc}$ -DTPA. The counts of radioisotope per pixel in the target (the kidney) and background tissues as well as the clearance half-life of these two radiopharmaceuticals were measured and compared.

**Results:** Mean counts of radioisotope per pixel in the target tissue was not different between  $^{99m}\text{Tc}$ -EC and  $^{99m}\text{Tc}$ -DTPA scans, but in the background tissue, it was less for  $^{99m}\text{Tc}$ -EC ( $P = .003$ ). Target-background ratio was higher for  $^{99m}\text{Tc}$ -EC scan ( $3.80 \pm 2.11$  versus  $2.48 \pm 1.39$ ;  $P < .001$ ). Renal clearance half-life of radioisotope was shorter for  $^{99m}\text{Tc}$ -EC scan than  $^{99m}\text{Tc}$ -DTPA scan ( $58.15 \pm 15.17$  minutes versus  $78.65 \pm 19.99$  minutes;  $P = .033$ ). The results were similar for uremic patients (with a serum creatinine level  $> 2\text{mg/dL}$ ).

**Conclusion:** Target-background ratio of radiopharmaceutical uptake rates in diuretic renography was a good indicator of the higher resolution of  $^{99m}\text{Tc}$ -EC than  $^{99m}\text{Tc}$ -DTPA scan. We also demonstrated the faster clearance of  $^{99m}\text{Tc}$ -EC than  $^{99m}\text{Tc}$ -DTPA. This results in less radiation that is especially useful in children. To our opinion,  $^{99m}\text{Tc}$ -EC can better depict the kidneys in comparison with  $^{99m}\text{Tc}$ -DTPA.

**KEY WORDS:** radioisotope renography, kidney function, diethylenetriamine pentaacetic acid, L,L-ethylenedicysteine, radiopharmaceutical, ureteral obstruction

#### Introduction

Today, the advanced urology is based on disease knowledge, the most cost-effective diagnostic methods, the simplest treatment modality with

minimal tissue injury, and finally, the most efficient and economical methods for follow-up. In other words, the use of invasive and expensive methods is not popular anymore. Diuretic renography plays a special role in the measurement of the kidney function and the location of obstruction in the upper urinary tract system. In Iran and many other countries, the

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standard radiopharmaceutical for diuretic renography is technetium Tc 99m diethylenetriamine pentaacetic acid ( $^{99m}\text{Tc}$ -DTPA). But, notwithstanding its easy application and widespread clinical use, the background of images (especially in uremic patients and severely hydronephrotic kidneys) is obscured due to high uptake of radioactive substance by the liver and the spleen. Consequently, it cannot provide sufficient anatomic resolution for clinical judgment and decision-making in some cases of upper urinary tract obstruction. For this reason, it is inevitable for physicians to use invasive methods, although they usually impose high expenses to patients by accepting the risk of anesthesia and iatrogenic damage to the urinary tract. The most important cause of obscured images on  $^{99m}\text{Tc}$ -DTPA scans is a tight protein binding of  $^{99m}\text{Tc}$ -DTPA to plasma albumin and its tendency to be absorbed in the gastrointestinal tract.<sup>(1)</sup> Thus, it is reasonable to use radiopharmaceuticals with weaker protein binding and lower visceral uptake. One of these pharmaceuticals, which has recently been considered, is technetium Tc 99m L,L-ethylenedicysteine ( $^{99m}\text{Tc}$ -EC)<sup>(1)</sup>; however, sufficient clinical evidence of its efficacy is lacking.<sup>(1)</sup> In this study, we compared the results of diuretic renography using  $^{99m}\text{Tc}$ -EC and  $^{99m}\text{Tc}$ -DTPA in a group of patients with upper urinary tract obstruction.

### Materials and Methods

From April 2004 to March 2005, a total of 135 consecutive patients with upper urinary tract obstruction who had referred to Hasheminajad Hospital were initially evaluated by ultrasonography, intravenous urography, and, where required, retrograde and/or antegrade pyelography. Serum creatinine level was measured and urinalysis and urine culture were done. After documentation of obstruction with radiologic findings, 33 patients who had no indications for urgent interventions (eg, acute pyelonephritis, high fever, and sepsis) were randomly selected. All of the patients gave written informed consent. This study was approved by the ethics committee of Iran University of Medical Sciences.

