ORIGINAL ARTICLE

ESTIMATION OF GLOMERULAR FILTRATION RATE BY USING TC-99M DTPA PLASMA 1 SAMPLE METHOD, GATES METHOD, COCKCROFT-GAULT METHOD AND PREDICTED CREATININE CLEARANCE METHOD: A PROSPECTIVE COMPARATIVE ANALYSIS WITH PLASMA 2 - SAMPLE CLEARANCE METHOD.

Nosheen Fatima, Maseeh-Uz-Zaman, Khalid Niaz, Salman Habib, Sharjeel Usmani, Shahid Kamal, Abid Hameed

Study Objective: To compare diagnostic accuracy of predicted clearance method, Gates method, Cockcroft-Gault method and plasma 1- sample clearance method with plasma 2-samples clearance method with Tc-99m DTPA for the estimation of glomerular filtration rate(GFR).

Study Design: Comparative study.

Materials and Methods: This study included 91 consecutive patients who were referred for evaluation of renal function to the Nuclear Medicine section of Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN) from September 2004 to September 2005. The GFR was determined simultaneously by 5 methods including Plasma two-Sample Clearance method after Tc-99m DTPA injection (PSC 2); Plasma one-Sample Clearance method after Tc-99 m DTPA injection (PSC 1); Gamma camera uptake method after Tc-99m DTPA injection (Gates method); Predicted Creatinine Clearance by Modification of Diet and Renal Diseases (MDRD); and Cockcroft-Gault's equation for GFR estimation (CG). PSC 2 was chosen as a reference.

Results: Out of the 91 patients, 71 were males and 20 females with age ranging from 16-68 years. The regression equation of the PSC 1, Gates, MDRD and CG method against the PSC 2 was Y = 1.884 +0.970X (r=0.90, p<0.001, SEE value=10.23 ml/min/1.73m2), Y = - 9.944 + 1.083X (r=0.82, p<0.001, SEE value=11.02 ml/min/1.73m2), Y =25.606+ 0.640X (r=0.71, p=0.002, SEE value=15.56 ml/min/1.73m2), and Y =14.981+ 0.714X (r=0.77, p=0.002, SEE value=14.44 ml/min/1.73m2) respectively. In comparison with the GFR by PSC 2, the PSC 1 and Gates tended to overestimate by 1% (p=0.359) and 2% (p=0.265) respectively, MDRD and CG tended to underestimate GFR by 11% and 14% respectively (p<0.001).

Conclusions: PSC 1 correlate well with PSC 2 and either can be substituted for the other as ideal GFR markers. The Gates method shows good correlation with PSC 2 however it is less precise than PSC 1. MDRD and CG methods due to significant underestimation are not considered as ideal GFR marker.

Keywords: Glomerular filtration rate, Plasma Sample Clearance, Gates method, Cockcroft-Gault's equation, Radionuclide scan.

INTRODUCTION

The glomerular filtration rate (GFR) is considered to be a representative parameter for evaluating the functional state of the kidney.[1] Inulin clearance is the gold standard for GFR estimation. However, this method is not performed in clinical practice, because of technical complexity and limited availability. [2]

Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN), Karachi, Pakistan.
Correspondence: Dr. Nosheen Fatima, Department of Nuclear Medicine Karachi Institute of Radiotherapy and Nuclear Medicine Pakistan.
E-mail: dr_nosheenfatima@yahoo.com
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Measurements of GFR are based on the renal clearance of a marker in plasma, expressed as the volume of plasma completely cleared of the marker per unit time.[3]

Plasma sample method following a single-injection after Tc-99m DTPA (Diethylene Triamine Penta-acetic acid) injection has been proved effective as an alternative to the continuous infusion method with inulin for the determination of GFR in clinical practice.[4] In view of the accuracy and technical simplicity, the single-sample method (sample at 180 minutes) is the first choice in routine

practice.[3-5] The two-sample method (sample at 60 and 180 minutes) is essential for patients in whom the GFR is expected to be below 30 ml/min/1.73 m.[2-4]

In Tc-99m DTPA renography, the GFR is calculated without blood or urine sampling. The method introduced by Gates has been most common in the routine setting, although the diagnostic accuracy of the gamma camera methods is debatable.[3]

