Comparison of glomerular filtration rate measured by plasma sample technique, Cockroft Gault method and Gates' method in voluntary kidney donors and renal transplant recipients

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Background: There are numerous methods for calculation of glomerular filtration rate (GFR), which is a crucial ABSTRACT measurement to identify patients with renal disease. Aims: The aim of this study is to compare four different methods of GFR calculation. Settings and Design: Clinical setup, prospective study. Materials and Methods: Data was collected from routine renal scans done for voluntary kidney donors (VKD) or renal transplant recipients 6 months after transplantation. Following technetium-99m diethylene triamine penta acetic acid injection, venous blood samples were collected from contralateral arm at 120, 180, and 240 min through an indwelling venous cannula and direct collection by syringe. A total volume of 1 ml of plasma from each sample and standards were counted in an automatic gamma counter for 1 min. Blood samples taken at 120 min and 240 min were used for double plasma sample method (DPSM) and a sample taken at 180 min for single plasma sample method (SPSM). Russell's formulae for SPSM and DPSM were used for GFR estimation. Gates' method GFR was calculated by vendor provided software. Correlation analysis was performed using Pearson's correlation test. Results: SPSM correlated well with DPSM. GFR value in healthy potential kidney donors has a significant role in the selection of donors. The mean GFR ± (standard deviation) in VKD using SPSM, DPSM, camera depth method and Cockroft Gault method was 134.6 (25.9), 137.5 (42.4), 98.6 (15.9), 83.5 (21.1) respectively. Gates' GFR calculation did not correlate well with plasma sampling method. Conclusions: Calculation of GFR plays a vital role in the management of renal patients, hence it was noted that Gates GFR may not be a reliable method of calculation. SPSM was more reliable. DPSM is reliable but cumbersome. It is difficult to accurately calculate GFR without a gold standard.

Keywords: Cockroft Gault method, double plasma sample method, Gates method, glomerular filtration rate, post-renal transplant recipients, single plasma sampling method, voluntary kidney donors

INTRODUCTION

Glomerular filtration rate (GFR) is defined as the volume of plasma that can be completely cleared of a particular substance by the kidneys in unit time. GFR is customarily assessed by measuring the concentrations of serum markers such as blood urea nitrogen and serum creatinine (Scr). Although widely used, these endogenous markers are not ideal and occasionally



do not perform well. The other method for determining GFR is to measure the clearance of exogenous substances such as inulin, iohexol, chromium-51-ethylenediaminetetraacetic acid (EDTA), technetium-99m labeled diethylene triamine penta acetic acid (Tc-99m DTPA) or I-125 labeled iothalamate.

As the definition of classifying chronic renal disease becomes more dependent on accurate calculation of GFR, it is imperative that a reliable method to calculate GFR is obtained. GFR can be calculated from the rate of clearance of tracer activity from the plasma following a single intravenous injection of a suitable radiopharmaceutical. As long as the radiopharmaceutical is excreted exclusively by glomerular filtration and is not bound to plasma protein or to any other component of blood or other tissue, the GFR can be calculated simply by dividing the administered dose by the integral of plasma time-activity curve. Initially GFR was calculated from the multisampling technique

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with the samples taken at 5, 10, 15, 30, 45, 60, 120, 180, 240 min. A time-activity curve was plotted. GFR was calculated from the dose divided by the area under the curve. Since it was exhaustive and difficult to perform in routine clinical practice, single and double plasma sampling GFR formulae were derived from multi sample technique.

Fairly accurate methods have been proposed in which the GFR is estimated from only one or two plasma samples rather than from a multi sample time-activity curve.^[1] In routine nuclear practice, the gamma camera (GC) method is popular as it can provide immediate calculation of individual kidney function as well as of global renal function. Gary Gates^[2] computed the GFR from the scintigraphic determination of Tc-99m-DTPA uptake within the kidneys and ever since then this has become universal and versatile.

With the above factors in mind, it was decided to compare the single and double plasma sampling method with Gates GFR and observe the reliability of these measures in routine clinical practice.

MATERIALS AND METHODS

A total of 88 patients, who were sent to our department for routine renal study, were either voluntary kidney donors (VKD) or 6 months post-renal transplant recipients (PTR) were included in this prospective study. Fifty patients in VKD and 38 patients in PTR group were analyzed. The patient selection process involved identifying those patients who fulfilled the criteria given below.

