Accuracy of Using 30-Minute Post-Dialysis BUN to Determine Equilibrated Kt/V

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Background: The equilibrated Kt/V (eKt/V), a clinical index of hemodialysis adequacy, can be calculated by several means. The commonly used methods are second generation of natural logarithm by Daugirdas and rate adjustment methods. However, these two methods used immediate post-dialysis blood urea nitrogen (BUN) (C0). The authors investigated the accuracy of 30-minute post-dialysis BUN (C30), equilibrated BUN at the end of urea rebound time, to determine the eKt/V.

Material and Method: We measured 7 values of eKt/V in 30 hemodialysis sessions by using the 5 following methods: 1). Empirical method (Emp) 2). Smye method (Sm) 3). Daugirdas method using C0 and C30 (Dau0, Dau30) 4). Rate adjustment method using C0 and C30 (Rate0, Rate30) 5). Double Pool urea kinetic model (DP), and compared with the gold standard values calculated by the modified Direct Dialysate Quantitative method (mDDQ).

Results: All patients had adequate hemodialysis with $eKt/V (mDDQ) = 1.80 \pm 0.22$. Compared with mDDQ, the median of absolute difference of eKt/V were Rate30 (0.10); Dau30 (0.11), Rate0 (0.11), Sm (0.11); Emp (0.13); DP (0.15); Dau0 (0.35) while the correlation coefficient (r^2) were 0.926, 0.948, 0.785, 0.629, 0.551, 0.833, and 0.806 respectively.

Conclusion: By using 30-minute post-dialysis BUN to calculate, the values of eKt/V by Daugirdas and rate adjustment methods were associated with better accuracy and correlation than immediate post-dialysis BUN. In the demand of the accurate eKt/V measurement, the Dau30 and Rate30 may be the suitable method to determine the eKt/V in clinical hemodialysis.

Keywords: Hemodialysis adequacy, Equilibrated Kt/V, 30-minute post-dialysis BUN

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At present, the adequacy of hemodialysis is usually evaluated by determining the value of $Kt/V^{(1-5)}$. This is the proportion of urea clearance volume from the body normalized for urea distribution volume. It is considered that the calculation of the value of Kt/Vin the dialysate aspect by mean of modified direct dialysate quantitative method (mDDQ) is the gold standard method^(6,7). There are, however, difficulty and inconvenience in determination and calculation of Kt/VV by this method. Several alternative methods^(8,9) to calculate the values of Kt/V in blood side have been discovered and these include fixed volume single pool (FVSP) urea kinetic model (UKM), variable volume single pool (VVSP) UKM, variable volume double pool (VVDP) UKM, empirical method, Smye method, second generation of natural logarithm of Daugirdas, and rate adjustment method.

The important problem in calculating the value of Kt/V in blood side is the urea rebound effect^(10,11). This is caused by the access recirculation, cardiopulmonary recirculation, compartmental effect, double pool effect and regional blood flow effect. The double pool effect is the unbalance of urea level between intracellular and extracellular compartment. The regional blood flow effect is the unbalance of blood quantity supplied

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to each organ and the urea quantity accumulated in such organ⁽¹²⁻¹⁴⁾. The recirculation problem could be solved by a special method in blood sampling while the problem of compartmental effect would be partially solved by using the equilibrated 30-minute post-hemodialysis blood urea nitrogen (BUN) to calculate the values of equilibrated Kt/V (eKt/V)⁽²⁾. From the recent HEMO pilot study⁽¹⁵⁾, it was found that the rate adjustment method for determining the value of eKt/V in blood aspect was able to solve the problem of regional blood flow and could provide more advantage than other methods. According to the report, however, the equilibrated BUN had not been used in calculating the values of eKt/V in some formulas. Moreover, the studies were performed in hemodialysis patients attending hemo dialysis (HD) 3 times a week.

In chronic hemodialysis patients receiving HD 2 times a week, the authors have studied the hemodialysis adequacy by determining the values of eKt/V derived from various methods of blood calculation by using the equilibrated BUN and compared such eKt/V values with that obtained by the mDDQ method.