Serum creatinine is a useful marker of stable renal function, but it is unreliable when GFR is rapidly changing. Numerous formulae have been developed to estimate GFR or creatinine clearance from serum creatinine and other variables including the "Modification of Diet in Renal Disease" (MDRD) Study and Cockcroft-Gault (CG) equations in adults.[3] The intrinsic creatinine clearance (CrCl) has been widely performed as only alternative to inulin clearance in routine practice.[3,6] This method, however, is not accurate compared to inulin clearance.[3,6] Therefore, simple and accurate determination of the GFR is still a clinical challenge.[6]

The aim of this study was to estimate GFR using predicted clearance method, Gates method, Cockcroft-Gault method and plasma 1 sample clearance method and compare these with plasma 2 samples clearance method considering it as the gold standard to find a reliable and precise test in routine clinical practice.

PATIENTS AND METHODS

The study included 91 consecutive patients who were referred for evaluation of renal function to the Nuclear Medicine section of Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN) from September 2004 to September 2005. Informed consent was taken from all the subjects. The demographics, body surface area in m^2 and reasons for referral were noted. Those with hypertension/ diabetes, taking potentially nephrotoxic agents and with previous history of renal disease were excluded.

The radiopharmaceutical used for the study was 99mTc-DTPA. The kit for preparing 99mTc-DTPA was provided by Isotope Production Division, PINSTECH Islamabad, Pakistan, under the name of "PINSCAN-DTPA". The labeling and quality control tests were carried out according to instructions of manufacture. The radiochemical purity was ensured to be more than 90 % before injection. The GFR of each subject was measured simultaneously by PSC2, PSC1, Gates method, MDRD and CG method.

Plasma Sample Clearance Methods

Tc-99m DTPA was prepared by following the package insert directions, aseptically two or more 5-mCi aliquots with a 3-cc syringe having 22-gauge needle were drawn. One of the aliquots was set, aside as the standard and the remainding were used for patients doses. The standard and the doses were calibrated carefully in a way that the percent difference between standard and dose did not exceed 5% under any circumstance.

The patient was injected under the gamma camera the renogram was also acquired and the time of injection was recorded. The empty syringe was also recorded in the same way as full syringe both with camera and with counter, being less than 3% of the dose. In two- samples method, the samples were drawn first at 60 minutes and then at 180 minutes from the contalateral arm in a collection bottle containing EDTA (Ethylene Diamine Tri Acetic acid), mixed well and centrifuged for 10 minutes. The sample was removed as soon as the centrifuge stopped. The 0.1 ml of filtrate was pipetted out by using micropipette into labeled test tube. The standard and sample test tubes were counted in a gamma scintillation counter set for 140 KeV 99mTc photopeak with a 20% window, background, correction was done and sample was counted for one minute to ensure good counting statistics. PSC 2 and PSC 1 methods were automatically calculated by Biodex Medical System Atomlab 950 version 3.08 by Russell method.[7,8]

Gamma Camera Uptake Method (Gates Method)

The patient was hydrated with 300 ml of water 20 minutes prior to the examination. The patient was laid down in supine position. 5 mCi of Tc-99m-DTPA was given through an indwelling butterfly needle in an antecubital vein under the gamma camera and was followed by infusion of 20 ml of normal saline. Frames of 64× 64 matrix were recorded with an online-computer, initially at one second for one minute and then at 10 seconds for 20 minutes. The post-injection syringe was again counted by the two devices in the same way as pre-injection. The GFR was automatically calculated by Gates method in ml/min/ 1.73 m^2.

Predicted Creatinine Clearance by MDRD method

In this method simply blood sample of the patients was

required for serum creatinine (Scr), serum albumin (Alb) and blood urea nitrogen (BUN) the GFR was calculated in ml/min/1.73m^2,by putting the age and gender in the following formula

$$GFR\ (ml/min/1.73m^2) = 170 \times (Scr)^{-0.999} \times (Age)^{-0.175} \times (BUN)^{-0.130} \times (Alb)^{0.318} \times (0.762 \text{ if female}) \times (1.180 \text{ if black})$$

where Scr= serum creatinine, BUN= blood Urea Nitrogen and Alb= serum albumin.

