Evaluation of the accuracy of Bio-impedance in predicting creatinine clearance in ICU patients with acute kidney injury; Comparison with measured creatinine clearance and calculated by formulas

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ABSTRACT

Introduction: It is still of top priority to find a method to measure creatinine clearance (CrCl) in patients with acute kidney injury (AKI) to regulate drug dosage and avoid treatment failure. Therefore, this study designed to compare CrCl calculated with 6-hour urine output, by formulas, and obtained with the bio-impedance method in patients with AKI hospitalized in ICU.

Materials and Methods: In this prospective cross-sectional study, 28 adult patients with an increase in serum creatinine of at least 0.3 according to AKIN criteria and admitted in ICU of Imam Hussein Hospital were selected as the study samples. CrCl was calculated by 6-hour urine output collection, through electrical bio-impedance method, and formulas of Cockcroft and Gault, MDRD, and CKD-EPI. After the required data were collected, they were recorded in pre-prepared checklists, and finally fed into software to be statistically analyzed. Lastly, the obtained CrCl values were compared with those measured by 6-hour urine collection to determine the best formula or method to determine CrCl in patients with AKI.

Results: The results showed that the bias values of bio-impedance compared to 6-hour urinary clearance, MDRD, Cockcroft, and CKD-EPI formulas were 6.34, 3.31, 5.01, and 15.14, respectively. Also, error values of bio-impedance compared to 6-hour urinary clearance, MDRD, Cockcroft, and CKD-EPI were respectively 140%, 28%, 60%, and 47%. The internal consistency of the bio-impedance values by the above methods were 0.782, 0.983, 0.939, and 0.893, respectively.

Conclusion: According to the obtained results, it can be concluded that none of the formulas listed, including MDRD, Cockcroft, and Gault, and CKD-EPI could predict the CrCl correctly compared to 6-hour urine collection as standard. Also, estimated glomerular filtration rate (GFR) by bio-impedance did not reveal acceptable correlation with 6-hour urine collection. Therefore, this group of patients needs a more precise and specific method(s) to determine the CrCl and GFR.

Keywords: bio-impedance, creatinine clearance, acute kidney injury (AKI)


INTRODUCTION

Acute kidney injury (AKI) refers to a state in which kidney function decline leads to electrolyte and fluid disorders and acid-base balance following a decrease in GFR. As a common complication in ICU, AKI leads to an increase in mortality among the hospitalized patients.1-4 Almost 7% of patients admitted to hospitals are suffering from AKI.5 This figure was reported to be 37-67% for patients with specific and critical diseases, depending on different definitions of AKI.6-9 The incidence of AKI is related to the patients’ mortality, such that an approximate mortality rate of 50-70% was reported among patients with AKI who need renal replacement therapy (RRT).10-13

Determining serum creatinine (Scr) is the old method of diagnosing AKI in ICU, and etiology of AKI is carried out by evaluating medical background, physical examination, renal ultrasound, sodium and urea excretion, blood urea nitrogen (BUN) and urine microscopy.7-9,14 Nowadays, different criteria are utilized to diagnose AKI, including RIFLE and AKIN criteria.7,8

One of the major challenges in patients suffering AKI is measurement or prediction of renal function to adjust the dose of medications.15,16 One of the recommended methods of measuring CrCl is to collect 24-hour urine output and determine clearance through an appropriate formula (Table 1).17 Due to the problems involved with collecting 24-hour urine output, different studies used shorter periods of time like 2 and 4 hours for critically ill patients to collect urine output and measure CrCl with acceptable correlation with the 24-hour urinary collection.18-21

The value of using serum creatinine in estimating GFR in patients with AKI is limited. In fact,
the recommended dosages in most studies and almost in all FDA and EMEA medical brochures are adopted from studies carried out on patients with CKD who have received RRT. In recent studies, it is well shown that estimating CrCl through the proposed formulas such as the Modification of Diet in Renal Disease Study (MDRD), Cockcroft and Gault (CG), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) is not an appropriate criterion for estimating GFR in patients with AKI hospitalized in ICUs, further investigation is required to propose another solution for evaluating renal function in such patients and regulating their drug dosages. Moreover, there is much emphasis on the importance of regulating drug dosage of these patients.22,23

BioScan device is an apparatus that operates based on bioelectrical impedance analysis (BIA). Using measured and entered data including height, weight, age, gender, and Scr, BIA presents the CrCl of the patient. Data about the accuracy of this prediction are scanty. The goal of this study was to compare the CrCl measured by 6-hour urine output collection with creatinine clearances calculated using different formulas and bio-impedance method.22,23