Material and Method

Patients

The present study was conducted in 30 hemodialysis sessions of 23 chronic patients who had been treated with hemodialysis twice a week at Chulalongkorn University Hospital. This practice is common in developing countries like Thailand where hemodialysis service is still inadequate. All patients were 15 years or older and had been hemodialysis for more than 1 month. Patients were excluded from the present study if they had heart failure, fever, concurrent infection or other acute systemic illness, and had venovenous access such as double lumen catheter as a vascular access. The protocol was approved by the Ethical Committee for Clinical Research Study of the Faculty of Medicine, Chulalongkorn University Hospital, Bangkok, Thailand. Informed consents were obtained from all the studied patients.

The studies were performed on the second hemodialysis session of the week using Fresenius 4008E machines. The HD period was 4-5 hours; the blood flow rate was 200-450 mL/min while the dialysate flow was 500-800 mL/min.

Pre-dialysis BUN was obtained from the arterial arterio venous (AV) fistula needle prior to hemodialysis. Post-dialysis BUN was collected from the venous AV fistula needle immediately after cessation of HD. Equilibrated BUN was taken from the venous

AV fistula needle at 30 minutes after HD was completed. All blood specimens were run in duplicate and the average values were used for calculation. Hematocrit was measured from the pre-dialysis blood.

All dialysate output during a HD session was collected in a pre-weighed container. At the end of HD session, two 10-ml aliquots of the pooled dialysate were also collected. All aliquots were kept at -20°C and sent for urea within 24 hours. The volume of dialysate was calculated by using a specific gravity of dialysate at 32° C of $1.003^{(16)}$.

Calculation of eKt/V

1. Empirical Method (Emp)

By this method, the values of eKt/V were determined by direct substituting the values of K, t, and V. By using the blood samplings from arterial and venous port after starting HD 30-minute, the value of K from in vivo dialyzer urea clearance⁽¹⁷⁻¹⁹⁾ was calculated from the following formula and was adjusted for the results of water content in plasma and erythrocyte equivalent to 93% and 72%, respectively.

- $Q_{\rm p}$ = plasma flow rate (mL/min)
- $Q_{\rm R}$ = blood flow rate (mL/min)
- Q_{e} = ultrafiltration rate (mL/min)
- K = in vivo urea clearance of dialyzer (mL/min)
- $C_A = BUN$ level from arterial port (mg/dL)
- $C_v = BUN$ level from venous port (mg/dL)
- Hct = Hematocrit level (%)

The value of V was determined from the value of anthropometric urea distribution volume from bio electrical impedance method (BEI)^(20,21), which is the method to study total body water in chronic renal failure patients and is more accurate than other methods. The value of V from BEI-derived formula was derived according to the following equation:

 $TBW = -(0.07493713 \text{ x age}) - (1.01767992 \text{ x male}) + \\ (0.12703384 \text{ x height}) - (0.04012056 \text{ x weight}) + \\ (0.57894981 \text{ x diabetic}) - (0.00067247 \text{ x weight}^2) \\ - (0.0348146 \text{ x age x male}) + (0.11262857 \text{ x male} \\ \text{ x weight}) + (0.00104135) \text{ x age x weight}) + \\ (0.00186104 \text{ x height x weight})$

equation 2

If patients were male or diabetic, the "male" or "diabetic" value would be 1, otherwise it was reinstituted with 0.

2. Smye method (Sm)^(22,23)

The value of equilibrated BUN (C_{eq}) was calculated from the Smye method according to the equation as follows:

$$C_{eq} = C_0 x Exp \left[-\left\{ t / (t - t_s) \right\} x Ln \left(C_s / C_t\right)\right]$$

equation 3

- $C_s = BUN$ at 70-minute after starting HD
- = time at 70-minute after starting HD

The value of C_{eq} was utilized to calculate the value of Kt/V (Sm) by using the formula of second generation of natural logarithm of Daugirdas from equation 4.