Cockcroft-Gault Method

By putting the serum creatinine, age, height and gender factors in the following formula the GFR in ml/min was calculated:

$$GFR\ (ml/min) = \frac{(140 - Age) \times Weight \times (0.85 \text{ if female})}{72 \times Scr}$$

The GFR (ml/min) values as obtained by the 5 methods were normalized for a body surface area (BSA) of 1.73 m^2 in order to interpret the result and compare it with the reference range. Values of BSA were estimated from patient's height and weight using the following Haycock formula:

$$BSA\ (m^2) = 0.024265 \times Wt^{0.5378} \times Ht^{0.3964}$$

where Wt = patient's body weight in kilograms (Kg) and Ht = patient's height in centimeters (cm).

For method of comparison, standard linear least-squares regression analysis was used. p-value of 0.001 or less were considered significant. Bland and Altman's analysis was referred agreement between the two methods.

RESULTS

Out of the 91 patients, 71 were males and 20 females with age ranging from16 - 68 years (mean age, 46.05 years ± 13.71; median age 48 years) and average body surface area was 1.62 ± 0.14 m^2 (ranging from 1.17 to 1.92 m^2). There was a range of renal function including 55 cancer patients with normal renal status as a baseline GFR for chemotherapy, 10 patients were hypothyroids, 10 hypertensive, 11 diabetics and had chronic renal failure 5

The regression equation and correlation coefficient of PSC 1 and Gates methods against PSC 2 was Y = 1.884 +0.970X (r= 0.90, p<0.001, SEE value=10.23 ml/min/1.73m^2) and Y = -9.944+ 1.108X (r= 0.82, p<0.001, SEE value=11.02 ml/min/1.73m^2) respectively as illustrated in Figures 1 and 2. The correlation coefficient of MDRD and CG's method against PSC 2 was least significant and regression equation was Y = 26.752+ 0.631X (r= 0.72, p= 0.002, SEE value= 15.56ml/min/1.73m2), and Y =18.694+ 0.678X (r= 0.77, p= 0.002, SEE value=14.44 ml/min/1.73m2) respectively as demonstrated in Figures 3 and 4.

The average difference of GFR between PSC 2 method and other methods was calculated as shown in Table I. It was found that PSC 1 method overestimated by 1% (-1.06ml/min/1.73m2, p= 0.359), Gates method overestimated by 2% (-1.71 ml/min/1.73m2, p= 0.265), Predicted Creatinine Clearance by MDRD method underestimated by 11% (9.19 ml/min/1.73m2, p<0.001) and CG's method underestimated by 13% (12.39 ml/min/1.73m2, p<0.001) of PSC 2 method. The values of difference indicated the bias or deviations of individual method from PSC 2. The PSC 1 and Gates tended to overestimate the GFR as shown in figures 5 and 6. The mean difference PSC 2 - PSC 1 method was small as compared to the PSC 2 - Gates methods. The difference of PSC 2-MDRD and PSC2-CG methods showed that both significantly underestimated the GFR.

Table 1: Results on agreement of differences in GFR between the PSC 1, Gates, MDRD or CG's method against the PSC 2 method.

Methods of GFR Estimation	Mean difference in GFR ± Standard Deviation (SD) (ml/min/1.73m2)	Standard Error Mean (ml/min/1.73m2)	95% Confidence Interval of Difference (CID)	
			lower	upper
GFRPSC 2 – GFRPSC 1	– 1.06 ± 10.97	1.15	-3.34	1.23
GFRPSC 2 – GFRGates	– 1.71 ± 14.57	1.15	-4.75	1.32
GFRPSC 2 – GFRMDRD	9.18 ± 18.08*	1.89	5.42	12.95
GFRPSC 2 – GFRCG	12.39 ± 16.52*	1.73	8.96	15.84

