Target Quantity for Twice-a-Week Hemodialysis: The EKR (Equivalent Renal Urea Clearance) Approach

Krissanapong Manotham MD*, Khajohn Tiranathanagul MD**,
Kearkiat Praditpornsilpa MD**, Somchai Eiam-Ong MD**

** Nephrology unit, Medicine, Leardsin General Hospital*
** Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University Hospital*

Objective: *The targets of dialysis per session, in terms of Kt/V and URR are well established for thrice-a-week hemodialysis (HD). The target values of these parameters could not be applied for the patients undergoing twice-a-week HD, which is performed in several developing countries. The equivalent renal urea clearance EKR (EKR [mL/min) = G (mg/min)/TAC (mg/mL)], which measures urea clearance in a continuous fashion, has been used in comparing amount of dialysis among the different modalities. For any chronic dialysis regimens the target EKRc, which was normalized to urea volume of distribution of 40 L, would be above 13 mL/min. Therefore, there is no data available regarding Kt/V, URR, and EKRc for twice-a-week HD.*
Material and Method: *The EKRc of 26 Thai patients treated with twice-a-week high flux HD were measured monthly for 12 months. The Kt/V, URR, and serum albumin were also measured monthly.*
Results: *Overall, the mean EKRc of 294 patient-month analysis was 11.68 0.16 mL/min. Monthly EKRc had a high correlation to Kt/V (r = 0.80) and URR (r = 0.82). When serum albumin was employed as a surrogate marker for treatment failure, ROC analysis revealed that EKRc above 13 mL/min had 90% and 100% probabilities to maintain monthly and 12-month serum albumin levels above 4 gm/dL, respectively. To obtain the target EKRc above 13 mL/min at 90 and 95% confidence, the values of Kt/V per session were 2.11 and 2.25, respectively while those of URR were 82.89 and 84.52%, respectively.*
Conclusion: *For twice-a-week HD, to have the EKRc level above 13 mL/min, at 95% confidence, the Kt/V should exceed 2.2 and the URR should exceed 85% per session.*

Keywords: *EKR, Kt/V, URR, Twice-a-week hemodialysis.*

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Thrice-a-week chronic hemodialysis (HD) is the established standard treatment in patients with end stage renal disease (ESRD). However, a certain portion of hemodialysis patients receives twice-a-week HD in several countries including Thailand. Recently, K/DOQI has advocated the values of Kt/V > 1.2 per session, or 3.6 per week, and URR > 65% per session as the targets for thrice-a-week HD[1]. The appropriate target of Kt/V > 1.2 per session in thrice-a-week HD has been recently confirmed by the HEMO study[2]. The appropriate value of Kt/V for twice-a-week HD is still unestablished. The value could not simply be determined just by dividing the value of 3.6 by 2, which is equal to 1.8 per session.

Recently, Casino and Lopez have introduced the equivalent renal urea clearance (EKR) that measures urea clearance in a continuous fashion[3]. EKR concept is straightforward and based on the familiar clearance concept. Blood urea nitrogen (BUN) in a healthy person is maintained in a stable state because urea Generation rate (G) is equal to net urea removal rate or amount of urea in urine per time of collection[4]. The urea removal rate is generally expressed in the terms of urea clearance: urea clearance = U x V/BUN = G/ BUN, where U = urine urea nitrogen and V = urine volume. In hemodialysis patients, the value of G is easily

Correspondence to : Eiam-Ong S, Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University Hospital, Bangkok 10330, Thailand. E-mail: EiamOng@netscape.net, Somchai80754@yahoo.com

calculated from urea kinetic model (UKM)[5]. The BUN levels in dialysis patients are not steady as in a non-dialysis person but oscillate between the dialysis and non-dialysis days. The average levels of BUN, TAC, can be computed either by the UKM method or by actual calculation using multiple blood samplings[6]. Thus, EKR is equal to G/TAC. Of interest, EKR represents both dialytic and interdialytic periods whereas Kt/V and URR reflects only the dialytic time. This disparity would underscore the superiority of EKR and, hence, could provide an opportunity to use EKR to compare the amount of dialysis among different dialysis regimens. In general, the values of EKR were normalized to urea volume of distribution of 40 L and, thus, were presented as EKRc. For thrice-a-week HD regimen, a target EKRc at > 13 mL/min has been currently established and corresponds to Kt/ V > 1.2 per session[3,7].