3. The second generation of natural logarithm formula of Daugirdas (Dau)^(24,25)

The single pool urea kinetic model was calculated from the second generation of natural logarithm of Daugirdas according to the following equation:

$$Kt/V = -Ln (R - 0.008 x t) + (4 - 3.5 x R) x UF / W$$

equation 4

$$R = Ct/C0$$

- Ct = post-dialysis BUN (milligram/decilitre)
- C0 = pre-dialysis BUN (milligram/decilitre)
- Ln = natural logarithm
- = hemodialysis time (hour) t
- UF = quantity of ultrafiltrate (litre)
- W = post-dialysis weight (kilogram)

The value of Kt/V (Dau0) was determined by using immediate, non-equilibrated, post-dialysis BUN while the value of Kt/V (Dau30) was determined by using the equilibrated BUN (30-minute post-HD) to substitute the value of post-dialysis BUN.

4. Rate adjustment method (Rate)^(26,27)

The rate adjusted Kt/V was obtained by the following equation.

 ${}_{e}^{Kt/V} = {}_{sp}Kt/V - 0.6 x \left({}_{sp}Kt/V \right) / t + 0.03 \quad equation 5 \\ {}_{sp}Kt/V = single \ pool \ Kt/V$

The values of Dau0-Kt/V and Dau30-Kt/V were used to calculate the values of Kt/V (Rate0) and Kt/V (Rate30), respectively.

5. Double pool urea kinetic model method (**DP**)⁽²⁸⁾

The computer program was created to calculate the value of Kt/V according to the method of VVDP UKM in the type of variable extracellular fluid volume (VE)⁽⁸⁾. The program would calculate by mean of the numerical iterative solution method to adjust the values of VE and G. The computer language used was C ++ created on the program of C++ BUILDER for Windows. The value of V was calculated by the calculus method from computer program created by using the value of $K_{cu} = 800 \text{ mL/min}^{(29,30)}$ and prescribed $V_1: V_E = 2:1$. The value of K derived from calculation of equation 1 was then taken to calculate the value of Kt/V (DP) by using equilibrated BUN (30- minute post-HD) to substitute the value of post-dialysis BUN.

6. Modified direct dialysate quantitative method (mDDQ)

The value of Kt/V (mDDQ) was calculated by using the value of urea clearance quantity (U) (the multiplication product of total urea derived from dialysate and total dialysate volume) according to the method of Milchesky⁽⁶⁾. The double pool kinetic effect was adjusted and the result of ultrafiltration was corrected as the mDDQ method⁽³¹⁾ according to the following equation.

$$V = \frac{U - G(t + 30) - UF(C_0 / 0.93)}{C_0 / 0.93 - C_{eq} / 0.93}$$

equation 6

- U = total urea removal in dialysate (mg)
- = HD time (min) t

V

- G = urea generation rate (mg/min)
- UF = ultrafiltrate volume (mL)
- 30 = time of urea rebound
- 0.93 = the multiplier to transform serum to be plasma water concentration

$$C_0 = \text{pre-dialysis BUN} (\text{mg/dL})$$

$$C_{ac}$$
 = equilibrated BUN of 30-minute post-HD (mg/dL)

$$G = \frac{V(C_0/0.93 - C_{torr}/0.93 + Wtg(C_0/0.93) + C_uV_u)}{t_{id} - 30}$$

equation 7

- Wtg = interdialytic weight gain (g)
 - T_{id} = time during each HD (min)
- V_u^{n} = urea concentration in urine (mg/dL) V_u^{n} = urine volume (mL)
- C_{tcorr} = previous 30-minute post HD BUN estimated from BUN rebound of current HD (mg/dL)

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From the equation 6 and 7, it was able to solve the equation to obtain the value of V and G

$$K = \frac{U \ln (C_{eq} / C_0)}{t (C_{eq} - C_0) / 0.93}$$

equation 8

K = whole body urea clearance (mL/min)

Then, the value of K and V were taken to directly calculate the value of Kt/V.

Data analysis

1. The standard method used to compare with other methods was the value of eKt/V calculated from the mDDQ method by using equilibrated BUN from sample of blood compiled at 30-minute post-HD.

2. The created computer program was used to adjust iterative solving of VVDP UKM. The value of post-dialysis BUN was determined by using the values of V_E and G differed from the value of actually measured post-dialysis BUN by less than 0.1%.

3. The values of Kt/V calculated from various methods were compared with the mDDQ method by using Pearson correlation coefficient from SPSS7.5 program for Windows. Statistical significance was considered when p < 0.05.

