A Comparison of the Accuracy of Different Single Plasma Sample Methods for Measuring Glomerular Filtration Rate Using ^{51}Cr -EDTA in Children

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Abstract

Purpose Among the different methods of measuring glomerular filtration rate (GFR) using ^{51}Cr -ethylenediaminetetraacetic acid clearance, the two-plasma-sample method (TPSM) is widely used, and highly accurate. The single-plasma-sample method (SPSM) is occasionally used for simplicity, at the expense of accuracy. Our aims were (1) to investigate the correlation and (2) to compare the accuracy of six known SPSMs in pediatric patients in reference to TPSM.

Methods We retrospectively reviewed 122 pediatric cases (65 boys, age 7.3 ± 4.6 years) and analyzed 307 GFR measurements. SPSMs included Groth and Aasted at 120 min, Ham at 120 min, Christensen and Groth at 120 and 240 min, and Jacobsson at 120 and 240 min. Reference GFR (GFR_{ref}) was defined using TPSM GFR corrected by the Jodal and Brochner-Mortensen equation. $\text{GFR}_{\text{ref}} < 30 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ were excluded. The standard error of the estimate (SEE) and the number of cases with differences $> 10\%$ ($N_{10\%}$) were used to evaluate accuracy.

Results SPSMs generally correlated well with GFR_{ref} ($r = 0.92\sim 0.99$) and were relatively accurate ($\text{SEE} = 9.21\sim 15.60$). Groth and Aasted showed the smallest SEE, while Jacobsson at 240 min showed the smallest $N_{10\%}$ for all GFR_{ref} ranges. As for the decreased GFR_{ref} , Ham was most accurate followed by Jacobsson at 240 min.

Conclusions Jacobsson at 240 min provided good accuracy in all GFR_{ref} ranges and was well correlated with TPSM. Jacobsson at 240 min might be the most appropriate method to substitute for TPSM in pediatric patients. Ham could be an alternative in patients with impaired renal function.

Keywords Glomerular filtration rate · Children · Single plasma sample method · ^{51}Cr -EDTA

Introduction

The glomerular filtration rate (GFR) is widely used to evaluate renal diseases [1, 2] and to monitor kidney function when using nephrotoxic drugs, such as chemotherapeutic or immunosuppressive drugs [3]. GFR measurement methods based on serum creatinine or cystatin C are simple, but their accuracy is not always reliable [4]. The GFR measurement method based on renal clearance during a continuous infusion of inulin is known to be the most accurate method, but it is too complex to be

performed in clinical practice. Therefore, simpler GFR measurement methods using multiple-plasma samples after a single intravenous injection of radionuclides, such as ^{51}Cr ethylenediaminetetraacetic acid (^{51}Cr -EDTA) or $^{99\text{m}}\text{Tc}$ diethylenetriaminepentaacetic acid ($^{99\text{m}}\text{Tc}$ -DTPA) have replaced the inulin infusion method [5–7]. However, multiple-plasma-sample methods (MPSM) are still too complicated to be routinely used in clinical practice.

With regard to simplicity, the two-plasma-sample method (TPSM) requires only two plasma samplings and it is widely used in clinical practice. However, in some cases, such as pediatric patients, patients in extremely poor medical condition, or minimally cooperative patients, it is not always easy to obtain two plasma samples. A more simplified method is the single-plasma-sample method (SPSM). SPSMs use empirical equations involving volumes of distribution and plasma clearances [8]. While SPSM is simple

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and convenient [6, 9–11], its accuracy raises concerns [5, 6, 12]. There are no fewer studies on the accuracy of SPSM compared with studies on TPSM. Therefore, the aims of this study were (1) to investigate the correlation and (2) to compare the accuracy of six known SPSMs in children, using the TPSM as a reference.

Materials and Methods

Subjects

We retrospectively reviewed the medical records of 122 consecutive children who were referred for measurements of GFR between July 2015 (when we started to create the GFR database) and August 2017. The inclusion criteria were (1) patients aged 6 months to 15 years, (2) patients whose 1st blood samples were obtained between 110 and 130 min after a radiotracer injection [10], and (3) patients whose 2nd blood samples were obtained more than 180 min after a radiotracer injection [5, 13]. The exclusion criteria were (1) patients with a history of administration of radioactive material within 1 week of the GFR measurement [8] and (2) patients whose reference GFR was below $30 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ because SPSMs are known to be inaccurate with a GFR less than $30 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ [11, 14–17]. Serum creatinine levels and estimated GFRs using cystatin C were recorded. This study was approved by our Institutional Review Board (IRB No. 2017-1843), and informed consents were waived.