Diuretic renography was performed by either  $^{99m}\text{Tc}$ -EC or  $^{99m}\text{Tc}$ -DTPA while a Foley catheter was fixed and furosemide (in patients with normal serum creatinine levels, 20 mg; in those

with impaired kidney function, 40 mg) was given 20 minutes after radiopharmaceutical injection (F+20 protocol). After a 2- or 3-day interval, the other radiopharmaceutical was used in a second diuretic renography with the same method. Bolus injections of 220 MBq to 300 MBq of  $^{99m}\text{Tc}$ -EC and 450 MBq to 550 MBq of  $^{99m}\text{Tc}$ -DTPA were administered. Both radioisotopes were made by the Iranian Atomic Energy Organization. Labeling was performed at the nuclear medicine department of the hospital in room temperature (Hot Lab). The kits were prepared rapidly and all at a same duration. Kidney imaging was performed using a single gamma camera in supine position with the nearest possible distance from the body surface. After assuring that the patient is hydrated, dynamic imaging was performed in vascular and excretory phases (within 20 minutes after the radiopharmaceutical injection) and after diuretic administration (at 10, 15, and 20 minutes after the injection). Delayed images were obtained up to 4 hours after the procedure, if necessary (in case of radiotracer in the pyelocaliceal system).

A serum creatinine level higher than 2 mg/dL was considered as uremic. The examined parameters in this study were as follow: uptake rate of the radiopharmaceutical in the target tissue (kidney) and the background tissue (using count per pixel unit), target-background ratio of uptake, and clearance half-life of radiopharmaceutical from the kidneys.

The collected data were analyzed using SPSS software (Statistical Package for the Social Sciences, version 11.5, SPSS Inc, Chicago, Ill, USA). Paired t test was used to compare the uptake parameters of each scan. Continuous variables were demonstrated as means  $\pm$  standard deviations and a *P* value less than .05 was considered significant.

### Results

Thirty-three patients were enrolled in this study and 43 obstructive urinary tract units were evaluated. Twenty of the patients were men and 13 were women. Mean age of the patients was  $54 \pm 8$  years. Mean serum level of creatinine was  $4.2 \pm 1.2$  mg/dL. The serum level of creatinine was 2 mg/dL or less in 12 patients (nonuremic) and greater than 2 mg/dL in 21 (uremic).

Mean counts of radioisotope per pixel in the target tissue was  $85.91 \pm 50.87$  and  $87.50 \pm 55.27$  in  $^{99m}\text{Tc}$ -EC and  $^{99m}\text{Tc}$ -DTPA scans (*P* = .802), and

in the background tissue, it was  $25.76 \pm 11.12$  and  $41.64 \pm 23.52$ , respectively ( $P = .003$ ). Mean counts of radioisotope per pixel in the target tissue were not significantly different between  $^{99m}\text{Tc}$ -EC and  $^{99m}\text{Tc}$ -DTPA scans neither in uremic nor in nonuremic patients. But, this rate in the background tissue was significantly lower for  $^{99m}\text{Tc}$ -EC scan than  $^{99m}\text{Tc}$ -DTPA scan in both groups of patients (Table 1).

Target-background ratio was higher in  $^{99m}\text{Tc}$ -EC scan ( $3.80 \pm 2.11$  versus  $2.48 \pm 1.39$ ;  $P < .001$ ). In both nonuremic and uremic patients, this ratio was significantly higher for  $^{99m}\text{Tc}$ -EC scan (Table 1, Figure 1).