Results

The values of Kt/V were determined in 30 hemodialysis sessions of 23 chronic twice-a week hemodialysis patients, 8 males and 15 females, with the average age of 48 ± 13 (mean \pm SD) years old and average body weight of 51 ± 8 kg. The residual renal function represented by the value of creatinine clearance was averaged 1 ± 0.6 mL/min. The underlying etiologies of chronic renal failure were chronic glomerulonephritis (8), diabetes mellitus (4), obstructive uropathy (1), sys-

temic lupus erythromatosus (1), congenital urogenital anomaly (1), and unidentified causes (7).

Table 1 details the average values of Kt/V calculated from several methods. By the mDDQ method, all patients had adequate hemodialysis with the Kt/V values of 1.80 ± 0.22 .

The values of Kt/V of each hemodialysis derived from several methods were compared with the mDDQ-derived value by creating a graph that could be able to determine the relation of linear regression analysis as follows: 1) comparison of the empirical method (Emp) and mDDQ method (Fig. 1). 2) comparison of the method of second generation of natural logarithm of Daugirdas as calculated by using the immediate post-dialysis BUN (Dau₀) and 30-minute post-dialysis BUN (Dau₃₀) and the mDDQ method (Fig. 2). 3) comparison of the Smye method (Sm) and mDDQ method (Fig. 3). 4) comparison of the VVDP method (DP) and mDDQ method (Fig. 4). 5) comparison of the rate adjustment method as calculated by using the immediate post-dialysis BUN (Rate_o) and 30-minute post-dialysis BUN (Rate₂₀) and mDDQ method (Fig. 4, 5).

 Table 1. The values of Kt/V derived from various methods

Method	Values of Kt/V \pm SD*
mDDQ Emp Sm Dau0 Dau30 Rate0 Rate30 DP	$\begin{array}{c} 1.80 \pm 0.22 \\ 1.86 \pm 0.25 \\ 1.83 \pm 0.23 \\ 2.17 \pm 0.25 \\ 1.91 \pm 0.24 \\ 1.92 \pm 0.22 \\ 1.69 \pm 0.22 \\ 1.68 \pm 0.24 \end{array}$

* SD = standard deviation

 Table 2. The median of absolute difference and correlation coefficient of the values of Kt/V as calculated from several methods and mDDQ method

Comparison between method	Median of absolute difference between both methods	Coefficient of determination (r ²) between both methods
Emp vs mDDQ	0.13	0.551
Sm vs mDDQ	0.11	0.629
Dau0 vs mDDQ	0.35	0.806
Dau30 vs mDDQ	0.11	0.948
Rate0 vs mDDQ	0.11	0.785
Rate30 vs mDDQ	0.10	0.926
DP vs mDDQ	0.15	0.833



Fig. 1 Comparison of eKt/V between empirical method (Emp) and mDDQ method



Fig. 2 Comparison of eKt/V between the second generation of natural logarithm of Daugirdas method, as calculated by using the immediate post-dialysis BUN (Dau0) and 30-minute post-dialysis Bun (Dau30), and mDDQ method

Table 2 shows the median of absolute difference (M.A.D.) and correlation coefficient of determination(r^2) between the values of Kt/V obtained from various methods and the ones from the mDDQ method. The values of Kt/V with the lowest M.A.D. and high C.C. were derived by the Rate₃₀ and Dau₃₀ methods.

Discussion

In the present study, the values of blood side Kt/V calculated by several methods were compared with the dialysate side Kt/v determined by the mDDQ method that is considered as the gold standard to calculate Kt/V^(8,32). The results demonstrated that the



Fig. 3 Comparison of eKt/V between Smye method (Sm) and mDDQ method



Fig. 4 Comparison of eKt/V between the VVDP UKM method (DP) and mDDQ method



Fig. 5 Comparison of eKt/V between the rate adjustment method, as calculated by using the immediate post-dialysis BUN (Rate0) and 30-minute post-dialysis BUN (Rate30), and mDDQ method

Rate30 and Dau30 methods provided the lowest values of median of absolute difference and highest values of correlation coefficient (Table 2, Fig. 2, 5).