The present study was carried out to use the EKRc values of $\geq$ 13 mL/min to identify the appropriately target quantity in terms of Kt/V and URR in twice-a-week HD.

Material and Method

Patients

This 12-month cross-sectional study was performed in 26 Thai end stage renal disease (ESRD) patients who were treated with twice-a-week high flux HD. The study was approved by the Ethical Committee, Faculty of Medicine, Chulalongkorn University. Each patient participating in the present study gave informed consent. Patients were excluded from the present study if they were switched to transplantation.

At first, the values of EKRc were determined in twice-a-week HD patients who had the values of Kt/V > 3.6 per week or > 1.8 per session. The dialysis prescription for each patient was adjusted monthly by a renal staff, non-involved in the study, with targeting Kt/V (second generation Daugirdas)[8] > 1.8 per session. At the end of each month, pre dialysis blood from each patient was collected from the arterial port while post dialysis blood was drawn using the slow flow-stop pump technique. Pre-dialysis blood for the next session was also collected[9]. Blood samples were immediately centrifuged and analyzed for serum chemistry. The single pool Kt/V was calculated by the UKM method[4]. The dialyzer clearance was corrected with blood and dialysate flow as previously described[10]. Renal clearance (Kr) was calculated from interdialytic urine collection. Those whose daily urine less than 100 mL/day were considered as no residual renal function or Kr = 0 mL/min. The values of URR delivery were also determined. The G and the urea volume of distribution (V) were also calculated from the UKM method[4]. The validation of V_{UKM} was compared with V derived from bio-impedance formula and the data were excluded from analysis if there was more than 10% difference between these two methods. The time average urea concentration (TAC) was directly calculated from the three BUN methods. The value of EKR, computed by the formula: EKR = G/TAC, was normalized to V of 40 L and was designated as EKRc[3].

Treatment failure included both clinical and laboratory levels. Clinical failure comprised death, hospitalization (except for access problem and non related diseases), and switching to peritoneal dialysis for any reasons. Pre-dialysis serum albumin levels were measured monthly and used as a surrogate laboratory marker for treatment failure, which was defined by serum albumin < 4g/dL. Also, the 12 month treatment failure was diagnosed when the 12-month mean values of albumin were below 4g/dL.

Statistical analysis

EKRc was tested for the correlation with other parameters (Kt/V and URR) by linear and logarithm models. The curve estimation was performed to reassure the correlation model. Each monthly parameter was compared with the monthly serum albumin, a surrogate laboratory marker for treatment failure. The mean of each parameter in the treatment failure and success were compared by using independent-sample t test. The significant difference was attained when $p < 0.05$. The suitable cut off value for each parameter at 90 and 95 probabilities to treatment success were extracted. The target EKRc was established and converted to the term of Kt/V and URR by ROC at 90 and 95 probabilities.

Results

Demographic data

Twenty six patients, receiving twice-a-week HD with high flux dialyzer participated in the study. There were 10 male and 16 female patients. The average age was 51 $\pm$ 2.9 years. The average duration of dialysis was 5.6 $\pm$ 0.4 years. The vascular accesses of the patients comprised arteriovenous fistula[22] and arteriovenous graft[4]. The underlying etiologies of ESRD included diabetic nephropathy[18], chronic glomerulonephritis[6], and unknown causes[2]. Most patients, 25 from 26 had no residual renal function.

Baseline dialysis amount

From the 26 patients, there were monthly data available for 265 patients to be analyzed. Of these, 16 values were excluded because of the high discrepancies between the levels of V derived from UKM and bioimpedance methods. The values of EKRc were distributed in a normal distribution pattern. The mean EKRc of over all patients was 11.68 ± 0.16 mL/min (Table1). It is obviously seen that, in twice-a-week HD, when the values of prescribed Kt/V were 1.8 per session, only 30 percent of the data had EKRc above13 mL/min.