Renal clearance half-life of the radioisotope was shorter for  $^{99m}\text{Tc}$ -EC scan than  $^{99m}\text{Tc}$ -DTPA scan ( $58.15 \pm 15.17$  minutes versus  $78.65 \pm 19.99$  minutes;  $P = .033$ ). In nonuremic patients, renal clearance half-life of the radioisotope substance was shorter for  $^{99m}\text{Tc}$ -EC scan ( $23 \pm 7.17$  minutes versus  $26.80 \pm 9.5$  minutes;  $P = .087$ ), and it was  $72.83 \pm 28.35$  minutes versus  $100.25 \pm 38.68$  minutes in uremic patients ( $P = .043$ ) (Figure 2).

## Discussion

Technetium Tc 99m DTPA is an appropriate

radiopharmaceutical for the evaluation of the kidney and glomerular filtration by diuretic renography. Of other characteristics of this radiopharmaceutical are low-dose radiation exposure to patient, reasonable cost, and availability. However, it is not suitable for the assessment of the renal cortex. Technetium Tc 99m EC is a tubular radiopharmaceutical with a N2S2 ligand. It is virtually a diacid derivative of a radiopharmaceutical used in brain scans called  $^{99m}\text{Tc}$ -L,L-ethylenedicycysteine diethylester. L,L-ethylenedicycysteine easily binds to  $^{99m}\text{Tc}$  in laboratory conditions and room temperature.<sup>(2)</sup>

In this study, we showed that there is no significant difference between the uptake rate of the radioactive substance in the kidney tissue for  $^{99m}\text{Tc}$ -EC and  $^{99m}\text{Tc}$ -DTPA scans. In contrast, the mean rate of radioactive substance uptake in the background tissue was considerably less in  $^{99m}\text{Tc}$ -EC scan; this could be due to the less protein binding and the weak binding of EC to red blood cells which eventually lead to a faster excretion of the radiopharmaceutical from the kidney (Figure 3).<sup>(3)</sup>

Mean target-background uptake ratio of radioactive substance was greater for  $^{99m}\text{Tc}$ -EC scan. This difference causes a higher resolution

**TABLE 1.** Counts of radioisotope per pixel in target (the kidney) and background tissues and target-background ratio for  $^{99m}\text{Tc}$ -EC than  $^{99m}\text{Tc}$ -DTPA scans

	$^{99m}\text{Tc}$ -EC	$^{99m}\text{Tc}$ -DTPA	P value
All patients			
Target tissue*	$85.91 \pm 50.87$	$87.50 \pm 55.27$	.80
Background tissue*	$25.76 \pm 11.12$	$41.64 \pm 23.52$	.003
Target-background	$3.80 \pm 2.11$	$2.48 \pm 1.39$	< .001
Patients with serum creatinine of 2 mg/dL or less			
Target tissue	$97.87 \pm 53.21$	$118.19 \pm 49.76$	.11
Background tissue	$17.62 \pm 10.97$	$32.62 \pm 25.25$	.086
Target-background	$5.97 \pm 1.69$	$4.01 \pm 1.68$	.019
Patients with serum creatinine greater than 2 mg/dL			
Target tissue	$81.08 \pm 48.06$	$84.67 \pm 58.42$	.68
Background tissue	$29.15 \pm 9.67$	$45.40 \pm 22.82$	.020
Target-background	$2.89 \pm 1.55$	$1.85 \pm 0.54$	.007

\*counts per pixel

$^{99m}\text{Tc}$ -EC: technetium Tc 99m L,L-ethylenedicycysteine,  $^{99m}\text{Tc}$ -DTPA: technetium Tc 99m diethylenetriamine pentaacetic acid