Inclusion criteria

Patients aged 18 years and above, undergoing nuclear medicine imaging either as a VKD or post 6 months PTR.

Exclusion criteria

Patients aged below 18 years, pedal edema or patients who underwent diuretic studies.

All patients were seen during the consultation, informed of the nature of the study and informed consent was obtained.

Methodology and data collection

We compared the single plasma sampling method (SPSM), double plasma sample method (DPSM), Gates camera method, and Cockroft Gault (CG) method.

Plasma sampling methods

Tc-99m-DTPA plasma clearance measured by DPSM and SPSM: Patients were requested to drink 300-500 ml water after breakfast and 20 min prior to taking the plasma sample. Radioactivity in the syringe containing Tc-99m-DTPA was measured before injection. A bolus of about 185 MBq Tc-99m-DTPA was injected into the patients' forearm. Residual radioactivity in the syringe was measured again and injected dosage of radioactivity was calculated. After scintigraphy, the site of injection on the arm was scanned under the GC. The residual radioactivity at the injection site was less than 0.1% in all subjects.

Following Tc-99m-DTPA injection, venous blood samples (4 ml) were collected in a syringe from the contralateral arm at 120, 180, and 240 min through an in-dwelling venous cannula. The blood samples were centrifuged and 1 ml of plasma from the sample as well as the standards was counted in an automatic gamma counter (Cobra II, Packard) for 1 min at the same time. The blood samples were centrifuged at 1000 g for 10 min to separate the red blood cells from the plasma. A test dose of 1 ml of plasma was pipetted meticulously by taking care to avoid disturbing the interface between the plasma and the red cells. Decay of radioactivity was corrected. Time at which the blood sample was taken was recorded on the worksheet. As the procedure takes a minute or two, the time of sampling was taken as the midpoint of the blood collection time and was recorded to the nearest minute.

The blood samples taken at 120 min and 240 min were used for the DPSM and a sample taken at 180 min was used for SPSM. Russell's method was used for GFR estimation.

(a) Tc-99m-DTPA plasma clearance by SPSM (true GFR) was calculated according to the following equation: Russell's method: The GFR, in ml/min, is given by: $A \ln D/P + B$ Where: A = -0.278T + 119.1 + 2450/T, B = 2.886T - 1222.9 - 16820/T, D = total injected dose counts (cpm), P = plasma activity (cpm/ml), T = sampling time (180 min).

(b) Tc-99m-DTPA plasma clearance by DPSM (tGFR) was calculated according to the following equation i.e.,

Russell's DPSM:
$$\frac{D \ln (P_1 / P_2)}{T_2 - T_1 \exp^{(T_1 \ln P_2) - (T_2 \ln P_1)/T_2 - T_1}}$$
(1)

Where D = total injected dose counts (cpm), $P_1 =$ activity (cpm/ml) at the time of T_1 , $P_2 =$ activity (cpm/ml) at the time of T_2 , $T_1 = 120$ min, $T_2 = 240$ min.

Counting

After selection of the energy peak and window of Tc-99 m, the plasma samples were counted with appropriate standards and blanks for background in a well counter. The background counts were subtracted. This was done on the same day of the test and correction factor was applied for the decay of Tc-99m during the counting process.

Quality control

Quality control was performed on all equipments (balance, dose calibrator, well counter etc.) used in the procedure. As Tc-99m-DTPA was prepared in-house at our center, regular chromatography for the labeling efficiency was performed. The radiochemical purity was > 95%.

The correction for body surface area

In order to interpret the result and compare it with the reference range, the same was corrected for the effect of body size on GFR. It is conventionally assumed that the normal value of GFR for any individual scales with their BSA. Hence the measured GFR was corrected to a nominal BSA figure for "standard man," with BSA value of 1.73 m². The GFR value was therefore corrected to the standard BSA using the equation:

$$GFR_{Corr} = GFR \times (1.73/BSA m^2)$$
(2)

Values of BSA were estimated from the height and weight of the patient using the Haycock^[3] formula:

BSA (m²) =
$$0.024265 \times Wt^{0.5378} \times Ht^{0.3964}$$
 (3)

Where Wt = the patient's body weight in kilograms and Ht = height in centimeters. The BSA corrected GFR was distinguished by referring to it in units of ml/min/1.73 m².

