Original Article

Comparison between Two-sample Method with ^{99m}Tc-diethylenetriaminepentaacetic acid, Gates' Method and Estimated Glomerular Filtration Rate Values by Formula Based Methods in Healthy Kidney Donor Population

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Abstract

Purpose of the Study: Glomerular filtration rate (GFR) is the most important parameter for the assessment of renal function. GFR by plasma sampling technique is considered accurate in the selection of donors for renal transplantation. Estimated GFR (eGFR) calculations using Gates' method and Modification of Diet in Renal Disease (MDRD) and Cockcroft–Gault (CG) equations are simple methods but have not been validated in the Indian population. Hence, we aimed to assess the correlation between these three techniques. **Materials and Methods:** The plasma sampling technique was done using two samples at 60 and 180 min after injection of 1 mCi (37MBq) ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) in 66 healthy donors. Age, sex, height, weight, and plasma creatinine were recorded. Normalized GFR (nGFR) by two-sample method and eGFR (for Gates', MDRD, and CG) values were calculated using formulae. **Results:** There were 14 male and 52 female donors. Mean age was 46.56 ± 12.88 years (24–69 years). Mean height was 153.74 ± 8.35 cm, whereas mean weight was 56.97 ± 11.88 kg. Mean nGFR value was 80.4 for two-sample method while mean eGFR value for Gates', CG, and MDRD were 83.3, 89.36, and 97.47 ml/min/1.73 m^2 (eligibility value at our institution = 70), respectively. While the correlation between nGFR and eGFR CG and MDRD was weak moderate (correlation coefficient = 0.5), nGFR and eGFR Gates' had a moderate correlation (0.686). Mean total bias for eGFR Gates', CG, and MDRD were 2.87, 8.93, and 17.0, respectively. P_{30} of eGFR Gates', CG and MDRD were 60.6%, 57.6%, and 62.1%, respectively. **Conclusions:** Due to the large variability in eGFR Gates', CG and MDRD, nGFR estimation using the plasma sampling technique with ^{99m}Tc-DTPA appears necessary while screening healthy donors for renal transplantation.

Keywords: *Cockcroft–Gault, Gates' method, glomerular filtration rate, Modification of Diet in Renal Disease, two-sample method*

Introduction

Glomerular filtration rate (GFR) is the rate at which fluid is filtered by the kidneys. It is a measure commonly used to assess renal function, especially in donors for renal transplant. According to a recent review, the prevalence of end-stage renal disease that requires transplant in India is approximately 151–232 per million population. This implies around 220,000 people require a kidney transplant. However, the actual number of transplants taking place stands at just around 7500, majority of which come from live donors (~90%).[1]

For high survival rate, donor kidney should be properly assessed for renal function and morphology. Among various other assessment parameters, GFR is routinely advised for potential renal donors and is considered the best index of overall kidney function.[2,3] For patients with normal creatinine clearance rate, a global GFR >70 ml/min is considered normal.[4]

GFR can be estimated using different methods and different radiopharmaceuticals. Earlier inulin clearance used to be considered the gold standard for GFR studies, but it is relatively invasive and not easy to perform in routine clinical practice.[5] Currently, estimation of Tc-99m diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) plasma clearance is used for the determination of global GFR due to its simplicity and precision.[6-9] It is also

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reported that there is a correlation between ^{99m}Tc-DTPA and inulin clearances when measuring GFR in clinical applications.[10]

As mentioned previously, various techniques have been employed to estimate GFR. One of the oldest techniques is multi-sample technique in which blood samples are taken at 5, 10, 15, 30, 45, 60, 120, 180, and 240 min. A time-activity curve is plotted and GFR is calculated from dose divided by the area under the curve. Since it is exhaustive and difficult to perform in routine clinical practice, single plasma sample method (SPSM) and double plasma sample method of GFR estimation were derived from the multi-sample technique. Multi, double, and single sample techniques were observed to have a significant correlation.[11,12] A few other computer-based methods have also been developed among which gamma camera (GC) method is highly popular as it can provide an immediate calculation of individual kidney function as well as of global renal function. Gary Gates first computed GFR from the scintigraphic determination of ^{99m}Tc-DTPA uptake within the kidneys, and since then this method has become universal and versatile, but accuracy is debated.[13,14]

GFR can also be calculated through prediction equations using parameters such as age, sex, and serum creatinine level. The most widely accepted prediction equations are the Modification of Diet for Renal Disease (MDRD) and the Cockcroft–Gault (CG).