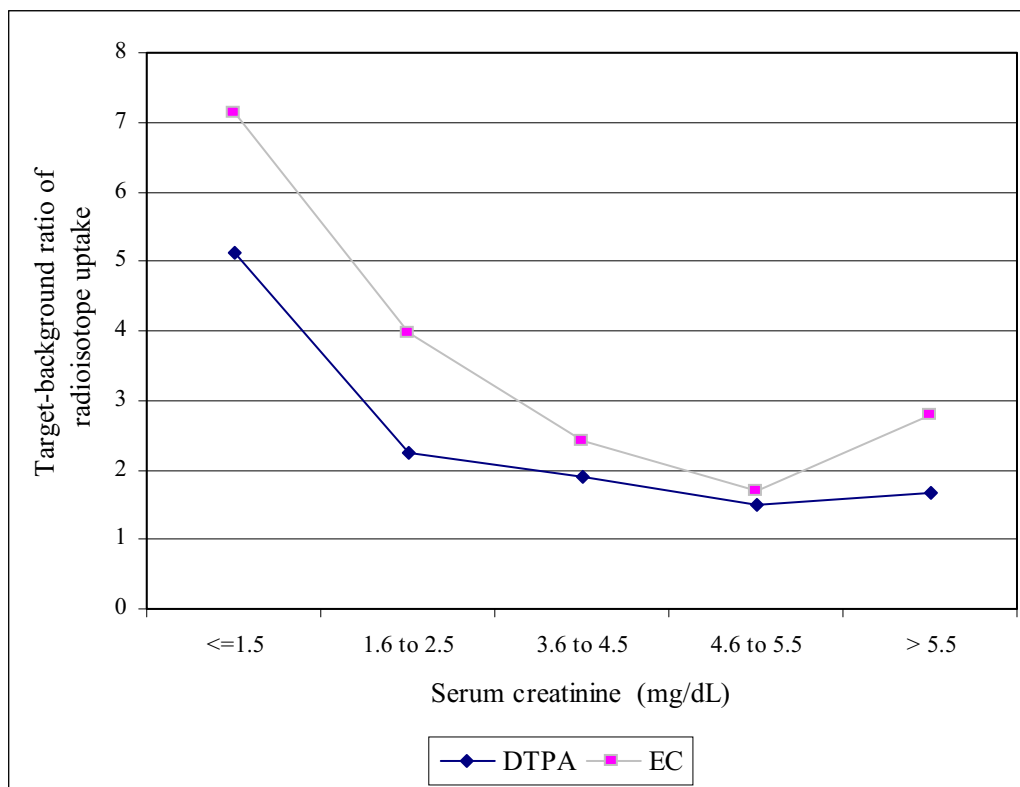


FIG. 1. Comparison of target-background ratio of  $^{99m}\text{Tc}$ -EC and  $^{99m}\text{Tc}$ -DTPA uptakes according to the serum creatinine level