The empirical method, which is considered as a direct method and is easy to understand, provided the appropriate value of Kt/V (M.A.D. = 0.13) but the lowest value of correlation coefficient of determination (r^2 = 0.551) (Fig. 1). As such, the empirical method is not the appropriate method to calculate the actual delivered Kt/V. This method may not concern the urea level actually reduced in the body. However, this method is useful in the starting HD period to adjust the important variables including type of dialyzer and time of HD to correspond with each patient.

The equation of Daugirdas has been developed by using the principle of variable volume single pool urea kinetic model from the values of Kt/V = -In R in fixed volume single pool model to adjust the confounder resulting from urea generation rate and ultrafiltration. Consequently, it has been developed to be the second generation of natural logarithm of Daugirdas that can be used to calculate the values of Kt/V in the broader range, 0.6-2.6. The present study suggested that the eKt/V of the Dau30 method, using equilibrated BUN to reduce the confounder resulting from urea rebound provided low value of M.A.D. and high value of r^2 In contrast, the calculation of Kt/V by the Dau0 method using immediate post-dialysis BUN, caused more errors (Table 2, Fig. 2). The Dau0 method was overestimated Kt/V by 0.35, which may cause danger in clinical practice.

Even though, the use of equilibrated BUN would reduce the confounder resulting from urea rebound it could also cause an inconvenience in practical aspect. Thus, in the Smye method, the additional intradialytic blood sampling at 70-minute after starting HD was used to estimate equilibrated BUN. It was reported that the Smye method could reduce errors in calculating the value of Kt/V of single pool urea kinetic model when compared with the double pool urea kinetic model by more than 50%⁽²³⁾. In the present study, although the Smye method could provide a comparably accurate value as the Dau30 and Rate30 methods but the relation with the value of mDDQ-derived Kt/V method was much lower than other methods ($r^2 = 0.629$) (Table 2, Fig. 3).

The VVDP was the method to calculate the value of Kt/V by correcting the value of V to be more equivalent with the actual value. In this respect, it was based on the spreading of urea in plasma and cell, extracellular and intracellular. In the present study, the DP method provided moderate accuracy (M.A.D. = 0.15) as well as moderate correlation with the value derived from mDDQ method ($r^2 = 0.833$) (Table 2, Fig. 4).



Fig. 6 Difference between the Rate0 method and Rate30 method in correction the effect of compartmental effect of urea rebound

The rate adjustment method used the single pool Kt/V to estimate the value of equilibrated Kt/V. This method has been developed from regional blood flow model by finding that the errors of the value of Kt/ V was related to the HD velocity (K/V)⁽²⁶⁾ (equation 5). In the present study, the value of Kt/V derived by Rate0 method provided good accuracy (M.A.D. = 0.11) and high correlation with mDDQ method (r^2 = 0.785). When using 30-minute post-dialysis BUN, the Rate30 method, it was found that the value of Kt/V was more accurate and higher correlative with mDDQ method (M.A.D. = 0.10, r^2 =0.926) (Table 2, Fig.5). Therefore, it was distinctively shown that flow-volume (regional blood flow) disequilibrium and double pool effect caused the compartmental effect of urea rebound. It was hypothesized that the Rate0 method would help to solve the confounder from flow-volume disequilibrium as the major aspect and the Rate30 method, which was the method jointly used to equilibrated BUN with the rate adjustment method, would solve the problem of both factors (Fig. 6). This result is in agreement with the study of HEMO pilot study⁽¹⁵⁾, which found that the rate adjustment method was the most accurate method in calculating the values of eKt/V. Of note, the HEMO pilot study used only the Rate0 method but not the Rate30 method.

The hemodialysis adequacy, measured by eKt/V, is related with morbidity and mortality in chronic hemodialysis patients⁽³³⁾. Although the higher eKt/V above the recommendation did not show obvious major benefit, the lower eKt/V should be avoided⁽³⁴⁾. This suggests that the accurate method is required to determine eKt/V. Using the immediate post-dialysis BUN usually resulted in overestimation of eKt/V, whereas the 30-minute post-dialysis BUN can correct this error (Table 2). Recently, in the rate equation, it was found that the use of the blood drawn immediately or 20-second post-dialysis caused a lowering in the slope coefficient for rate of dialysis (K/V) from 0.6 to 0.39⁽³⁵⁾. As such, for the vigorous measurement, the equilibrated BUN should be used to yield the accurate eKt/V.