The formulae based methods are much simpler but have not been validated in Indian population. Since, there is a vast difference in demography and epidemiology of India and western countries, extrapolating the data generated in Western countries for Indian population is likely to yield erroneous results. In view of this, this study was planned on the Indian population. The aim of this prospective study was to compare and establish the variability/reliability in GFR calculation by Gates', MDRD, and CG formulae-based methods in comparison with the two-plasma sample (TPS) technique.

Materials and Methods

^{99m}Tc-DTPA was prepared in-house from DTPA kit procured from BRIT, Mumbai, India. Sixty-six patients undergoing evaluation as voluntary kidney donors were included in the study as per the following inclusion criteria:

- Age – 18 years and above
- Healthy voluntary kidney donors advised nuclear medicine diagnostic test for preoperative screening
- Serum creatinine level ≤1.3 mg%
- Willing to give informed written consent to be included in the study.

Any patient not meeting the above criteria and pregnant women were excluded from the study. Voluntary kidney donors referred to our department for routine renal screening underwent a detailed workup and clinical history and the previous pathological (serum creatinine and urea) and radiological tests were obtained. Informed written consent was obtained from all the donors after giving specific information of the study was conducted and on the radiation exposure received during the procedure. GFR was estimated for these donors using the following techniques.

1. Two-plasma sample method (TPSM): 1 mCi ^{99m}Tc-DTPA was injected intravenously (IV) and venous blood samples were collected from the contralateral arm at 60 and 180 min. Plasma was separated from whole blood samples. About 1 ml of plasma from each sample and an equal volume of standards were counted in an automatic gamma counter. Height and weight of the donors were recorded. Russell's formula was used for GFR estimation
2. Gates' method: ^{99m}Tc-DTPA was administered IV under GC and transit of tracer through the kidneys was recorded for 6 min. Administered dose of ^{99m}Tc-DTPA was calculated from pre- and post-injection counting of the syringe under the camera. The renal region of interest (ROI) and semilunar background ROI were drawn at the inferior pole of the kidney avoiding the liver, spleen, and iliac vessels in all frames of the dynamic study to obtain time-activity curves. GFR was calculated, starting from renal uptake during 2–3 min period after injection, corrected for background activity, linear attenuation, and depth (the distance estimated on the basis of body height and weight). The background curve was multiplied by each side to intersect the renal curve 120 s after the rise in kidney activity. The area subtended by the relative kidney function curve between 120 and 180 s, corrected for the background curve, was taken for the total renal counts. To calculate quantitative GFR values, the total counts were then normalized with regards to the injected activity dose and time interval. Resulting values were defined as clearance equivalent and converted to individual and total quantitative renal clearance values expressed in ml/min. The quantitative GFR was obtained by multiplying the regression coefficient (9.75621) with the total renal uptake percent subtracting the intercept value (6.1983) used in the Gates method
3. Formulae-based GFR estimation: GFR was estimated from the serum creatinine levels measured within 7 days before or after renography using CG and simplified MDRD formulae. Serum creatinine levels were measured at different laboratories. Serum Creatinine test was invariably advised by the consulting nephrologist, and hence the patients got the test done from their convenient pathology laboratories.

Cockcroft–Gault's method

For male: GFR (ml/min) = ([140−age] × weight)/(SCr × 72)

For female: GFR (ml/min) = 0.85 × ([140−age] × weight)/(SCr × 72)

Modification of Diet in Renal Disease method

For male: GFR = 186 × $(SCr)^{-1.154}$ × $(age)^{-0.203}$

For female: GFR = 186 × $(SCr)^{-1.154}$ × $(age)^{-0.203}$ × 0.742

Where, weight: Body weight (kg); SCr: Serum creatinine level (mg/dl); Age: Years

The GFR values estimated by Gates' and formulae-based were compared to that of two-sample methods taking the latter as the gold standard.

