Correction Formula for Creatinine Concentration with Glucose in Dialysate

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Objective: *Previous studies showed that high glucose in dialysate could interfere with creatinine measurement. This error might produce some mistakes in peritoneal dialysis (PD) treatment. The correction of creatinine is essentially needed.*
Material and Method: *Creatinine powder diluted in 0.1 N HCl was used as the standard reference. Different creatinine measurements obtained from unused dialysate solutions in various glucose concentrations were performed. Creatinine correction was performed by Twardowski's formula which was recommended by Nephrology Society of Thailand and by Tam's formula which utilized unused dialysate creatinine and glucose ratio. Comparison of the results in determination of membrane transport characteristics was based on the criteria proposed by Twardowski et al in used dialysate solutions derived from 17 CAPD patients with different approaches.*
Results: *The mean creatinine concentrations obtained from the standard creatinine solution and the above two correction methods were different. The mean creatinine derived from Twardowski's formula was the lowest. The correlation coefficients between glucose and creatinine interference obtained by direct measurement and by Twardowski's formula were high (r = 0.80-0.98) at all creatinine levels. However, the correlation between glucose and creatinine interference were significant only at creatinine concentrations of 2.9 and 17.5 mg%. Classification of membrane transport was discordant when different correction formulae were used.*
Conclusion: *Creatinine correction in dialysate was crucial. Creatinine correction with fresh dialysate creatinine and glucose ratio might be suitable in clinical practice.*

Keywords: *Creatinine correction, Dialysate, Glucose, Jaffe alkaline picrate method*

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Creatinine measurement in dialysate is essential to evaluate the adequacy of waste product removal and to determine the membrane solute transport characteristics by using the peritoneal equilibration test (PET). This test is useful to determine the dialysis prescription and to investigate the causes of ultrafiltration failure. PET is the ratio between creatinine in dialysis solution and plasma at certain hour (D/Pcr). Therefore, the precision of creatinine measurement is crucial.

The value of creatinine is routinely measured by Jaffe alkaline picrate reaction. The disadvantage of this method is the interference of measurement by some substances, including glucose[1]. Glucose probably reacts with picrate to produce chromogen, resulting in artificial high creatinine result[2]. In clinical biological fluid, glucose concentrations are not high and the interferences are not significant. In dialysate, particularly in solution with 4.25% dextrose, the error in creatinine measurement could not be ignored.

This glucose interference with creatinine measurement could be coped with the followings: (1) Creatinine is measured by highly specific methods for creatinine such as isotope-dilution mass spectrometry (IDMS) and high performance liquid chromatography (HPLC)[1]. Both tests are sophisticated and not available in clinical practice, (2) Creatinine is determined by an enzymatic method that is also interfere by glucose, even in a lesser value[2,3], and (3) Measured creatinine is

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modified by certain correction formulae such as the one reported by Twardowski et al[4] and is recommended by the Nephrology Society of Thailand[5]. Another correction formula by Tam et al calculated correction factor by using ratio between creatinine and glucose in fresh dialysate[6]. Unfortunately, the standard correction formula is not available. Farrell and Bailey[7] found that many factors could affect the result of creatinine measurement and the correction formula should be individualizd.

The aims of the present study were to compare and evaluate the determination of membrane characteristics based on different correction formulae.

Material and Method

There were two types of specimens as following:

(1) Standard creatinine specimens (without glucose) were prepared by using creatinine powder (BDH chemical Ltd) diluted in 0.1 N HCl to a concentration of 100 mg%, and then diluted with 0.1 N HCl to a series of concentration of 3, 6, 9, 12, 15, and 18 mg% by weight. Creatinine powder was also diluted in Dianeal PD-2 with 4.25% Dextrose (Baxter (India) Pvt, Ltd., Haryana, India) to a series of concentration of 3, 6, 9, 12, 15, and 18 mg% by weight as well. Each creatinine concentration in dialysate and six glucose concentrations were performed, ranging from 390-4,200 mg%. All specimens were determined for creatinine and glucose.