***Significantly higher (p-value<0.001)**

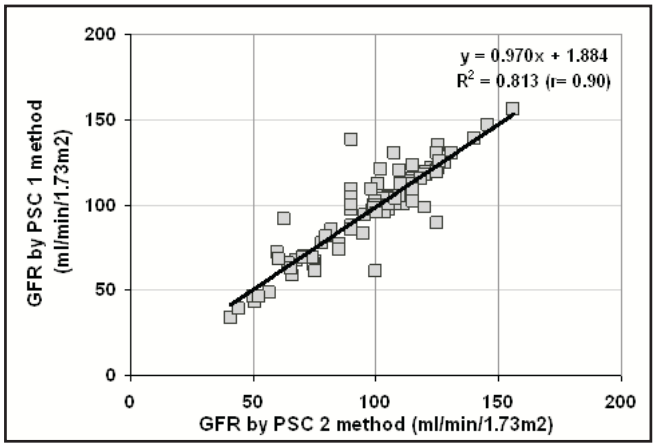

Figure I: Scatter plot of Plasma one sample clearance (PSC 1) against Plasma two sample clearance (PSC 2) method and the solid line indicates the regression line.

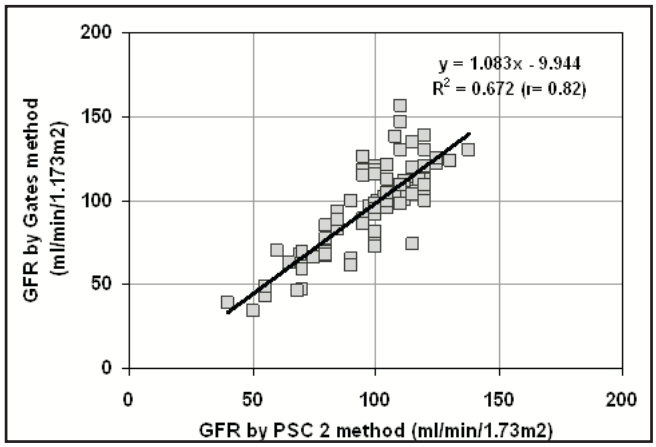

Figure II: Scatter plot of Gates against Plasma two-sample clearance (PSC 2) method and the solid line indicates the regression line.

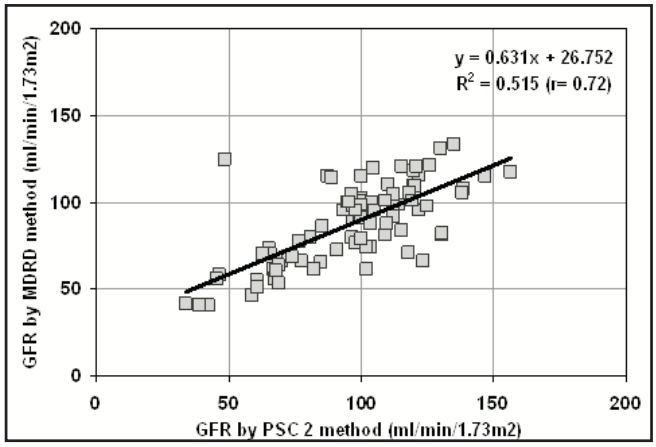

Figure III: Scatter plot of Predicted creatinine clearance by MDRD against Plasma two sample clearance (PSC 2) method and the solid line indicates the regression line.

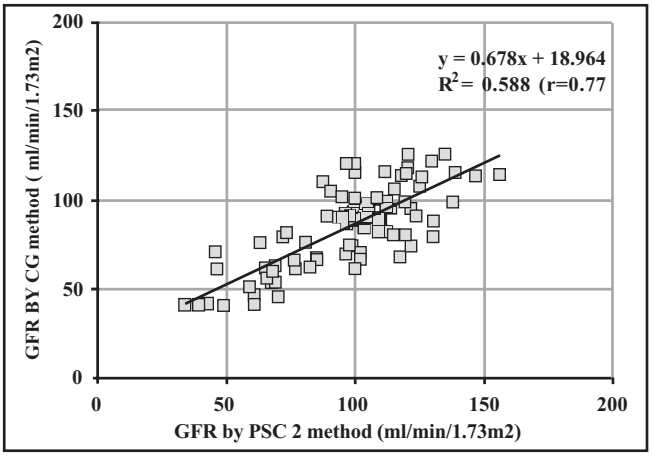

Figure IV: Scatter plot of Cockcroft-Gault's method (CG) against Plasma two - sample clearance (PSC 2) method and the solid line indicates the regression line.