GC Gates method

In this method, the GFR was automatically calculated by the software in Infinia Hawkeye (GE) GC. A region of interest (ROI) was drawn manually for each kidney from 2 to 3 min summed images. The infrarenal background ROI was assigned. Firstly, fractionated uptake (FU) of each kidney was assessed according to the equation.

$$FU = (renal count/e^{-\mu y})/total injected dose counts \times 100$$
(4)

Where the renal count was background subtracted and the dose counts were expressed in counts per minute (cpm). The renal count was calculated from the renal uptake between 2 and 3 min in the renogram; μ = attenuation coefficient of Tc-99m (0.153) and *y* = kidney depth (cm), which was calculated as described in Tonnesen's formula.^[4]

The GFR, in ml/min, was calculated as:	
$9.75621 \times FU - 6.19843$	(5)

CG method

This was developed in 1973 with data from 249 men with creatinine clearances (Ccr) from 30 to 130 ml/min.^[5] The estimating equation is:

 $Ccr = (140 - age) \times IBW/(Scr \times 72)$ in males and $\times 0.85$ (if the subject is female) (6)

where Ccr is expressed in milliliters per minute, age in years, Ideal body weight (IBW) in kilograms and Scr in milligrams per deciliter. Estimate Ideal body weight in (kg).

Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet.

Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet.

Statistical analysis

All statistical analyses were performed using SPSS 16.0 (SPSS

Inc., Chicago, USA), Stata 10 (StataCorp LP, College Station, USA) was used for Bland Altman plotting in order to define the 95% limits of agreement. All the data were expressed as mean ± standard deviation (SD) of the mean. Correlation analysis was performed between SPSM, DPSM, CG, and Gates' camera method using Pearson's correlation test. Bland Altman plot was done for those methods which had significant correlation.

RESULTS

The study had 88 participants consisting of VKD (n = 50) and PTR (n = 38). The mean age in VKD group and in PTR group was 40 years. In VKD 56% were females and 44% were males, whereas in PTR 18% were females and 82% were males.

VKD group

The mean \pm (SD) GFR using SPSM, DPSM, camera depth method and CG method was 134.6 (25.9), 137.5 (42.4), 98.6 (15.9), 83.5 (21.1) respectively [Table 1].

There was good and significant correlation between SPSM and DPSM. There was poor and non-significant correlation between SPSM and camera depth method and DPSM and camera depth method. The CG method had moderately significant correlation with SPSM, DPSM but not with camera method [Table 2a].

Bland Altman plot for SPSM and DPSM for VKD showed mean difference of -2.80 (95% confidence interval [CI] = -10.7-5.1). The limit of agreement ranged from -58.79 to -53.11 [Figure 1a]. And similarly for SPSM and depth corrected camera method for VKD the mean difference was 36.1, 95% CI (28.3, 43.8). The limit of agreement ranges from -18.4 to 90.6 [Figure 1b].

PTR group

In PTR the mean \pm (SD) GFR using SPSM, DPSM, camera depth method and CG method was 98.7 (22.7), 97.4 (28.1), 57.1 (23.5), 65.2 (15.4) respectively [Table 1]. There was good and significant correlation between SPSM and DPSM. There was moderate, but significant correlation between SPSM and camera depth method. The correlation between CG method and SPSM, DPSM was moderate, but not significant with camera depth method [Table 2b].

Bland Altman plot for single plasma sample and double plasma sample for PTR showed mean difference of 3.02%, 95% CI (-3.34-3.39), with a limit of agreement range from -34.6 to 40.7 [Figure 2].

Table 1: Summary statistics mean GFR±(SD) for each of the method in two groups

Patient type	Single	Double	Depth	CG	
Transplant (n=38)	98.7 (22.7)	97.4 (28.1)	57.1 (23.5)	65.2 (15.4)	
VKD (<i>n</i> =50)	134.6 (25.9)	137.5 (42.4)	98.6 (15.9)	83.5 (21.1)	
VKD: Voluntary kidney donors, GFR: Glomerular filtration rate, SD: Standard deviation, CG: Cockroft Gault					







Figure 1b: Comparison of single plasma sample method with depth corrected camera method for voluntary kidney donors







Figure 3: Comparison of single plasma sample method with depth corrected camera method for transplant patient