Statistical analysis

All statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Stata 10 (StataCorp LP, College Station, USA) was used for plotting Bland–Altman; 95% limits of agreement were defined. All the data were expressed as the mean ± standard deviation of the mean. Correlation analysis was performed between TPSM, MDRD, CG, and Gates' method using Pearsons correlation test. Bland–Altman plot was done for those methods, which had a significant correlation.

Results

Of the 66 donors included in the study, 14 were male and 52 were female. Mean age of donors was 46.56 ± 12.88 years (24–69 years). Mean height was 153.74 ± 8.35 cm (138–175 cm). Mean weight was 56.97 ± 11.88 kg (32–96 kg). Mean serum creatinine was 0.76 ± 0.17 mg/dl (0.5–1.4 mg/dl). Mean normalized GFR (nGFR) value, calculated by TPSM, was 80.4 ± 21.67 ml/min/1.73 m^2. The nGFR value acceptable at our institute in donors is 70 ml/min/1.73 m^2.

The mean value of estimated GFR (eGFR) as calculated by Gates' method was 83.3 ± 24.9 ml/min/1.73 m^2. Mean eGFR calculated by CG formula was 89.36 ± 29.55 ml/min/1.73 m^2 and that calculated by MDRD formula was 97.47 ± 22.85 ml/min/1.73 m^2.

The coefficient of correlation between nGFR and eGFR Gates' was 0.686, that between nGFR and eGFR CG was 0.49 and between nGFR and eGFR MDRD was 0.54. Mean total bias for eGFR Gates', CG, and MDRD were 2.87, 8.93, and 17.0, respectively. eGFR Gates' values of 60.6% of patients were within 30% of nGFR values (P_{30}). P_{30} for CG and MDRD was 57.6% and 62.1%, respectively. Table 1 summarizes the results.

Bland–Altman plot for TPSM and Gates showed a mean difference of −3.17 (95% confidence interval [CI] = −7.8–1.46). The limit of agreement ranged from −54.3 to 49.7 [Figure 1]. Bland–Altman plot for TPSM and CG method showed the mean difference of −8.93, 95% CI (−15.47, −2.39). The limit of agreement ranges from −67.8 to 49.6 [Figure 2]. Bland–Altman plot for TPSM and MDRD showed mean difference was −17.04, 95% CI (−22.3, −11.77). The limit of agreement ranged from −69.3 to 28.8 [Figure 3].

Discussion

GFR is the most important parameter for the assessment of renal function. In the case of potential kidney donor for a transplant, the renal function assessment becomes even more important due to its direct influence on the success of the transplant. Therefore, so it is imperative that a reliable method to calculate GFR is obtained. As mentioned earlier, among the various methods of GFR estimation, plasma technique is the most reliable. Statistically, the more the number of samples the better the estimate. However, multi-sample technique, used earlier is time-consuming and tedious. Hence, over time variations of multi-sample technique have been explored. Two-sample technique (TPSM), a derivation of the multi-sample technique, shows significant correlation and is currently the method of choice for GFR estimation.[11,12]

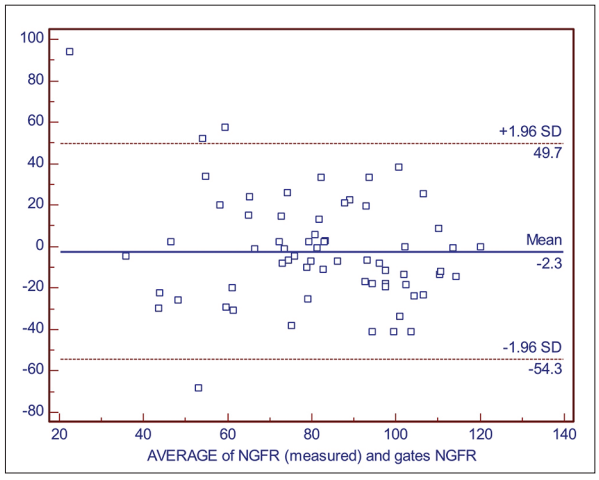

Figure 1: Comparison of normalized glomerular filtration rate two-plasma sample method with estimated glomerular filtration rate Gates method for voluntary kidney donors