Procedure

Prior to the injection of ^{51}Cr -EDTA (GE healthcare Ltd., Amersham, Buckinghamshire, UK) in each patient, we created a standard by taking 1 mL of aliquot of the ^{51}Cr -EDTA solution from the syringe, transferring it to a volumetric flask, and diluting it to a total volume of 200 mL. Fifty to eighty microcuries (1.85–2.96 MBq) of ^{51}Cr -EDTA were injected through an indwelling butterfly needle, which was then immediately flushed with 4 mL of normal saline. Next, patency of the vein was assured via an injection of 5 mL of normal saline before the ^{51}Cr -EDTA injection. Each patient was instructed to be sufficiently hydrated prior to the study, and patient movements were not restricted [18, 19]. The syringe was weighed before and after drawing the standard dose in order to calculate the standard mass. The syringe was weighed again after injecting the ^{51}Cr -EDTA into the patient to calculate injection mass.

Two blood samples of at least 5 mL each were taken from the contralateral arm and ejected into EDTA anticoagulant tubes at 120 and 240 min after the radiotracer injection [8]. Sampling times were recorded.

Each blood sample was centrifuged for 4 min at $1753\times g$, and then 1 mL of the plasma sample was taken from each centrifuged tube. The activity of the standard and the 120- and 240-min plasma samples (1 mL each) were counted up to 10,000 counts [8] in a well-type scintillation counter (Packard Cobra II E5003, GMI, Ramsey, MN).

Calculation of GFR

Reference two Plasma Sample Method

The reference GFR (GFR_{ref}) was determined by a slope-intercept GFR model, corrected by Jodal and Brochner-Mortensen (JBM) equation (Appendix 1), using two plasma samples collected at 120 and 240 min after the injection of ^{51}Cr -EDTA.

Single Plasma Sample Methods

The estimated GFR (GFR_{est}) was calculated using six methods: (1) Groth and Aasted's method at 120 min (G&A) [20], (2) Ham's method at 120 min (Ham) [10], (3) Christensen and Groth's method at 120 min (C&G120) [21], (4) Christensen and Groth's method at 240 min (C&G240), (5) Jacobsson's method at 120 min (Jacobsson120) [22], and (6) Jacobsson's method at 240 min (Jacobsson240) (Appendices 2, 3, 4, and 5).

Normalization of GFR

Body surface area (BSA) was calculated using Haycock's equation [23]:

$$\text{BSA (m}^2\text{)} = 0.024265 \times \text{height}^{0.3964} \text{ (cm)} \times \text{weight}^{0.5378} \text{ (kg)}$$

All of the GFR values were normalized for a standard body surface area of 1.73 m^2 .

Statistical Analysis

Commercially available software, SPSS for Windows (version 21.0; IBM, Chicago, IL, USA), was used for the statistical analyses. A linear regression analysis between GFR_{ref} and GFR_{est} calculated from SPSMs was performed. The correlation between GFR_{ref} and GFR_{est} was evaluated using the Pearson correlation (r). A Bland-Altman analysis plotting the percentage difference between GFR_{ref} and GFR_{est} against GFR_{ref} was drawn [24, 25].

Standard error of the estimates (SEE) between GFR_{ref} and GFR_{est} [10, 11, 26–28] was calculated as shown:

$$SEE = \sqrt{\frac{\sum_1^n (GFR_{ref} - GFR_{est})^2}{n}}$$

The cases where the difference between GFR_{est} and GFR_{ref} was > 10% when referring to GFR_{ref} ($N_{10\%}$) were used to evaluate the accuracy of GFR_{est} [29].