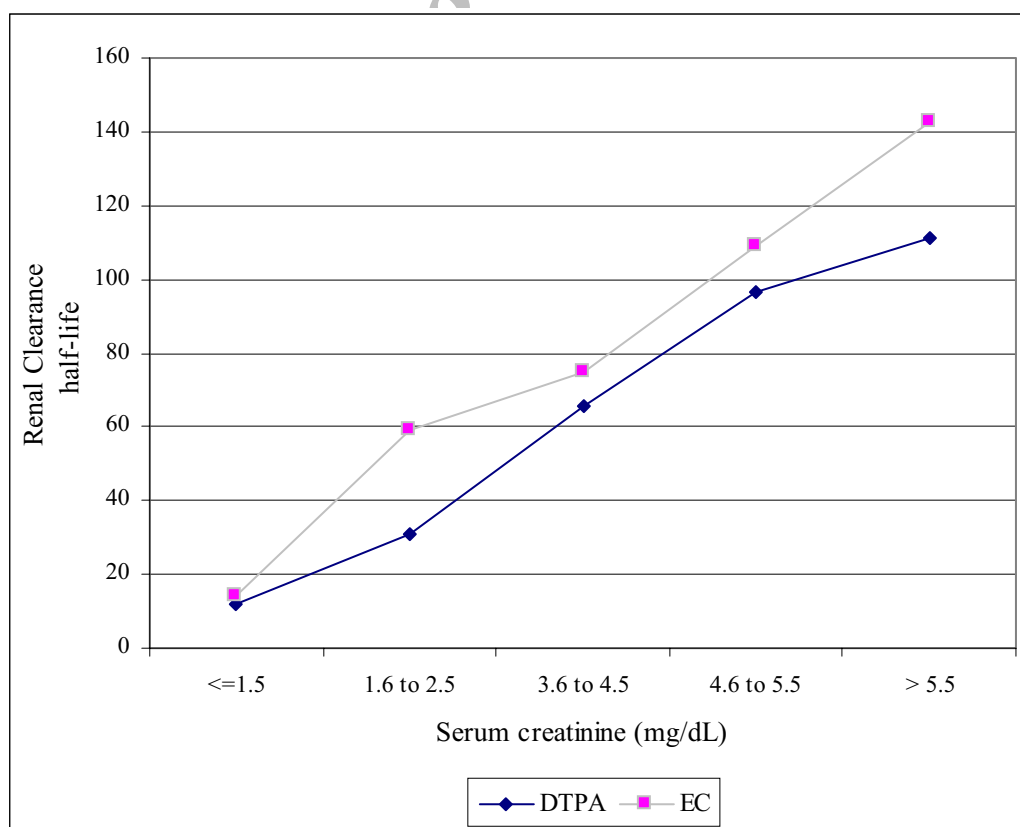
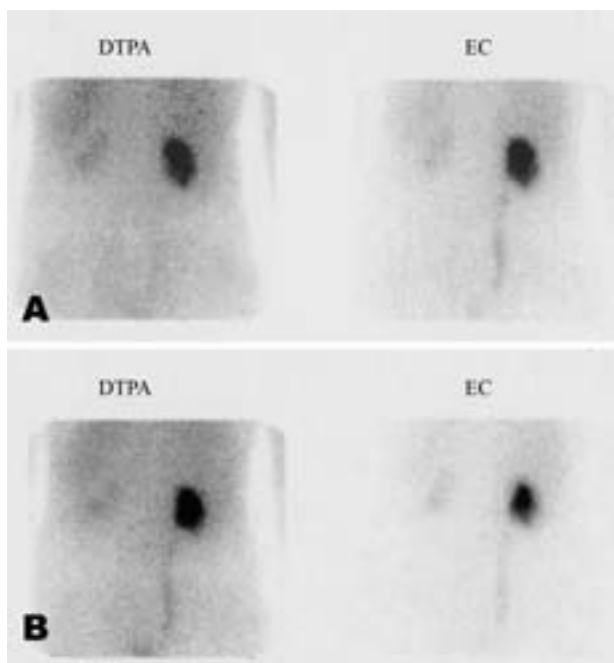


FIG. 2. Comparison of  $^{99m}\text{Tc}$ -EC and  $^{99m}\text{Tc}$ -DTPA renal clearance half-life according to the serum levels of creatinine



**FIG. 3.** Comparison of  $^{99m}\text{Tc}$ -EC and  $^{99m}\text{Tc}$ -DTPA scans in a 67-year-old patient with prostate cancer, 20 minutes after radiopharmaceutical injection (A) and 20 minutes after furosemide injection. The  $^{99m}\text{Tc}$ -EC scan could rule out ureterovesical junction obstruction 20 minutes after diuretic injection, because more than 50% of the radiopharmaceutical was excreted, but  $^{99m}\text{Tc}$ -DTPA scan findings showed equivocal obstruction and more invasive methods such as nephrostography was needed to rule out obstruction.

for imaging with  $^{99m}\text{Tc}$ -EC compared to  $^{99m}\text{Tc}$ -DTPA regardless of the serum levels of creatinine.

Das and colleagues compared  $^{99m}\text{Tc}$ -EC scan and  $^{99m}\text{Tc}$ -DTPA scan in a prospective study. In patients with a normal renal function, the results of these two scans were not significantly different, but  $^{99m}\text{Tc}$ -EC scan had a higher imaging resolution and a faster clearance. In another group of patients who had an increased serum level of creatinine to a maximum of 3 mg/dL, reduction in glomerular filtration had confounded the background of the images and lack of sufficient resolution in images were significant in  $^{99m}\text{Tc}$ -DTPA scan, whereas in  $^{99m}\text{Tc}$ -EC scan, the images had a higher resolution, radioactive concentration in background tissue was less, and retention and concentration time of radioactive substance in the kidneys were shorter. They also studied a third group of patients who had a pathologic finding in the kidneys but were not uremic; there were no significant differences between the results of the two scans except for a higher resolution and a faster clearance of  $^{99m}\text{Tc}$ -EC. Their study demonstrated the

superiority of imaging with  $^{99m}\text{Tc}$ -EC pharmaceutical in uremic patients, but it lacked a quantitative measurement of the parameters.<sup>(4)</sup>