Table 1: Comparison of Gates', Cockcroft-Gault and Modification of Diet in Renal Disease methods

Method	Mean GFR (ml/min/1.73 m^2)	Mean total bias	Correlation coefficient (*r*)	*P*	P_{30} (%)
Plasma method	80.4				
Gates'	83.3	2.87	0.685	<0.08	60.6
CG	89.36	8.93	0.495	<0.004	57.6
MDRD	97.4	17.0	0.54	<0.000	62.1

CG: Cockcroft-Gault, MDRD: Modification of Diet in Renal Disease, GFR: Glomerular filtration rate

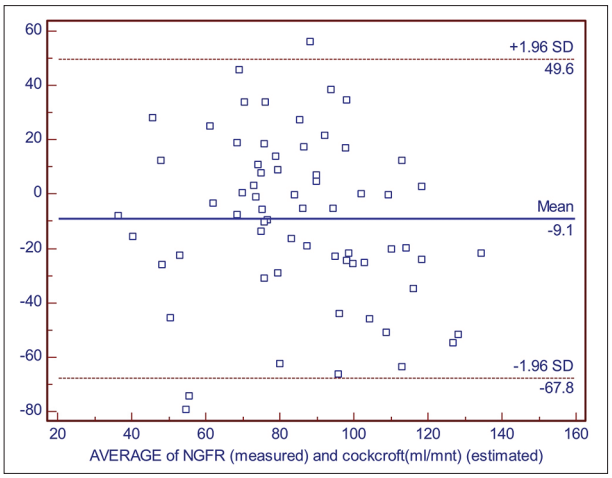

Figure 2: Comparison of normalized glomerular filtration rate two-plasma sample method with estimated glomerular filtration rate Cockcroft–Gaults equation for voluntary kidney donors

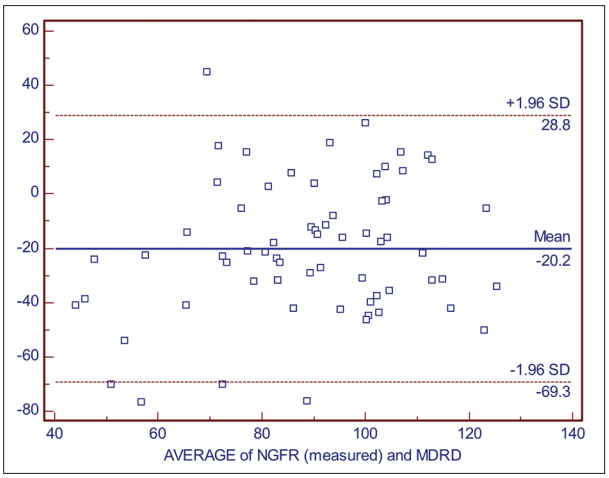

Figure 3: Comparison of normalized glomerular filtration rate two-plasma sample method with estimated glomerular filtration rate Modification of Diet in Renal Disease equation for voluntary kidney donors

Later, formulae-based and camera-based techniques of GFR estimation were proposed that are easier and faster.[13,14] Since then various studies have been conducted to test the reliability of these methods. These methods use age, weight, and highly gender- and ethnicity-biased. While most of the studies have been done in the western population, the data on Indian population is limited.

In our study, direct comparison of GFR values estimated by Gates', CG, and MDRD method was done with nGFR values calculated by plasma technique, which is considered the gold standard in this study. Of the three methods, Gates' method most closely correlated to the plasma technique. eGFR Gates' shared a moderate positive correlation while eGFR CG and MDRD had a weak-moderate positive correlation with nGFR. Accordingly, eGFR Gates' had the lowest mean total bias while eGFR MDRD had the highest mean total bias.

The accuracy of the GFR estimates was assessed in terms of the proportion of predicted values falling within 30% of the nGFR estimated by plasma technique (P_{30}). In accordance with the data trend of other parameters, P_{30} was highest for MDRD method followed by Gates' and CG methods, in descending order. However, in terms of number of patients, the Gates' and MDRD methods differ in P_{30} by just one patient.