Results

Patient Characteristics

A total of 122 children (65 boys and 57 girls, mean age 7.3 ± 4.6 years) were included, and 307 GFR measurements were analyzed in this study. The number of patients who underwent GFR measurement once, twice, three times, four times, five times, six times, seven times, eight times, and nine times was 45, 32, 15, 13, 8, 5, 2, 1, and 1, respectively. The baseline characteristics of the patients according to GFR_{ref} are summarized in Table 1. The reasons for the GFR measurements were to monitor kidney function during chemotherapy ($n = 228$), to evaluate kidney function before the use of nephrotoxic drugs ($n = 70$), before solid organ or bone marrow transplantation ($n = 4$), before nephrectomy ($n = 1$), and a suspicion of renal disease ($n = 4$).

Correlation and Accuracy of Estimated GFR

GFR_{est} calculated from the different SPSMs generally correlated well with GFR_{ref} ($r = 0.92\sim 0.99$) while all SPSMs

overestimated GFR. SPSMs were relatively accurate (SEE = $9.21\sim 15.60$) (Table 2; Fig. 2); however, the accuracy of each SPSM was different according to the range of GFR_{ref} (Tables 2 and 3). For whole ranges of GFR_{ref} , G&A showed the smallest SEE (SEE = $9.21 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$, $N_{10\%} = 119$ (39%)) while Jacobsson240 showed the smallest $N_{10\%}$ (SEE = $10.54 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$, $N_{10\%} = 80$ (26%)). Jacobsson240 provided good accuracy in all GFR_{ref} ranges, whereas G&A was less accurate in cases of decreased GFR_{ref} ($30 \leq GFR_{ref} < 90 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$). For $30 \leq GFR_{ref} < 90 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ (decreased renal function [30]), Ham was the most accurate method (SEE = $4.46 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$, $N_{10\%} = 10$ (10%)) followed by Jacobsson240 (SEE = $6.24 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$, $N_{10\%} = 19$ (18%)).

For $60 \leq GFR_{ref} < 90 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ (mildly decreased renal function [30]), Ham was the most accurate (SEE = $3.46 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$, $N_{10\%} = 3$ (4%)). For $30 \leq GFR_{ref} < 60 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ (moderately decreased renal function [30]), Jacobsson240 was the most accurate (SEE = $3.55 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$, $N_{10\%} = 3$ (14%)).

In the Bland-Altman analysis, GFR_{est} calculated from SPSMs tended to be overestimated when compared with GFR_{ref} (Table 3). For whole ranges of GFR_{ref} , Jacobsson240 showed the smallest mean difference (2.28%) and G&A showed the smallest standard deviation (SD, 7.03%). For $GFR_{ref} \geq 90 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$, Jacobsson240 showed the smallest mean difference (0.71%) while C&G120 showed the smallest SD (3.88%). For $30 \leq GFR_{ref} < 90 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$, Ham showed the smallest mean difference (4.35%) while Jacobsson240 showed the smallest SD (6.35%). For $60 \leq GFR_{ref} < 90 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ (mildly decreased renal function),

Table 1 Baseline patient characteristics according to the different ranges of glomerular filtration rate (GFR)

Characteristics	Total	$30 \leq GFR_{ref} < 60$ ($\text{mL min}^{-1} 1.73 \text{ m}^{-2}$)	$60 \leq GFR_{ref} < 90$ ($\text{mL min}^{-1} 1.73 \text{ m}^{-2}$)	$90 \leq GFR_{ref}$ ($\text{mL min}^{-1} 1.73 \text{ m}^{-2}$)
No. of patients	122 ^a	17	50	94
Sex (boys:girls)	65:57 ^a	6:11	27:23	51:43
No. of GFR measurements	307	22	82	203
Age < 2 years	48	7	15	26
$2 \leq \text{Age} < 5$ years	75	3	25	47
$5 \leq \text{Age} < 10$ years	86	6	21	59
$10 \leq \text{Age} < 15$ years	98	6	21	71
Age (years)	7.3 ± 4.6	6.5 ± 5.2	6.5 ± 4.6	7.7 ± 4.5
Height (cm)	119.2 ± 30.6	108.5 ± 34.7	114.0 ± 31.3	122.4 ± 29.5
Weight (kg)	27.4 ± 18.2	23.2 ± 18.5	25.5 ± 19.4	28.7 ± 17.6
BSA (m^2)	0.9 ± 0.4	0.8 ± 0.5	0.9 ± 0.4	1.0 ± 0.4
Serum creatinine (mg dL^{-1})	0.41 ± 0.18	0.65 ± 0.31	0.44 ± 0.20	0.37 ± 0.13