(2) Used dialysate samples were obtained from 17 patients' abdominal cavity during the PET as proposed by Twardowski et al[4]. This brief procedure was followed, the patients performed PD as usual. At dialysis unit, the dialysate was drained, then fresh dialysate with dextrose 2.5% 2 liters was infused and the time was recorded as 0. At the time 0, and the end of the 2nd and 4th hour of dwell, the dialysate was drained and measured for creatinine and glucose. Plasma was drawn and sent for creatinine and glucose at the end of the 2nd hour of dwell.

Sample measurement

Creatinine was measured by Jaffe alkaline picrate method by Konelab 60 analyzer (Thermo Scientific, Finland). Glucose was measured using enzymatic glucose oxidase method with the same instrument. The samples were measured in duplication.

Calculations

1. Interference of creatinine measurement was calculated by the value of creatinine obtained from standard creatinine solution in 0.1 N HCl minus with the value of creatinine obtained from dialysate with glucose at the contemporaneous creatinine concentration.

2. Creatinine corrections were calculated by using the Twardowski's(4) formulae. (D-Cr_{TW}) and the Tam's formula[6], (D-CrT),

- D-Cr_{TW} (mg/dl) = measured D-Cr (mg/dl)-[D-glucose (mg/dl) x 0.0005]

- D-CrT (mg/dl) = measured D-Cr (mg/dl)-[(Cr of unused dialysate/glucose of unused dialysate) x D-glucose (mg/dl)]; Cr = 0.7 mg/dl and glucose = 4,376 mg/dl in Hat Yai Hospital.

3. Characteristics of membrane transport were determined by D/Pcr at the end of the 2nd and 4th hour (D/Pcr2 and D/Pcr4, respectively) using the criteria suggested by Twardowski et al[4].

Statistical analysis

Data were presented as mean $\pm$ standard deviation. Either Student-t test or paired sample test was used for comparison where appropriate. The association between parameters was analyzed by Pearson or Spearman correlation coefficient. A p-value less than 0.05 was considered as statistically significant. Analysis were performed by using SPSS 11.5 (SPSS Inc, Chicago, IL USA).

Results

Creatinine concentrations by different correction methods in unused dialysate

As shown in Table 1, the mean values of creatinine derived from 3 different methods were significantly different when compared with the standard creatinine. The mean creatinine concentration of direct measurement was the highest while the value derived from the Twardowski's formula was the lowest.

The patterns of creatinine interference with glucose were different among the three methods. The correlation coefficients between glucose and creatinine interference obtained by glucose and that obtained by the Twardowski's formula were high (r = 0.80-0.98) at all creatinine levels (Table 1). In contradistinction, the correlation between direct measurement and the Tam's formula were significant only at creatinine concentrations of 2.9 and 17.5 mg/dl. Of note, creatinine interference was increased with the increasing level of glucose concentrations in both direct measurement and the Twardowski's formula. However, the direction of correlation of creatinine interference

Table 1. The mean creatinine concentrations obtained from standard solution and that in dialysate solution and correlation coefficient between creatinine interference and glucose concentration

Standard Cr (mg/dl)	Directly measured Cr (mg/dl)		$D\text{-}Cr_{TW}$** (mg/dl)		$D\text{-}Cr_{T}$** (mg/dl)	
	mean (SD)	r (p-value)	mean (SD)	r (p-value)	mean (SD)	r (p-value)
2.9	2.91 (0.39)	- 0.98*	1.81 (0.39)	0.98*	2.58 (0.17)	0.88*
5.8	6.02 (0.27)	- 0.89*	4.90 (0.52)	0.97*	5.68 (0.13)	0.15
8.3	8.90 (0.24)	- 0.91*	7.88 (0.52)	0.98*	8.66 (0.10)	0.04
11.5	11.64 (0.36)	- 0.80	10.52 (0.56)	0.97*	11.31 (0.15)	0.15
14.5	14.59 (0.36)	- 0.94*	13.50 (0.38)	0.95*	14.27 (0.17)	0.74
17.5	17.48 (0.36)	- 0.97*	16.39 (0.36)	0.97*	17.16 (0.17)	0.83*

* $p < 0.05$, ** Cr-TW and Cr-T, creatinine obtained by Twardoski's and Tam's formula, respectively

was opposite.