Conclusion

This comparative study of using both values of immediate and 30-minute post-dialysis BUN to determine equilibrated Kt/V by various methods, demonstrates a newer method to correct the effect of compartments by regional blood flow of urea rebound. Utilizing equilibrated BUN to calculate equilibrated Kt/ V by Daugirdas and rate adjustment methods were associated with better accuracy and correlation. In the demand of the accurate equilibrated Kt/V measurement, Daugirdas and rate adjustment methods, using 30minute post-dialysis BUN, would be the suitable methods to determine the equilibrated Kt/V in hemodialysis.

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ความถูกต้องของการใช้ค่ายูเรียในเลือดที่ 30 นาทีหลังเสร็จสิ้นการฟอกเลือดเพื่อประเมินค่าสัดส่วน อีควิลิเบรทเคทีต่อวี

ธนิต จิรนันท์ธวัช, เกรียง ตั้งสง่า, สมชาย เอี่ยมอ่อง

ที่มา: ค่าสัดส่วนอีควิลิเบรทเคทีต่อวี (eKt/V) เป็นดัชนีทางคลินิกที่ใช้ประเมินความเพียงพอของการฟอกเลือด วิธีหาค่า eKt/V ที่นิยมใช้คือวิธี Second generation of natural logarithm โดย Daugirdas และวิธี Rate adjustment อย่างไรก็ตามทั้งสองวิธีนี้ใช้ค่ายูเรียหลังสิ้นสุดการฟอกเลือดทันที (C0) ในการคำนวณ การศึกษานี้เพื่อประเมินความ ถูกต้องของการใช้ค่ายูเรียในเลือดที่ 30 นาทีหลังเสร็จสิ้นการฟอกเลือด (C30) ซึ่งเป็นระยะเวลาที่สิ้นสุดภาวะ urea rebound มาใช้คำนวณค่า eKt/V

วัสดุและวิธีการ: คำนวณค่า eKt/V จากการฟอกเลือด 30 ครั้ง โดยใช้วิธีคำนวณ 5 วิธี รวม 7 ค่า คือ 1. วิธี Empirical (Emp) 2. วิธี Smye (Sm) 3. วิธี Daugirdas โดยใช้ค่า C0 และ C30 (Dau0, Dau30) 4. วิธี Rate adjustment โดย ใช้ค่า C0 และ C30 (Rate0, Rate30) 5. วิธี double pool urea kinetic model (DP) นำไปเทียบกับวิธีมาตรฐานคือ modified direct dialysate quantitative (mDDQ)

ผลการศึกษา: ผู้ป่วยได้รับการฟอกเลือดที่เพียงพอโดยมีค่า eKtV (mDDQ) =1.80 <u>+</u> 0.22 วิธีที่มีค่ามัธยฐานของ ความแตกต่างสมบูรณ์ของค่า eKtV เทียบกับวิธี mDDQ จากน้อยไปมากคือ Rate30 (0.10); Dau30, Rate0, Sm (0.11); Emp (0.13); DP (0.15); Dau0 (0.35) โดยมีค่าสัมประสิทธิ์ความสัมพันธ์ (r²) ตามลำดับดังนี้ 0.926; 0.948; 0.785; 0.629; 0.551; 0.833; 0.806

สรุป: การใช้ค่ายูเรียในเลือดที่ 30 นาทีหลังเสร็จสิ้นการฟอกเลือดเพื่อประเมินค่าสัดส่วนอีควิลิเบรทเคทีต่อวีมี ความถูกต้องและความสัมพันธ์ที่ดีกว่าใช้ค่ายูเรียหลังสิ้นสุดการฟอกเลือดทันที ในความต้องการประเมินค่าสัดส่วน อีควิลิเบรทเคทีต่อวีที่มีความถูกต้องสูง การใช้วิธี Rate30 และ Dau30 จึงอาจเป็นวิธีการที่เหมาะสม เพื่อใช้คำนวณค่า สัดส่วนอีควิลิเบรทเคทีต่อวีในการฟอกเลือดทางคลินิก