Continuous values are in mean value $\pm$ standard deviation, except number of patients and number of GFR measurements

GFR_{ref} , reference GFR

^a Some patients underwent GFR tests more than once

Table 2 Linear regression and correlation analysis of the estimated GFR (GFR_{est}) by single-plasma-sample methods (SPSMs) against the reference GFR (GFR_{ref})

GFR_{ref} (mL min ⁻¹ 1.73 m ⁻²)	Method	Correlation analysis		Linear regression equation	
		r^a	SEE	Slope	Intercept
$30 \leq GFR_{ref}$ ($n = 307$)	G&A	0.98	9.21	0.94	13.55
	Ham	0.98	15.60	1.32	-21.94
	C&G120	0.99	11.75	1.29	-21.41
	C&G240	0.93	15.55	1.00	10.65
	Jacobsson120	0.97	11.26	1.02	6.74
	Jacobsson240	0.92	10.54	0.84	16.74
$30 \leq GFR_{ref} < 90$ ($n = 104$)	G&A	0.97	9.07	1.09	1.56
	Ham	0.97	4.46	0.96	5.45
	C&G120	0.97	7.72	1.40	-30.25
	C&G240	0.95	11.63	1.32	-13.97
	Jacobsson120	0.88	11.25	1.14	-2.87
	Jacobsson240	0.95	6.24	1.06	-0.58
$30 \leq GFR_{ref} < 60$ ($n = 22$)	G&A	0.73	9.34	1.03	4.06
	Ham	0.70	7.03	0.65	21.45
	C&G120	0.72	14.38	1.28	-24.64
	C&G240	0.94	5.31	1.40	-17.52
	Jacobsson120	0.60	12.36	1.15	-3.51
	Jacobsson240	0.96	3.55	1.02	1.58
$60 \leq GFR_{ref} < 90$ ($n = 82$)	G&A	0.97	8.99	1.08	2.54
	Ham	0.97	3.46	1.08	-4.19
	C&G120	0.98	4.48	1.40	-30.59
	C&G240	0.87	12.80	1.36	-17.70
	Jacobsson120	0.80	10.93	1.15	-3.82
	Jacobsson240	0.87	6.78	1.09	-2.46
$90 \leq GFR_{ref}$ ($n = 203$)	G&A	0.97	9.29	0.83	26.75
	Ham	0.97	18.92	1.50	-44.03
	C&G120	0.99	13.35	1.21	-11.82
	C&G240	0.82	17.22	0.80	35.33
	Jacobsson120	0.97	11.26	0.92	19.39
	Jacobsson240	0.80	12.17	0.69	35.17

SEE, standard error of the estimate; r , correlation coefficient

Ham showed second smallest mean difference (2.92%) and the smallest SD (3.42%). For $30 \leq GFR_{ref} < 60$ mL min⁻¹ 1.73 m⁻² (moderately decreased renal function), C&G240 showed the smallest mean difference (3.73%), while Jacobsson240 showed the smallest SD (5.86%).

Among SPSMs at 120 min, G&A showed smallest SEE (SEE = 9.21 mL min⁻¹ 1.73 m⁻², $N_{10\%}$ = 119 (39%)) while Ham had the smallest $N_{10\%}$ (SEE = 15.60 mL min⁻¹ 1.73 m⁻², $N_{10\%}$ = 104 (34%)) for whole range of GFR_{ref} . Ham was most accurate (SEE = 4.46 mL min⁻¹ 1.73 m⁻², $N_{10\%}$ = 10 (10%)) for $30 \leq GFR_{ref} < 90$ mL min⁻¹ 1.73 m⁻², while the accuracy decreased for $GFR_{ref} \geq 90$ mL min⁻¹ 1.73 m⁻². In contrast, G&A was most accurate (SEE = 9.29 mL min⁻¹ 1.73 m⁻², $N_{10\%}$ = 58 (29%)) for $GFR_{ref} \geq 90$ mL min⁻¹ 1.73 m⁻², while it was less accurate for $30 \leq GFR_{ref} < 90$ mL min⁻¹ 1.73 m⁻².