METHODS

This prospective cross-sectional study was done in the intensive care unit of a tertiary teaching hospital affiliated to Shahid Beheshti Medical University, Tehran, Iran. In this study, adult ICU patients with an increase in serum creatinine of at least 0.3 g/dL in 48 hours (according to AKIN criteria) were recruited until the desired sample size was obtained. To calculate the sample size, the maximum value acceptable for intraclass correlation (ICC) of 0.65 and its expected value of 0.85 was taken into consideration. Type 1 error and test power were respectively 0.05 and 0.8. All of the calculations were carried out using ICCSample. Size package in R software. Accordingly, the sample size was calculated to be 28. Demographic data of all patients who entered the study were collected and recorded. Moreover, CrCl was calculated by the following methods and relevant formulas: 1) Six-hour urine was collected from all of the patients, the amount of urinary creatinine was measured, and the collected data were used to determine the patients’ CrCl as a standard. 2) On the same day of 6-hour urine collection, all of the patients’ CrCl and GFR was estimated by electrical bio-impedance method by an intensive care fellowship. 3) CrCl was calculated using the proposed formulas including the simplified refitted MDRD, Cockcroft and Gault, and CKD-EPI for all of the patients.

Lastly, the obtained CrCl was compared with the one measured by 6-hour urine output collection to figure out the best formula or method to determine the CrCl in patients with AKI. The collected data were analyzed using SPSS 22.0. The quantitative data were described through frequency and percentage, and qualitative data through standard deviation, median, and variation range. In the case of non-normal distribution of the data, nonparametric tests were employed. Bland-Altman specialized plots and ICC were utilized to compare the results. The value of α error was considered as 0.05. In the present study, the required examinations were routine, and no charges were imposed on the patients. Conducting the present study had no contradiction with international treaties in the field of medical science such as Nuremberg and Helsinki codes.

### Table 1 Formulae for estimating GFR

<table>
<thead>
<tr>
<th>Formula</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Measured 6 hr urinary creatinine clearance</strong></td>
<td>CICr = (Urine Creatinin * daily urine volume) / (serum Creatinin * 1440)</td>
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<tr>
<td><strong>Cockcroft and Gault</strong></td>
<td>(140 – age) × weight/72 × Scr × (0.85 if female)</td>
</tr>
<tr>
<td><strong>The simplified refitted MDRD</strong></td>
<td>175 × Scr^−1.154 × age^−0.203 (× 0.742 if female) (× 1.212 if black)</td>
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<tr>
<td><strong>The CKD-EPI equation</strong></td>
<td></td>
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<tr>
<td><strong>Women:</strong></td>
<td></td>
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<tr>
<td>GFR (mL/min/1.73 m²) = 144 × (Scr/0.7)−0.329 × 0.993age (× 1.15 if black) if S-creat ≤ 0.7 mg/dL</td>
<td></td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²) = 144 × (Scr/0.7)−1.209 × 0.993age (× 1.15 if black) if S-creat &gt; 0.7 mg/dL</td>
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<tr>
<td><strong>Men:</strong></td>
<td></td>
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<tr>
<td>GFR (mL/min/1.73 m²) = 141 × (Scr/0.9)−0.411 × 0.993age (× 1.16 if black) if S-creat ≤ 0.9 mg/dL</td>
<td></td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²) = 141 × (Scr/0.9)−1.209 × 0.993age (× 1.16 if black) if S-creat &gt; 0.9 mg/dL</td>
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### RESULTS

In the present study, 28 patients were examined. The basic characteristics can be seen in Table 2. The average GFR estimated by different methods can be observed in Table 3.

The bias values of GFR measured through 6-hour urinary clearance compared to bio-impedance, MDRD, CG, and CKD-EPI formulas were 6.34, 9.65, 11.34, and 21.48, respectively. Also, error values of GFR measured through 6-hour urinary clearance compared to bio-impedance, MDRD, CG, and CKD-EPI formulas were 140%, 140%, 163%, and 128% respectively. The internal consistency of GFR values measured through 6-hour urinary clearance by the above methods were 0.782, 0.743, 0.626, and 0.683, respectively.
The bias values of GFR measured by bio-impedance compared to 6-hour urinary clearance, MDRD, Cockcroft, and CKD-EPI formulas were 6.34, 3.31, 5.01, and 15.14, respectively. Also, error values of GFR measured by bio-impedance compared to 6-hour urinary clearance, MDRD, Cockcroft, and CKD-EPI formulas were 140%, 28%, 60%, and 47% respectively. The internal consistency of GFR measured by bio-impedance values by the above methods were 0.782, 0.983, 0.939, and 0.893, respectively. These results can be seen in Figure 1.