Creatinine concentration by different correction methods in used dialysate from CAPD patients

Seventeen CAPD patients, of whom 7 were men (47%), were recruited in the PET. The mean age was 52.2 $\pm$ 19.2 years old. The body weight after draining was 53.96 $\pm$ 13.43 kg. Plasma creatinine and glucose at the end of 2nd hour of study were 9.1 $\pm$ 4.1 mg/dl and 203.9 $\pm$ 21.7 mg/dl, respectively. Dialysate creatinine and glucose levels by direct measurement at the end of the 2nd hour of dwelling time were 4.7 $\pm$ 2.3 mg/dl and 1,236.3 $\pm$ 203.1 mg/dl, respectively. Dialysate creatinine and glucose concentrations after dwelling 4 hours were 6.4 $\pm$ 2.9 mg/dl and 767.9 $\pm$ 172.9 mg/dl, respectively. As illustrated in Table 2, the mean creatinine concentrations obtained by the two correction formulae were different from the direct measurement.

As detailed in Table 3, determination of membrane transport characteristics was discordant based on the creatinine obtained from different methods. When Twardowski formula was used, the prevalence of high transporter was the lowest while the prevalence of low transporter was the highest.

Table 2. Mean creatinine concentrations obtained from different correction methods after the 2nd and 4th dwelling

Method	D-Cr at 2 hr	D-Cr at 4 hr
Directly measured Cr (mg/dl)	4.7 $\pm$ 2.3	6.4 $\pm$ 2.9
$D\text{-}Cr_{TW}$ (mg/dl)	4.0 $\pm$ 2.3*	6.0 $\pm$ 2.9*
$D\text{-}Cr_{T}$ (mg/dl)	4.5 $\pm$ 2.3*	6.3 $\pm$ 2.9*

* $p < 0.05$ compared with direct measurement

Discussion

The results in the present study have shown that glucose in dialysate positively interfered creatinine measurement with Jaffe alkaline picrate method in a linear fashion. The creatinine interference with glucose was minimal with creatinine obtained from correction with the ratio between creatinine and glucose in unused dialysate.

The Jaffe alkaline picrate method is the most common method for creatinine measurement in clinical practice. The method is easy to perform and low cost. However, the major disadvantage of this method is the interference by certain substances, including glucose[1]. Therefore, the error of creatinine measurement in dialysate with high glucose has to be concerned. Although, the difference between creatinine obtained from different correction method is not high, for example, the differences between the values obtained from Twardowski's and Tam's formulae were only 0.5 and 0.3 mg/dl at the 2nd and 4th hour of dwelling (Table 2), this could tremendously affect the determination of peritoneal membrane characteristics (Table 3) and might induce misleading in dialysis treatment.

In general correction equation, corrected Cr = measured Cr- (correction factor x glucose). The problem is what the optimal factor is. The two most common methods to correct creatinine in clinical practice are either the fixed number such as 0.0005 as recommended by Twardowski et al or the number derived by calculating the ratio between creatinine and glucose in unused dialysate, as suggested by Tam et al the value of which was 0.00016 (0.7/4,376) in the present study.

Table 3. Characteristics of peritoneal membrane transport based on D/Pcr obtained from different correction methods after 2nd and 4th hour dwelling

Characteristic	Directly measured Cr		$D\text{-}Cr_{TW}$		$D\text{-}Cr_{T}$	
	2nd hr	4th hr	2nd hr	4th hr	2nd hr	4th hr
High transporter	4	5	1	3	4	5
HA transporter*	6	7	7	6	6	5
LA transporter*	5	5	3	6	4	7
Low transporter	2	0	6	2	3	0

* HA = high average, LA = low average

The obviously different values of correction factors, 0.0005 vs. 0.00016, could explain the disparity in creatinine concentrations from the two methods. Recently, Miller et al[8] found that interference of creatinine measurement was mainly due to the machine used. The Twardoski's study[4], conducted more than 20 years ago, used ABA-200 Automated Bichromatic Analyzer for creatinine measurement while the present study used the Konelab 60 analyzer (Thermo Scientific, Finland).