Discussion

In this study, we evaluated the accuracy of SPSMs and their correlation with reference to TPSPM in pediatric patients with a broad range of renal functions. All SPSMs were well correlated with TPSPM, although all SPSMs tended to overestimate the GFR. In patients whose renal function is unknown, Jacobsson240 would be the best method to replace TPSPM because it was accurate across a wide range of GFR_{ref} . Of note, Ham was the most accurate SPSM for patients with decreased renal function, although Ham overestimated GFR when $GFR_{ref} \geq 90$ mL min⁻¹ 1.73 m⁻². This suggests that Ham would be a good alternative for TPSPM in patients with a suspected decrease in renal function.

Table 3 Bland-Altman analysis of the GFR difference (%) between the estimated GFR (GFR_{est}) and the reference GFR (GFR_{ref})

GFR (mL min ⁻¹ 1.73 m ⁻²)	Method	$\frac{(\text{Estimated GFR} - \text{reference GFR})}{\text{Reference GFR}} (\%)$			<i>N</i> _{10%}
		Mean	SD	95% CI	
30 ≤ GFR _{ref} (<i>n</i> = 307)	G&A	8.52	7.03	− 5.27, 22.30	119 (39%)
	Ham	8.80	8.72	− 8.29, 25.89	104 (34%)
	C&G120	5.13	12.05	− 18.48, 28.75	128 (42%)
	C&G240	11.35	10.64	− 9.51, 32.21	163 (53%)
	Jacobsson120	9.28	9.77	− 9.88, 28.44	179 (58%)
	Jacobsson240	2.28	9.17	− 15.70, 20.26	80 (26%)
30 ≤ GFR _{ref} < 90 (<i>n</i> = 104)	G&A	11.30	9.31	− 6.95, 29.54	61 (59%)
	Ham	4.35	8.07	− 11.46, 20.16	10 (10%)
	C&G120	− 4.68	15.96	− 35.96, 26.61	29 (28%)
	C&G240	11.02	9.87	− 8.32, 30.36	49 (47%)
	Jacobsson120	9.52	15.38	− 20.63, 39.67	83 (80%)
	Jacobsson240	5.34	6.35	− 7.10, 17.79	19 (18%)
30 ≤ GFR _{ref} < 60 (<i>n</i> = 22)	G&A	11.95	19.47	− 26.20, 50.11	10 (45%)
	Ham	9.66	15.54	− 20.79, 40.11	7 (32%)
	C&G120	− 22.99	25.63	− 73.23, 27.25	19 (86%)
	C&G240	3.73	9.67	− 15.22, 22.68	5 (23%)
	Jacobsson120	8.15	27.36	− 45.48, 61.78	20 (91%)
	Jacobsson240	5.43	5.86	− 6.06, 16.91	3 (14%)
60 ≤ GFR _{ref} < 90 (<i>n</i> = 82)	G&A	11.12	3.43	4.39, 17.85	51 (62%)
	Ham	2.92	3.24	− 3.42, 9.27	3 (4%)
	C&G120	0.24	6.18	− 11.87, 12.34	10 (12%)
	C&G240	12.98	9.01	− 4.69, 30.65	44 (54%)
	Jacobsson120	9.89	10.30	− 10.30, 30.08	63 (77%)
	Jacobsson240	5.32	6.51	− 7.44, 18.08	16 (20%)
90 ≤ GFR _{ref} (<i>n</i> = 203)	G&A	7.09	4.97	− 2.66, 16.84	58 (29%)
	Ham	11.08	8.16	− 4.90, 27.07	94 (46%)
	C&G120	10.16	3.88	2.56, 17.76	99 (49%)
	C&G240	11.52	11.04	− 10.11, 33.15	114 (56%)
	Jacobsson120	9.16	4.90	− 0.45, 18.77	96 (47%)
	Jacobsson240	0.71	9.98	− 18.85, 20.28	61 (30%)

SD, standard deviation; CI, confidence interval; *N*_{10%}, the number of cases with difference between GFR_{est} and GFR_{ref} was >10% when referring to GFR_{ref}