Technique (<i>n</i> =50)	r (P value)				
	Single plasma	Double plasma	Camera depth	CG	
Single plasma	1	0.76 (<0.001)*	0.22 (0.21)	0.41 (<0.002)*	
Double plasma	0.76 (<0.001)*	1	0.27 (0.05)	0.36 (<0.05)*	
Camera depth	0.22 (0.21)	0.27 (0.05)	1	0.11 (0.43)	
CG	0.41 (<0.002)*	0.36 (<0.05)*	0.11 (0.43)	1	

VKD: Voluntary kidney donors, CG: Cockroft Gault, *Statistically significant

Technique	r (P value)				
	Single plasma	Double plasma	Camera depth	CG	
Single plasma (n=38)	1	0.74 (<0.001)*	0.56 (<0.001)*	0.40 (<0.01)*	
Double plasma ($n=36$)	0.74 (<0.001)*	1	0.44 (<0.006)*	0.52 (<0.001)*	
Camera depth $(n=38)$	0.56 (<0.001)*	0.44 (<0.006)*	1	0.31 (0.05)	
CG (<i>n</i> =38)	0.40 (<0.01)*	0.52 (<0.001)*	0.31 (0.05)	1	

CG: Cockroft Gault, *Statistically significant

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Bland Altman plot for SPSM and camera depth method for PTR showed mean difference of 41, 95% CI (33.9-48.1), with a limit of agreement range from -2.16 to 84.2 [Figure 3].

The Bland Altman plot was not utilized for the prediction equation (CG) as there was very poor correlation.

Scatter plot in Figures 4 and 5 shows the clustering of values toward the center in the SPSM and DPSM for GFR evaluation and skewed in other combination.

DISCUSSION

The estimation of GFR is indeed a challenging task in view of the fact that innumerable equations and methods have been derived and yet not one method correlates exactly with the other. However as GFR is a valuable measure in the assessment of renal patients there ought to be a reliable, reproducible method for estimation. The primary objective of this study was to estimate GFR using four different methods and to assess the correlation between one another and to assess the feasibility of these methods in day-to-day clinical practice.

The "gold standard" for the determination of GFR has been considered to be that of continuous infusion of inulin with urine and plasma sampling; however this method is technically difficult and is rarely performed in a clinical setting. Renal DTPA clearance can be determined from: (a) Measurement of activity in single or multiple blood samples^[6-8] (b) from the rate of removal of activity from blood or tissue^[9] (c) from the rate of appearance of tracer in urine^[10] and (d) from the rate of renal tracer uptake.^[11-13]

All clearance techniques are coupled with several potential errors, including errors in pipetting, sample timing and preparation of the standard against which the blood sample indicator concentrations are calibrated. Additional errors are associated with the measurement of administered indicator, failure to completely inject the syringe contents and unintentional partial extravascular injection of indicator and errors in measurement of the patient's height and weight all the more for patients who are severely ill or have special circumstances, such as being bed bound or being amputees. Therefore, when measuring GFR in a routine clinical setting, mechanisms for checking the dependability of the result are needed for illustration of good quality control and quality assurance.^[14] Blaufox *et al.*^[15] recommended SPSM as the first choice for determining GFR. Our analyses too were based on comparison of each method with the SPSM as it was not possible in our setup to acquire inulin, which is undoubtedly the gold standard method for calculating the GFR.

GFR, unlike tubular secretion is not influenced by normal variations in the degree of hydration because of autoregulation mechanisms. Although specific hydration is not usually required, a steady intake of fluids for the duration of study is recommended (approximately 200 ml/h). To estimate the GFR using radioisotopes very low levels of activity is sufficient, which is indeed a boon to avoid the hazardous effects of radiation and maintain the as low as reasonably achievable principle.

The Gates^[2] method was considered feasible as it did not involve the cumbersome method of calculation. Nuclear medicine, for many years has had methods for quantitation of renal function, which are simple, accurate and reproducible, do not require urine collection and can be performed on an outpatient basis. This method's reliability was questioned by many studies. The estimation of GFR using Gates method is very simple when compared to the plasma sampling method, which was very cumbersome. In the latter, the timing of sample collection should be accurate. In a busy department, collecting samples and processing them consumes a significant amount of valuable time and dedicated personnel ought to be available throughout the entire procedure.