P values for the difference between mean nGFR by plasma technique and eGFR Gates' was 0.08, indicating an insignificant difference. However, the difference between mean nGFR by plasma technique and eGFR CG and eGFR MDRD was significant, $P = 0.004$ and 0.000, respectively. The results suggest that Gates' method has a closer correlation with the plasma technique than CG and MDRD methods.

As per the Amsterdam Forum Guidelines 2005, a living donor with a GFR >80 ml/min/1.73 m^2 may be considered fit. However, the GFR value acceptable at our Institute >70 ml/min/1.73 m^2. Taking the cut-off value 70 ml/min/1.73 m^2, Gates' method would falsely accept 25% of patients, as donors, whereas 12% of patients would be falsely rejected. False acceptance for CG and MDRD methods would be 44% and 56% of patients while false rejection would be 14% and 6% of patients, respectively. Taking the cut-off value 80 ml/min/1.73 m^2, false acceptance for Gates', CG and MDRD would be 23%, 33%, and 57% of patients, respectively, and false rejection would be 22%, 25%, and 6% of patients, respectively. Gates' method had the lowest false acceptance rate in both the cut-off categories. One advantage of Gates' method over the rest is that it provides differential function while others provide global function. Hence, it can be helpful in deciding which kidney may be more suitable for donation. However, patients being evaluated for renal donor invariably undergo renography along with GFR, which also provides the similar information.

The literature reports wide variability in the correlation results of Gates', CG, and MDRD methods with plasma technique. van Deventer *et al*. compared the formulae based methods CG and MDRD of estimating GFR with the plasma technique in Black South African population. Contrary to our results, they found a strong correlation between these methods and concluded that these can be used reliably to estimate GFR in Black South African population.[15]

In another study in Indian population by Hephzibah *et al*., TPSM has been reported to be the most accurate and indispensable method of GFR estimation. Both the Gates' method and CG method were observed to underestimate GFR.[16] A comparison study of GFR by Gates method with CG equation in unilateral small kidney by Hassan *et al*. in Indian population found that difference was statistically insignificant indicating an agreement between both the methods in estimating GFR.[17]

Aydın *et al*. compared SPSM, TPSM, CG, and MDRD in 115 donors and reported that SPSM, TPSM reflect GFR more accurately than the other methods. Contrary to our results, neither the Gates method nor the prediction equations (CG and MDRD) could calculate GFR accurately. All these techniques could result in miss-management of potential kidney donors.[18] Like our results, they found a strong correlation between the TPS method and Gates' methods, moderate with MDRD, and poor to CG. Similarly, Assadi *et al*. revealed that the Gates' method has a good correlation with the plasma sample method and was more precise than the CG and MDRD equation.[19]

A study was conducted by Fatima *et al*., to compare the diagnostic accuracy of the different method of GFR estimation in 91 patients in Karachi, Pakistan. They found that SPSM correlate well with TPSM and either can be substituted for the other as ideal GFR markers. In accordance with our results, the Gates method showed good correlation with TPSM however it was found to be less precise than SPSM. MDRD and CG methods due to significant underestimation were not considered good GFR estimation methods.[20]

In Indian population, Prasad *et al*. compared Gates' method and MDRD method with plasma technique. They reported that Gates' method was better than MDRD for GFR estimation. Furthermore, the correlation values reported are similar to that reported in this study. They concluded that these methods are sub-optimal as compared to the plasma technique. Our results correlate well with the results reported by Prasad *et al*.[21]

Conclusions

The camera- and formulae-based methods of GFR estimation are easier and faster to perform, but their reliability could not be proved in our study population. It remains to be seen if an ethnicity factor calculated in any of the future studies, might improve their accuracy in Indian population. At present, the existing methods of Gates', CG, and MDRD display a huge variability and hence while screening healthy donors for renal transplantation, GFR estimation by a more reliable method that is the plasma sampling technique using ^{99m}Tc-DTPA should be preferred.

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Conflicts of interest

There are no conflicts of interest.

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