There have been some studies that directly compared the different SPSMs in children [12, 31, 32]. Henriksen et al. [12] assessed GFR in 75 children (age 1/2–13 years), comparing the G&A's method at 60, 90, and 120 min and the Ham's method at 120 min with using a two-exponential curve fitting of 10, 20, 30, 60, 90, and 120 min samples. They reported that the accuracy of both the G&A's and Ham's methods was excellent in majority (about 85%) of the children, and the differences in the samples between 60, 90, and 120 min was not important for the G&A's method. However, they could not explain why these two methods were less accurate in a small fraction (about 15%) of the children. Itoh et al. [31] assessed GFR in 14 patients (age 3–19 years) and compared the G&A's method at 90 and 120 min, the Ham's method at 120 min, the C&G's

method at 90, 120, and 150 min, the Jacobsson's method at 90, 120, and 150 min, and the Itoh's method at 90, 120, and 150 min using a two-exponential curve fitting of 5, 15, 60, 90, 120, 150, and 180 min samples. They reported that the C&G's and Jacobsson's methods designed for adults were more accurate than the G&A's and Ham's methods designed for children, even if they could not justify their results theoretically. They concluded that C&G and the Jacobsson's methods designed for adults could be applied to children, which is in partial concordance with our results. These two studies used GFR calculated from a two-exponential curve fitting using multiple plasma samples as the reference, while we used the GFR calculated from the TPSM as the reference. However, we corrected the slope-intercept GFR using the JBM equation [26, 29]. In

Fig. 1 Scatter plots of the GFR estimates calculated from SPSMs against the reference GFR: **a** Groth and Aasted's method, **b** Ham's method, **c** Christensen and Groth's method at 120 min, **d** Christensen and Groth's

method at 240 min, **e** Jacobsson's method at 120 min, and **f** Jacobsson's method at 240 min

addition, the number of patients included in this study was larger than that in previous studies, which might make up for the use of TPSM as the reference.

The principle of SPSMs is to relate radionuclide clearance and the volume of distribution at certain time point. As those equations are empirical models derived from different populations, ages, renal functions, and under different experimental conditions with respect to sampling times and references, those equations are not universal and require careful interpretation. The Groth and Aasted's method was derived from 130 children (aged 1 to 13 years) using a 120-min sample after a ⁵¹Cr-EDTA injection, using a two-exponential curve fitting with five samples. In that study, the GFRs of 19 children were less than 80 mL min⁻¹ 1.73 m⁻² and the GFRs of five children were less than 50 mL min⁻¹ 1.73 m⁻² [20]. However, in our study, the GFRs of 65 children were less than 80 mL min⁻¹ 1.73 m⁻² and the GFRs of 11 children were less than 50 mL min⁻¹ 1.73 m⁻². As SPSMs are essentially based on an empirical relationship between volumes of distribution and plasma clearances, the small number of children whose

GFR < 90 mL min⁻¹ 1.73 m⁻² used to derive the equation may be one of the reasons why G&A did not work well for 30 ≤ GFR_{ref} < 90 but worked well for GFR_{ref} ≥ 90 mL min⁻¹ 1.73 m⁻² in our study. Additionally, G&A tended to overestimate GFR, and this result is consistent with the result of Henriksen et al. [12]. Ham's method, mentioned in the European Association of Nuclear Medicine guidelines [5, 33] for GFR determination in children, was derived from 80 children (age < 15 years) using a 120-min sample after ⁵¹Cr-EDTA injection. The reference method was a one-exponential curve fitting two samples between 120 and 240 min with a composite correction constant of 0.85. The C&G's method was derived from 45 patients using samples drawn at 180 ≤ t ≤ 300 after ^{99m}Tc-DTPA injection [21]. The reference method was a two-exponential curve fitting 16 samples. C&G120 and the reference method revealed a good correlation, but the slope of the regression line between the C&G120 and the reference method was far different from the value of 1 (1.29). On the other hand, the slope of the regression line between C&G240 and the reference method

Fig. 2 Bland-Altman plots drawn by plotting the percentage difference between the estimated and reference values of GFR against reference values of GFR: **a** Groth and Aasted's method, **b** Ham's method, **c**