Compared with inulin clearance, the clearance of radionuclide agents has many advantages. Cr-51-EDTA and Tc-99m-DTPA



Figure 4: Scatter plot in post-renal transplant recipients



Figure 5: Scatter plot in voluntary kidney donors

are among the most commonly used radionuclide tracers for measuring GFR.^[16] Studies have shown that their renal clearance correlates well with inulin clearance; the Tc-99m-DTPA to inulin ratio was 0.97. Further, plasma clearance of Tc-99m-DTPA correlates well with inulin clearance (standardized estimation error is 3.5 ml/min).^[10,17] The alternative methods used, such as DPSM and SPSM were derived from empirical analysis of the relationship between the reference GFR and the volume of distribution and plasma concentration at sample time.^[1,18] Some studies have also shown that the DPSM in a mono-compartment model was proved to be more accurate in GFR determination than the SPSM.^[1,7,19]

In the present study, we did not use the DPSM following a single injection of Tc-99m-DTPA as the reference method; instead the SPSM was used as mentioned in the literature.^[20-22] In the present study, we found that the SPSM correlated well with the DPSM. Our results are consistent with other published data in the literature. In the large sense, it has been estimated that the GFR for the Indian population is much lower than the western population. Barai *et al.*, have suggested that the mean GFR value of a young healthy Indian adult potential kidney donor is 81.4 ± 19.4 ml/min/1.73 m² BSA, which is significantly different from the normal value of 109-125 ml/min derived from a western population.^[23] The demonstration of a lower GFR value in healthy Indian potential kidney donors can have significant

Similarly in our study, it was found that the mean GFR in VKD the mean \pm (SD) GFR using SPSM, DPSM, camera depth method and CG method were 134.6 (25.9), 137.5 (42.4), 98.6 (15.9), 83.5 (21.1) respectively. The CG and Gates method was more or less equivocal in terms of GFR in the Indian context going by the normal range as estimated in the literature; however, the SPSM and DPSM depicted a higher value in VKD.

In PTR, it was noted that the mean \pm (SD) GFR using SPSM, DPSM, camera depth method and CG method were 98.7 (22.7), 97.4 (28.1), 57.1 (23.5), 65.2 (15.4) respectively. This indicates a fairly higher value in SPSM and DPSM. CG method gave a value nearing the normal GFR for Indian population, but Gates method estimated very low values.

In a study by Mulligan *et al.*,^[24] the DPSM using Russell's formula has been vouched as a reliable method for the valid estimate of true GFR. When we look at this statement in the light of our study we have appreciated a fairly good correlation between SPSM, DPSM but not between CG and Gates method.

In a study by Itoh *et al.*^[21] on 50 patients with various degrees of renal dysfunction, it was found that the SPSM tended to show some scattering in GFR below 30 and above 140 ml/min/1.73 m². On the contrary, the DPSM tended to be scattered in GFR above 120 ml/min/1.73 m². They stated that: The DPSM is essentially a method of choice for a patient in whom the GFR is expected to be below 30 ml/min/1.73 m² and these two methods may be

chosen selectively in dependence on the preserved renal function, which is expected at the time of the test. In the same study, Russell's SPSM was compared with 10 sample method and the correlation coefficient was 0.971 and that of Gates and 10 sample method was 0.774. Zuo *et al.*^[25] reported that the DPSM should be used in order to obtain reliable reference GFR values, when GFR is less than 45 ml/min/1.73 m².

As the 10 sample study was cumbersome, we did not venture into this method; however, in our study, there was a fairly good and significant correlation between SPSM, DPSM for both VKD and PTR.

Aydin *et al.*^[12] also showed that in their study of 115 subjects who were VKD the SPSM correlated well with DPSM. There are controversial results for the Gates method in the literature.^[16,26] Several sources of errors in the measurement of GFR by scintigraphy include: Background correction, decay statistics, attenuation correction, estimation of arterial plasma activity, system dead time, volume measurements and radiopharmaceutical quality.^[3,27]

The Gates method overestimated GFR in the study by Aydin et al.^[12] However in the present study, the Gates method tended to underestimate GFR compared to the SPSM, DPSM. Itoh^[13] also reported overestimated GFR values with the Gates method and indicated that the overestimation might be attributable to insufficient correction for background activity in the kidney. Russell et al. suggested that the Gates method with a simple background activity correction is less accurate than the methods with more sophisticated background activity correction for the calculation of GFR.^[6,28] We used infra-renal background ROIs for background correction in the present study. The linear attenuation coefficient for Tc-99 m in water is 0.153/cm and our software program uses this value to correct for soft-tissue attenuation as is the case in other studies.^[13,29,30] However, the effective attenuation coefficient is lower in soft-tissue than in water because of the presence of scattering photons.^[31] This is another major drawback of the Gates method in the calculation of GFR. Our findings show that GFR with the Gates method is poorly correlated with SPSM and DPSM for VKD. There was moderate, but significant correlation between SPSM and camera depth method for PTR.