**Table 2** Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Means ± SEM</th>
<th>Min-Max</th>
</tr>
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<tbody>
<tr>
<td>Age (year)</td>
<td>17.85 ± 60.30</td>
<td>(16-89)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>4.82 ± 26.36</td>
<td>(20-35)</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>0.86 ± 1.96</td>
<td>(0.8-4)</td>
</tr>
<tr>
<td>Serum Albumin (g/dL)</td>
<td>0.47 ± 2.86</td>
<td>(2.3-4.5)</td>
</tr>
<tr>
<td>Serum Urea (mg/dL)</td>
<td>57.02 ± 97.84</td>
<td>(32-263)</td>
</tr>
<tr>
<td>Urine Volume (ml/day)</td>
<td>347.19 ± 485.0</td>
<td>(100-1400)</td>
</tr>
<tr>
<td>Urine Creatinine (mg/6h)</td>
<td>125.37 ± 167.63</td>
<td>(22-538)</td>
</tr>
<tr>
<td>Urine Urea (mg/6h)</td>
<td>7577.76 ± 8136.84</td>
<td>(1000-22000)</td>
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**Table 3** GFR estimation

<table>
<thead>
<tr>
<th></th>
<th>Min-Max</th>
<th>Means ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl (ml/min⁻¹)</td>
<td>(3.5-119.4)</td>
<td>32.81 ± 32.06</td>
</tr>
<tr>
<td>BIA (ml/min⁻¹)</td>
<td>(13.6-95.7)</td>
<td>24.17 ± 38.40</td>
</tr>
<tr>
<td>MDRD/ml/min⁻¹</td>
<td>(15.5-101.5)</td>
<td>25.97 ± 41.71</td>
</tr>
<tr>
<td>CG/ml/min⁻¹</td>
<td>(13.1-114.9)</td>
<td>27.54 ± 43.40</td>
</tr>
<tr>
<td>CKD-EPI/ml/min⁻¹</td>
<td>(16.4-128.1)</td>
<td>30.95 ± 53.54</td>
</tr>
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</table>

CrCl: 6-hour creatinine clearance, BIA: bioimpedance analyzer, MDRD: The simplified refitted MDRD, CG: Cockcroft and Gault

**Figure 1** Comparison of GFR measured by CrCl with BIA estimated GFR

The bias values of GFR measured by bio-impedance compared to 6-hour urinary clearance, MDRD, Cockcroft, and CKD-EPI formulas were 6.34, 3.31, 5.01, and 15.14, respectively. Also, error values of GFR measured by bio-impedance compared to 6-hour urinary clearance, MDRD, Cockcroft, and CKD-EPI formulas were 140%, 28%, 60%, and 47% respectively. The internal consistency of GFR measured by bio-impedance values by the above methods were 0.782, 0.983, 0.939, and 0.893, respectively. These results can be seen in Figure 1.

**Figure 2** Comparison of GFR measured by CrCl with MDRD calculated GFR

The bias values of GFR measured by bio-impedance compared to 6-hour urinary clearance, MDRD, Cockcroft, and CKD-EPI formulas were 6.34, 3.31, 5.01, and 15.14, respectively. Also, error values of GFR measured by bio-impedance compared to 6-hour urinary clearance, MDRD, Cockcroft, and CKD-EPI formulas were 140%, 28%, 60%, and 47% respectively. The internal consistency of GFR measured by bio-impedance values by the above methods were 0.782, 0.983, 0.939, and 0.893, respectively. These results can be seen in Figure 1.