Christensen and Groth's method at 120 min, **d** Christensen and Groth's method at 240 min, **e** Jacobsson's method at 120 min, and **f** Jacobsson's method at 240 min

was nearly 1 (1.00). This result may support the suggestion that C&G's method should only be used with the sample drawn at $180 \leq t \leq 300$. Jacobsson's method was originally derived from 39 patients using samples drawn between 240 and 300 min after a ^{99m}Tc -DTPA injection. The reference method was a one-exponential curve fitting four samples between 240 and 300 min using the Brochner-Mortensen equation for correction. Regarding the optimal sampling time, a 240-min sample would be more appropriate than a 120-min sample for Jacobsson's method because Jacobsson240 was more accurate than Jacobsson120. We used ^{51}Cr -EDTA instead of ^{99m}Tc -DTPA, the radionuclide was originally used to derive C&G's and Jacobsson's equations. It is well known that the volume of distribution is dependent on the type of radiotracer, and the use of different radiotracers, ^{51}Cr -EDTA in our case will affect the accuracy of the method. However, the error would not be significant since the GFR_{est} calculated from both methods is insensitive to the precise value of the volume of distribution [22] and the volume of distribution is included in both the numerator and the denominator.

In the current study, according to the linear regression analysis between GFR_{ref} and GFR_{est} (Table 2), the slope of the GFR_{est} calculated from Ham is larger than 1 (1.5), and that calculated from Jacobsson240 is smaller than 1 (0.69) for

$\text{GFR}_{\text{ref}} \geq 90 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$. Ham's method used a slope-intercept GFR corrected by a Chantler approximation with a correction constant of 0.85 as the reference while Jacobsson's method used a slope-intercept GFR corrected by the Brochner-Mortensen equation as the reference. Fleming reported that the Chantler approximation overestimates GFR over $100 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ [34], while the Brochner-Mortensen equation underestimates GFR over $180 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ [26, 34]. The regression lines of the scatter plots between GFR_{ref} and GFR_{est} calculated from Ham and Jacobsson240 are similar to the graphs of the slope-intercept GFRs corrected by the Chantler approximation and the Brochner-Mortensen equation referring to the true GFR, respectively. This may explain why Ham tended to overestimate GFR much more than other SPSMs for $\text{GFR} \geq 90 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$, and the difference becomes larger as the GFR_{ref} increases.

There is an outlier shown in Figs. 1 and 2 which is presented as a closed square. This patient was referred for GFR measurement based on a suspicion of acute renal failure, and her medical records and clinical course supported the presumed diagnosis. The patient's GFR_{ref} was $35.05 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ but Ham ($60.13 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$, 71.56%), G&A

(64.40 mL min⁻¹ 1.73 m⁻², 83.74%), C&G120 (50.06 mL min⁻¹ 1.73 m⁻², 42.84%), and Jacobsson120 (60.65 mL min⁻¹ 1.73 m⁻², 73.05%) all overestimated the GFR_{est} in this patient. C&G240 (39.91 mL min⁻¹ 1.73 m⁻², 13.88%) and Jacobsson240 (43.26 mL min⁻¹ 1.73 m⁻², 23.43%) also overestimated the GFR, but the errors were much smaller than those of the SPSMs using the 120-min sample. These results are consistent with previous reports of the improved accuracy of GFR_{est} with increased sampling times with respect to results obtained from C&G's and Jacobsson's methods [11, 21, 22]. Jacobsson's method is quite insensitive to the variation of the patient's volume of distribution [22].

This study has several limitations. First, we used the slope-intercept technique which is a one-exponential curve fitting two plasma samples instead of a two-exponential curve fitting multiple plasma samples to determine the GFR_{ref}. The slope-intercept technique ignores the faster part of the plasma concentration curve and only uses the slower part of the plasma concentration curve to determine GFR. This simplification resulted in an overestimation of GFR and therefore, various correction methods were developed. We corrected the slope-intercept GFR using the JBM equation instead of the Brochner-Mortensen equation to minimize errors [26, 29]. Second, we used samples at only two time points. More appropriate sampling times may exist, however, only 120 and 240 min samples were available because of the retrospective nature of this study.

Conclusion

Jacobsson240 showed a good accuracy in all GFR_{ref} ranges and was well correlated with TPSM. Jacobsson240 might be the most appropriate method to substitute for TPSM in pediatric patients. The Ham's method could be an alternative for patients with impaired renal function.

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Compliance with Ethical Standards

Conflicts of Interest Sejin Ha and Jong Jin Lee declare that they have no conflicts of interest.