In a study by Eftekhari and colleagues,<sup>(5)</sup> 23 patients underwent diuretic renography with  $^{99m}\text{Tc}$ -EC and  $^{99m}\text{Tc}$ -DTPA. The mean serum creatinine level of the patients was  $4.5 \pm 4.11$  mg/dL. In their study, mean target-background ratio of radioisotope uptake was greater for  $^{99m}\text{Tc}$ -EC compared to  $^{99m}\text{Tc}$ -DTPA. The mean counts of radioisotope per pixel in the background tissue was  $3.31 \pm 1.7$  and  $9.78 \pm 2.76$ , respectively. Furthermore, renal clearance half-life of the radioactive substance after diuretic administration was shorter for  $^{99m}\text{Tc}$ -EC. This means that  $^{99m}\text{Tc}$ -EC is excreted more rapidly compared to  $^{99m}\text{Tc}$ -DTPA; consequently, the exposure of patients to  $^{99m}\text{Tc}$ -EC scan is shorter. They also reported that measurements of uptake rate in the upper and lower backgrounds of the kidney are not significantly different, especially for  $^{99m}\text{Tc}$ -EC scan.

When we evaluated the variables categorized according to the serum levels of creatinine, the results were considerable; in both uremic and nonuremic patients, there was no remarkable difference between  $^{99m}\text{Tc}$ -EC and  $^{99m}\text{Tc}$ -DTPA in the mean uptake rate in the target tissue (the kidney). This finding shows that patient's creatinine level has similar effects on the absorption of these two radiopharmaceuticals, and what may actually cause a high resolution on imaging in  $^{99m}\text{Tc}$ -EC scans, especially in uremic patients, is the lower hepatobiliary excretion of this radiopharmaceutical. In 1998, Zakko and coworkers performed a study on 2213 people to evaluate the hepatobiliary excretion rate of  $^{99m}\text{Tc}$ -EC. They reported that only 9 cases of gallbladder visualizations and/or biliary excretion were identified. In no case did biliary excretion affect the interpretation of the renal study. They concluded that hepatic uptake of this pharmaceutical is little; however, their measurement method was not quantitative.<sup>(6)</sup>

Although the background uptake rate of  $^{99m}\text{Tc}$ -EC in both uremic and nonuremic patients was less, this difference was statistically significant only in uremic patients. In other words, the background on  $^{99m}\text{Tc}$ -DTPA scan can make the image more unclear if the patient's creatinine level is greater than 2 mg/dL.

In our patients, renal clearance half-life of  $^{99m}\text{Tc}$ -EC was significantly shorter after diuretic

administration. However, this difference between  $^{99m}\text{Tc}$ -EC and  $^{99m}\text{Tc}$ -DTPA was significant in uremic patients but not in nonuremic ones. Renal clearance half-life as well as target-background ratio shows that in uremic patients,  $^{99m}\text{Tc}$ -EC can be excreted from the kidneys more easily, hence creating a better anatomic visualization of the kidney. Meanwhile, in uremic patients, the shorter clearance of  $^{99m}\text{Tc}$ -EC in comparison with  $^{99m}\text{Tc}$ -DTPA reduces radiation exposure.