There are numerous equations described to estimate Ccr and a valid prediction of GFR by incorporating biometrical variables such as age, height, weight, gender and race with Scr concentration and other biochemical parameters.^[32] modification of diet in renal disease (MDRD) and CG formulae have been the most frequently used among them. However, it has been debated whether the equations accurately predict the GFR.^[13,32-34] In our study, the CG method showed poor correlation with SPSM, DPSM and camera method (r = 0.419, r = 0.360, 0.114 respectively) for VKD. In PTR, the correlation between CG method and SPSM, DPSM and Camera depth method was 0.409, 0.525 and 0.319 respectively. Other methods such as chronic kidney disease-epidemiology collaboration (CKD-EPI) have been studied. White *et al.*^[35] showed that MDRD could be replaced by CKD-EPI equation however, in a review article by Earley *et al.*^[36] it was concluded that "Neither the CKD-EPI nor the MDRD Study equation is optimal for all populations nor GFR ranges. Using a single equation for reporting requires a tradeoff to optimize performance at either higher or lower GFR ranges."

Lin *et al.*^[34] reported that neither the MDRD nor CG formulas may be sufficient for estimating GFR and radioisotope studies may be needed for better assessment. In their study, 117 potential kidney donors were included. Three blood samples post-administration of Tc-99m-DTPA was regarded as the reference method. The bias and correlation coefficient values were found to be 6 ml/min/1.73 m², -36.5 ml/min/1.73 m²; and 0.41 and 0.43 for CG and MDRD formulae, respectively.

In another study, Itoh^[13] studied 133 patients with a wide range of renal function and found that CG correlates well with Tc-99m-DTPA blood sampling method (r = 0.82). However, in this study, it was reported that the CG formula is not accurate for the measurement of GFR.

In the prediction equations, small changes in Scr result in large changes in MDRD or CG formulae. Other possible causes of measurement error in prediction equations could be the intra-individual variability in Scr and in other clinical or laboratory measurements.^[34]

A clinician's final decision regarding a potential kidney donor requires an accurate GFR measurement. Our study has investigated four methods and compared the results with the Tc-99m-DTPA SPSM, which was considered as the reference. Our results demonstrate that the SPSM correlate moderately well with the DPSM. Neither the Gates method nor the prediction equation (CG) could calculate GFR accurately.

All these techniques tend to underestimate GFR and may result in mistakes in the management of potential kidney donors or PTR.

Limitations of the study

The number of patients in our study was small. Gold standard "inulin" was not available and hence not compared. Normal GFR in the Indian population has not been standardized. GFR in renal transplant recipients using several methods has not been compared extensively.

CONCLUSION

The conclusions from this observational prospective study were as follows: Calculation of GFR plays a vital role in the management of renal patients, hence it was noted that Gates GFR may not be a reliable method of calculation. The SPSM was more reliable. DPSM is reliable but cumbersome. It is difficult to accurately calculate GFR without a gold standard. No single method can be taken as a valid one to assess GFR, these methods have to be compared and validated with a gold standard. If there are no such options the SPSM GFR can be used to assess GFR. Gates GFR cannot be used for estimation of GFR, however in view of its simplicity in performance it can still be approved if a depth corrected GFR is standardized for our Indian population based on studies with large numbers from multiple centers.

ACKNOWLEDGEMENT

Dr. Deepthi Kattula, Department of Gastrointestinal Sciences, Christian Medical College, Vellore, for the statistical analysis and Mr. Danie Kingslin Heck and Mr. Prabhu Titus, Technologists, Department of Nuclear Medicine, Christian Medical College Vellore for their support.

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How to cite this article: Hephzibah J, Shanthly N, Oommen R. Comparison of glomerular filtration rate measured by plasma sample technique, Cockroft Gault method and Gates' method in voluntary kidney donors and renal transplant recipients. Indian J Nucl Med 2013;28:144-51. Source of Support: Nil. Conflict of Interest: None declared.

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