Ethical Approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent This study was approved by our Institutional Review Board (IRB No. 2017-1843). The Institutional Review Board waived informed consent.

Appendix 1: Slope-Intercept GFR Corrected Using the Jodal and Bochner-Mortensen Equation (Reference GFR) [26]

Reference GFR (mL min⁻¹ 1.73 m⁻²)

$$= \text{SI-GFR}_{\text{cor}} / (1 + 0.00185 \times \text{BSA}^{-0.3} \times \text{SI-GFR}_{\text{cor}}),$$

$$\text{SI-GFR}_{\text{cor}} (\text{mL min}^{-1} 1.73 \text{ m}^{-2}) = \text{SI-GFR} \times (1.73 \text{ BSA m}^{-2})$$

$$\text{SI-GFR} (\text{mL min}^{-1}) = (w_i \times s \times 200 / w_s) \times (\ln(C_1 / C_2) / dt) \times (C_2^{(t_1/dt)} / C_1^{(t_2/dt)})$$

where w_i is injection mass (g), w_s is standard mass (g), t_1 is 1st plasma sample time (min), t_2 is 2nd plasma sample time (min), $dt = t_2 - t_1$ (min), s is standard count (cpm mL⁻¹), C_1 is 1st plasma sample count (cpm mL⁻¹), C_2 is 2nd plasma sample count (cpm mL⁻¹), and BSA is body surface area (m²).

Appendix 2: Groth and Aasted's Method [20]

$$\text{CI} (\text{mL min}^{-1} 1.73 \text{ m}^{-2}) = A + BX,$$

$$A = -553.124 \ln(t) + 3236.76,$$

$$B = 72.295 \ln(t) - 425.41,$$

$$X = \ln\{C(t) \times \text{BSA} \times 10^7 / \text{ID}\}$$

where t is sample time (90–120 min), $C(t)$ is sample activity at time = t (min) (cpm mL⁻¹), ID is injected dose (cpm).

Reference method of plasma clearance: two-exponential curve fitting five samples at 5, 15, 60, 90, and 120 min after the injection of ⁵¹Cr-EDTA.

Appendix 3: Ham's Method [6, 10]

$$\text{CI} (\text{mL min}^{-1}) = 2.602V_{120} - 0.273,$$

$$V_{120} (\text{L}) = \text{ID} / C_{120},$$

$$C_{120} = A(t) \times e^{(0.008)(t-120)}$$

where t is sample time (100–130 min), $A(t)$ is actual radioactivity at sample time = t (cpm mL⁻¹), C_{120} is radioactivity corresponding to sample time = t (cpm mL⁻¹), and V_{120} is volume of distribution at sample time = t (L).

Reference method of plasma clearance: one-exponential curve fitting two samples between 2 and 4 h after the injection of ⁵¹Cr-EDTA with composite correction constant of 0.85

Appendix 4: Christensen and Groth's Method [6, 21, 35]

$$Cl \text{ (mL min}^{-1}\text{)} = \left(-b + \sqrt{(b^2 - 4ac)} \right) / 2a,$$

$$a = 0.0000017t^2 - 0.0012t,$$

$$b = -0.000775t^2 + 1.31t,$$

$$c = ECV \times \ln(ECV/V(t))$$

where ECV is extracellular volume = $8116.6 \text{ BSA} - 28.2$ (mL), $V(t)$ is volume of distribution = $ID/C(t)$ (mL), t is sample time (180–300 min), BSA is body surface area (m^2), and ID is injected dose (cpm).

Reference method of plasma clearance: two-exponential curve fitting 16 samples from 0 to 300 min after the injection of ^{99m}Tc -DTPA.

Appendix 5: Jacobsson's Method [22]

$$Cl \text{ (mL min}^{-1}\text{)} = \ln(V(t)/V') / (t/V' + 0.0016)$$

where $V(t)$ is volume of distribution at sample time = t (mL), ID is injected dose (cpm), $C(t)$ is plasma radioactivity at sample time = t (cpm mL^{-1}), $V' = 0.246 \text{ BW}$, BW is body weight (g), t is sample time (min).

Reference method of plasma clearance: one-exponential curve fitting four samples from 240 to 300 min after the injection of ^{99m}Tc -DTPA with Brochner-Mortensen's correction.

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