Nowadays,  $^{99m}\text{Tc}$ -mercaptoacetyltryglycine ( $^{99m}\text{Tc}$ -MAG3) and iodine I 125 orthoiodohippurate (125I-OIH) are known as favorable radiopharmaceuticals for assessing the obstructive systems, which were not available for us. Stoffel and colleagues evaluated the safety and pharmacokinetics of iodine I 125 orthoiodohippurate (125I-OIH),  $^{99m}\text{Tc}$ -MAG3, and  $^{99m}\text{Tc}$ -EC. In their study, the clearance of  $^{99m}\text{Tc}$ -EC and  $^{99m}\text{Tc}$ -MAG3 averaged 71% and 52% of that of 125I-OIH, respectively. Volumes of distribution of 125I-OIH and  $^{99m}\text{Tc}$ -EC were almost equal (%20 of body weight). The reasons were lower plasma protein binding (31% versus 50% to 70%), lower erythrocyte binding (%2 versus %5), and lower extrarenal clearance of  $^{99m}\text{Tc}$ -EC which reduces its volume of distribution. These three factors result in equal volume of distribution for the two radiopharmaceuticals in uremic patients. Clearance of  $^{99m}\text{Tc}$ -EC was 10 mL/min to 15 mL/min, while it was 30 mL/min for 125I-OIH. Their study also showed that hepatobiliary clearance of  $^{99m}\text{Tc}$ -EC was a bit less than 125I-OIH.<sup>(2)</sup>

Renal clearance of  $^{99m}\text{Tc}$ -EC is fast.<sup>(1,7)</sup> Verbruggen and colleagues performed a study on mice, and compared 4 carriers of radioactive substances: OIH, DTPA, MAG3, and EC. They found that EC has a faster renal clearance and less retention in the kidneys, liver, intestines, and blood than did  $^{99m}\text{Tc}$ -MAG3. They showed that renal excretion of EC is moderately more than MAG3, while hepatobiliary absorption of EC is considerably lower. This can explain a more similarity between EC and OIH.<sup>(1)</sup>

Another study has revealed that lack of maturity in renal glomerular tissue of children usually results in better images by radiopharmaceuticals with tubular excretion (eg,  $^{99m}\text{Tc}$ -MAG3 and  $^{99m}\text{Tc}$ -EC) comparing with those with glomerular excretion (eg,  $^{99m}\text{Tc}$ -DTPA).<sup>(8)</sup> It has been demonstrated that the resolution of

$^{99m}\text{Tc}$ -EC scan is higher than  $^{99m}\text{Tc}$ -MAG3 scan because of its higher extraction fraction (70% versus 50%). This finding is mainly due to less background and hepatic absorption of  $^{99m}\text{Tc}$ -EC.<sup>(8)</sup> Taylor and coworkers published an article in 2004 in which they showed that the pharmacokinetic properties of  $^{99m}\text{Tc}$ -MAG3 is far different from 125I-OIH and cannot be a substitute for it. Thus, they introduced a combination of EC and MAG3 named mercaptoacetamide-ethylene-cysteine (MAEC) for assessment of obstruction in the urinary tract. They showed that  $^{99m}\text{Tc}$ -MAEC has a higher renal clearance compared to  $^{99m}\text{Tc}$ -MAG3, providing a better image; however, 125I-OIH was still superior regarding clearance.<sup>(9)</sup>

## Conclusion

Our study showed that target-background ratio of radiopharmaceutical uptake rates in diuretic renography can support the higher resolution of  $^{99m}\text{Tc}$ -EC than  $^{99m}\text{Tc}$ -DTPA scan. Hence, renography with  $^{99m}\text{Tc}$ -EC can be more contributory in surgeon's decision-making. We also revealed the faster clearance of  $^{99m}\text{Tc}$ -EC than  $^{99m}\text{Tc}$ -DTPA. This can help us reduce radiation, especially in children.

Comparing with the findings of previous studies on  $^{99m}\text{Tc}$ -MAG3 as the current standard radiopharmaceutical in diuretic renography,  $^{99m}\text{Tc}$ -EC has a higher laboratory stability, significantly lower hepatobiliary absorption, and shorter renal clearance time. In addition, it is produced more easily. We believe that  $^{99m}\text{Tc}$ -EC can better depict the kidney in comparison with  $^{99m}\text{Tc}$ -DTPA and can be an alternative to 125I-OIH.

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