**Figure 3** Comparison of GFR measured by CrCl with CKD-EPI calculated GFR

DISCUSSION

This study showed that none of the formulas, including MDRD, Cockcroft and Gault, and CKD-EPI, could predict the CrCl correctly compared to 6-hour urine collection as standard. Also estimated GFR by bio-impedance did not reveal acceptable correlation with 6-hour urine collection. In spite of routine utilization of the three common formulas of CrCl and 24-hour urine collection in ICU, to the best of our knowledge, the capacity of these methods to precisely evaluate CrCl in critically ill patients with AKI was evaluated only in one study carried out by Bragadottir et al. (2013). They concluded that the minimum difference in calculating and measuring GFR was related to Cr-EDTA, and other methods did not have the appropriate capacity. Moreover, bias in GFR measured by

**Figure 2** Comparison of GFR measured by CrCl with MDRD calculated GFR

(Means : 36.88 ± 26.59 Bias: 9.65 Error(%): 140 Limits of agreement: -61.5/42.5) (ICC : 0.743 95% CI: 0.463/0.877)

**Figure 3** Comparison of GFR measured by CrCl with CKD-EPI calculated GFR

above methods were 0.782, 0.983, 0.939, and 0.893, respectively. These results can be seen in figure 1.
urinary creatinine is lower than that calculated by using MDRD and Cockcroft-Gault formulas. The main difference between Bragadottir’s study and this study is that Bragadottir was using Cr-EDTA as the standard method which has a more precise measuring capacity than 6-hour urine collection. It should be considered that measuring CrCl using 6-hour urine collection is more practical than Cr-EDTA method and is available for all hospitals. Also, it could calculate the CrCl more precise than formulas in patients with AKI. According to the guidelines of Kidney Disease: Improving Global Outcomes (KIDIGO) in 2012, the formulas proposed to calculate CrCl are validated in patients with CKD but are not specific for those with AKI. Therefore, precise calculation of CrCl in patients with AKI is a dilemma yet. However, because there is no special formula for this group of patients, the standardized formulas for patients with CKD are inevitably utilized.

In 2012, Kirwan et al. studied 51 patients who had AKI based on the AKIN criterion. The results of their study showed that calculating CrCl to measure GFR and evaluate renal function in critically ill patients with AKI is not accurate enough. In another study, Robert et al. compared urinary CrCl with inulin clearance in 20 patients under mechanical ventilation with stable hemodynamics, without inotropic support, and with acute renal dysfunction. The results of their study showed that there was a poor relationship between the two methods of 30-minute and 24-hour creatinine and inulin clearance.

Another issue relevant to the disagreement among the results of measuring CrCl by different methods is the existence of laboratory errors in both formulas and bio-impedance. However, since all methods have the same basis, i.e., the patient’s creatinine, and albumin, this error is likely to run in all methods and cannot be an appropriate reason for justifying the observed difference in measurements.

Within-method repeatability is significant in studies that compare two methods because repeatability of each method can restrict the level of agreement between them. Therefore, Bland and Altman’s analysis has provided certain criteria to examine the level of agreement between two methods. In an attempt to propose the criteria to examine the level of agreement between two methods, Critchley et al. suggested that for a new method to be accepted, the between-method error should be lower than 30%. They also indicated that intergroup error in each of the both methods and the standard method should be 20% or lower to reach a between-method error of 3%. In this study, the intergroup error was 28% and acceptable only between the two methods of MDRD and BioScan.
The confidence range of 95% was also between 7.8 and 14.5. However, since none of these two methods is used as a standard method for patients with AKI, this finding is not much reliable.

Although 24-hour CrCl is referred to as the standard method, due to its problems in sample collection and waste of time due to prolonged waiting time to see the results, 6-hour CrCl was used instead of 24-hour CrCl in this study. In previous studies in which urinary CrCl was measured using a shorter period of urine output collection from critically ill patients, there was a good relationship among the measured values compared to the longer period.

Estimation formulas are also restricted by serum creatinine as a filtration marker. Precise measurement of GFR based on serum creatinine required a stable state. An increase in serum creatinine level is only observable after a loss of a significant amount of kidney function; therefore, serum creatinine concentration leads to a decrease in GFR and is influenced by other factors that affect renal function. As a result, in unstable conditions, estimating GFR using creatinine-based equations provides incorrect estimations of renal function.

In this study, an appropriate result to estimate GFR was not achieved, it is still of top priority to find a method to measure CrCl in patients with AKI to regulate drug dosage and avoid treatment failure.

CONCLUSION

According to the results of the present study, it can be stated that neither electrical bio-impedance nor the formulas MDRD, Cockcroft and Gault, and CKD-EPI revealed an acceptable relationship with measuring CrCl by collecting 6-hour urine output as a standard method. Therefore, this group of patients needs a more precise and specific method to measure CrCl and GFR.

REFERENCES