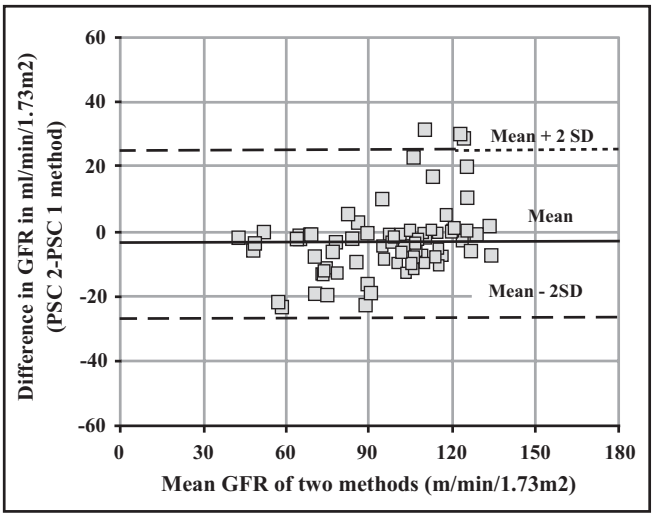

Figure V: Scatter plot of difference in GFR by plasma one - sample clearance (PSC 1) against the mean GFR of two methods. The solid line indicates the mean difference (GFRPSC2 – GFRPSC1) and dotted line the 95% of agreement (2SD).

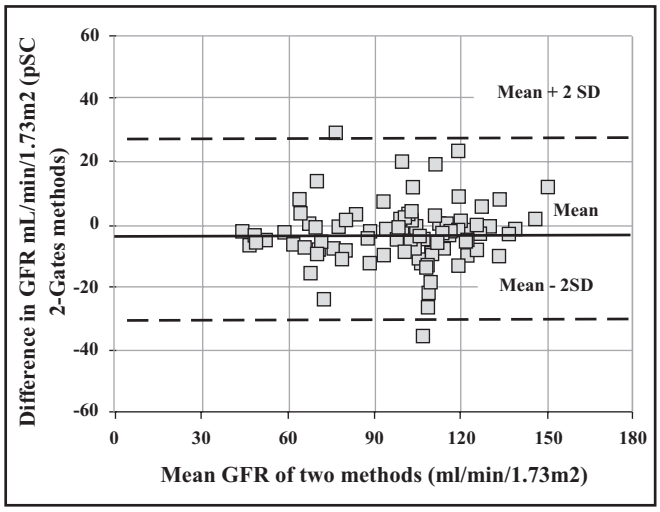

Figure VI: Scatter plot of difference in GFR by Gates against the mean GFR of two methods. The solid line indicates the mean difference (GFRPSC2 – GFRGates) and dotted line the 95% of agreement (2SD).

DISCUSSION

Various methods are available for determination of GFR. Inulin clearance, the gold standard for estimation of GFR is usually cumbersome and inconvenient for routine use.[9] Measurement of the plasma clearance of Chromium-51 Eethylene Diamine Tetra-Acetic acid (^{51}Cr-EDTA) and ^{99m}Tc-DTPA after a single intra venous injection is widely used for estimation of overall GFR due to its simplicity and accuracy.[10,11] The plasma clearance of 99mTc-DTPA generally correlates well with the plasma clearance of 51Cr-EDTA.[10] Multiple plasma sample technique

using ^{99m} Tc labeled DTPA correlates well with inulin clearance and is considered reliable.[3] Barbour et al. reported that the plasma clearance of ^{99m}Tc-DTPA overestimate GFR by 3.5 ml/min in average as compared to the renal clearance of inulin as a golden GFR marker.[12] A simplified method such as Russell two-sample method is sufficiently accurate as suggested by Biggi et al. for routine clinical use particularly in patients with variable renal function and in patients who require multiple GFR estimations.[7,8] The formulae of Russell can be adopted for both 99mTc-DTPA and 51Cr-EDTA. On the basis of these studies, PSC 2 was considered as the gold standard as compared to other methods of GFR estimation. PSC 2 measure average GFR of 97.31 ± 25.29 ml/min/1.73m^2 with the range of 33.78-156.42 ml/min/1.73m^2. The reason for using ^{99m}Tc-DTPA instead of ^{51}Cr-EDTA in the study were its low cost, easy availability, low radiation hazard, and shorter half-life.