Mak et al[2] demonstrated that interference was dependent on both glucose and creatinine concentrations. The present study showed that the interference was also affected by the creatinine concentration as well when using both correction formulae. This phenomenon was minimized by using the correction factor derived from Tam's formula. The interference was dependent only when the creatinine concentrations were very low or very high (2.9 and 17.5 mg/dl respectively) (Table 1). As such, the measured creatinine concentrations at the 2nd and 4th of dwelling time in the present study were 4.7 $\pm$ 2.3 and 6.4 $\pm$ 2.9 mg% respectively, of which both values should not be disturbed. Therefore, correction with Tam's formula should be appropriate in clinical practice.

The limitation of the present study was the gold standard for creatinine. Because the IDMS and HPLC are not available. The authors used the creatinine power diluted in 0.1 N HCl solution as a gold standard. The human error in dilution may occur. However, the 0.1 N HCl did not interfere with the creatinine measurement. Therefore, this creatinine should be acceptably reliable and can be used as the reference method.

In conclusion, in case of creatinine measurement with Jaffe alkaline picrate method, the present study showed that the correction factor could affect determination of solute transport characteristics. The authors proposed that the correction formula with fresh dialysate creatinine and glucose ratio might be suitable in clinical practice. However, the most appropriate method for correction needs further studies.

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Potential conflicts of interest

None.

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สูตรการปรับความเข้มข้นคริแอทินินในน้ำยาล้างช่องท้องด้วยกลูโคส

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วัตถุประสงค์*: การศึกษาพบว่าการวัดคริแอทินินในน้ำยาล้างช่องท้องที่มีความเข้มข้นของน้ำตาลสูงเกิดความคลาดเคลื่อน ทำให้เกิดความผิดพลาดในการพิจารณาการรักษา การแก้ไขให้ถูกต้องเป็นสิ่งจำเป็น*

วัสดุและวิธีการ*: ความเข้มข้นของผงคริแอทินินละลายใน 0.1 นอร์มัล กรดไฮโดรคลอริกเป็นสารละลายมาตราฐานสำหรับอ้างอิง โดยศึกษาในน้ำยาล้างไตที่มีความเข้มข้นของคริแอทินินและน้ำตาลระดับต่างๆ โดยปรับค่าคริแอทินินตามสูตรที่สมาคมโรคไตแห่งประเทศไทยเสนอแนะและการวัดหาสัดส่วนระหว่างคริแอทินินและกลูโคส จากนั้นจำแนกชนิดของเยื่อบุช่องท้องในผู้ป่วย 17 รายตามเกณฑ์ที่เสนอโดยทวาโดวสกี้และคณะ*

ผลการศึกษา*: คริอะตินีนในน้ำยาล้างไตที่ปรับด้วยสูตรทั้งสองแตกต่างกัน โดยค่าที่เสนอโดยสมาคมมีค่าต่ำสุด ความสัมพันธ์ระหว่างความคลาดเคลื่อนของการวัดคริแอทินินที่ได้จากสูตรที่สมาคมเสนอแนะ และวัดโดยตรงกับระดับกลูโคสเป็นเส้นตรงโดยมีค่าความสัมพันธ์ตั้งแต่ 0.80-0.98 ส่วนการแก้ไขคริแอทินินด้วยน้ำยาใหม่ไม่พบความสัมพันธ์ดังกล่าวยกเว้นที่ความเข้มข้นของคริแอทินิน 2.9 และ 17.5 มิลลิกรัม/เดซิลิตร*

สรุป*: การแก้ไขคริแอทินินในน้ำยาล้างช่องท้องเป็นสิ่งจำเป็น การแก้ไขโดยอาศัยสัดส่วนของคริแอทินิน และกลูโคสน่าจะเหมาะสมในเวชปฏิบัติ*