Comparison of this study with those in the published literature, the first observation was that the PSC 1 method and Gates techniques of GFR estimation seem to be highly correlated with PSC 2 method and the difference of correlation coefficients between PSC 1 method and Gates method is not significant (p= 0.109), while other methods showed less significant correlation coefficients (r). The correlation coefficient of PSC 1 method was 0.90 (p<0.001) and measured average GFR of 98.37 ± 23.51 ml/min/1.73m^2 with the range of 43.78-145.66 ml/min/1.73m^2. On the basis of best correlation and least non-significant negative bias (mean difference between PSC 2 and PSC 1 i.e. Bias= PSC 2-PSC 1 of -1.06 ml/min/1.73m^2 of PSC 1) method they can be substituted for each other. The reason of 1% over estimation of PSC 1 method in comparison with PSC 2 method is the effect of protein binding of DTPA. Biggi et al. observed that the protein binding increases with time from a mean of 3% at 60 minute after DTPA to a mean of 6% at 180 minutes after injection.[8] According to Russell et al., simplified methods have been proposed that require only one or two plasma samples in lieu of a more complete clearance curve but the error was introduced by this simplification.[7] The error resulting from replacement of complete clearance curve by a single 3-hour sample was about 8 ml/minute and by using two samples (at 1 and 3 hours), it could be reduced to 4 ml/minute.

The Gates correlated well with the plasma sample method.[3] In this study, the Gates measured average GFR of 99.02 ± 19.15 ml/min/1.73m^2 (range =40-125 ml/min/1.73m^2). On comparison with PSC 2 correlation coefficient of Gates was 0.82 (p<0.001) and tended to overestimate by 2% (-1.71 ml/min/1.73m^2). The bias for overestimation by the Gates may be attributed to insufficient correction of background count in the kidney.[13] Mitral et al.14 reported that the Gates technique, which calculates GFR by the renal uptake of ^{99m}Tc-DTPA, has been recommended but with rising levels of serum creatinine (> 4 mg/dl), it loses its value as the GFR estimation may not be accurate. In the present study the reason for very good correlation was probably due to the fact that serum creatinine level of about all patients did not exceed beyond 4 mg/dl with the exception of five patients of chronic renal failure in whom serum creatinine was more than 4 mg/dl at which the accuracy of Gates method become debatable according to Mitral et al.[14]

MDRD and CG's methods measure average GFR of 88.13 ± 22.23 ml/min/1.73m^2 (range=41-133.13 ml/min/1.73m^2) and 84.19 ± 22.36 ml/min/1.73m^2 (range=40.2-125.9ml/min/1.73m^2) respectively. The CG's method underestimated by 14% and Predicted Creatinine Clearance by MDRD method underestimated by 11% of PSC 2 method. Lin and colleagues described the sources of errors in CG's equation when compared with MDRD equations due to the inaccuracies of the formulas Multiple sources for measurement of error (including intra-assay serum creatinine = Scr variability, intra-individual Scr variability, lack of calibration of Scr assays across different laboratories, intra-assay GFR variability, intra-individual GFR variability, and measurement error of other variables in the prediction equations) can affect the precision and accuracy of renal clearance prediction equations.[15]

There are few limitations and possible biases in this study. Personal error could be due to incorrect dose calculation and injection of DTPA. The bias may affect the results if the sample is not drawn at the correct time and from the correct arm.

CONCLUSION

On the basis of the best correlation of PSC 1 method with PSC 2 method, both methods can substitute for each other in the assessment of GFR. Gates correlates well with PSC 2 method but less precisely with PSC 1 method. Due to significant underestimation, MDRD and CG's methods are not considered suitable for the accurate determination of GFR.

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