Correlation between EKRc and other parameters

In twice-a-week HD, EKRc was highly correlated to Kt/V. This correlation seemed to be linear especially at the lower range of Kt/V but it appeared to be a log scale correlation (r = 0.811) in the higher range (Fig. 1). As expected from computer simulation curve and mathematical equation, measured EKRc was related to Kt/V in logarithmic function. Yet, because of natural oscillating of the measured data, linear correlation was also statistically high enough in correlating the EKRc and Kt/V in the linear fashion (r = 0.80). Linear regression analysis was extracted from this advantage and EKRc = 5.259 Kt/V + 2.108 (range of Kt/V = 0.87-3.36). As such, this equation was useful in approximate transforming EKRc to Kt/V, leading to prescription of the dialysis time. As expected from the mathematical calculation, URR also had a high correlation to EKRc in exponential relation (r = 0.86). Again, linear correlation was high enough to determine EKRc = 0.265 URR – 8.48 (range of URR = 77-91).

Table1. Dialysis amount in various parameters

	EKRc	Kt/V	URR
Mean ± SE	11.68±0.16	1.86±0.02	76.93±0.51
50th percentile	11.69	1.89	78.8
70th percentile	13.05	2.08	82.49
90th percentile	15.22	2.34	86.05

Validation of target EKRc to treatment failure

In this 12-month cross-sectional study, no patients met clinical failure criteria. There were records of 9 admissions with non-related problems [AVF correction[4], gynecologic condition[1], duodenal ulcer with upper gastrointestinal hemorrhage[1], recurrent carcinoma bladder[1], and coronary angiography[2]]

Regarding laboratory aspect of treatment failure, as seen in Table 2, the mean of measured EKRc in the success group, serum albumin > 4 g/dL, was higher than the failure group, serum albumin < 4 g/dL ($p < 0.001$). This observation was also observed with Kt/V and URR.

ROC analysis for monthly EKRc and success was performed. The cut off point EKRc at 12 and 13 mL/min/40L were tested for successive confidence. At EKRc > 12 mL/min/40L, there was 74.8% confidence to get success and at EKRc > 13 mL/min/40L there was 88% confidence to get success.

When considering the mean 12-month albumin as a surrogate marker to represent 12-month dialysis result, the mean 12-month EKRc was higher in the success group and was still highly correlated to the treatment failure ($p < 0.001$). Although the mean Kt/V and URR were still correlated to treatment failure, the less statistical significance was noted (Table 2). ROC analysis between the mean 12-month EKRc and the 12-month failure revealed that the cut off of EKRc at 12 mL/min had 80% confidence to achieve the mean 12-month serum albumin above 4 gm/dL, while at 13 mL/min this confidence was up to100% of treatment success.

Table 2. Correlation between serum albumin levels and EKRc, Kt/V, and URR

Parameters	Treatment failure (serum albumin < 4 g/dL)	Treatment success (serum albumin < 4 g/dL)	p-value
Monthly			
EKRc (mL/min/40L)	10.66±0.23	12.78±0.16	<0.001
Kt/V	1.73±0.04	1.97±0.02	<0.001
URR (%)	73.52±0.78	80.39±0.46	<0.001
12-month			
EKRc (mL/min/40L)	10.13+0.62	12.86+0.24	<0.001
Kt/V	1.65+0.11	1.98+0.05	<0.05
URR (%)	71.62+2.2	80.37+0.89	<0.01

Target dose of EKRc at 13 mL/min in term of Kt/V and URR in twice-a-week HD

Target EKRc at 13 mL/min was translated into the terms Kt/V, and URR per session by performing the ROC analysis. To obtain this target EKRc dose at 90 and 95% confidence, the values of Kt/V per session were 2.11 and 2.25, respectively while those of URR were 82.89 and 84.52%, respectively. For practical intention, as such, the authors proposed that, in twice-a-week hemodialysis, the target Kt/V and URR should be 2.2 and 85%, respectively.

When tested with serum albumin levels, the surrogate laboratory marker of treatment failure, the target Kt/V, 2.2, and URR, 85%, had high statistical significance to predict the outcome of treatment ($p < 0.05$ and < 0.01, respectively).

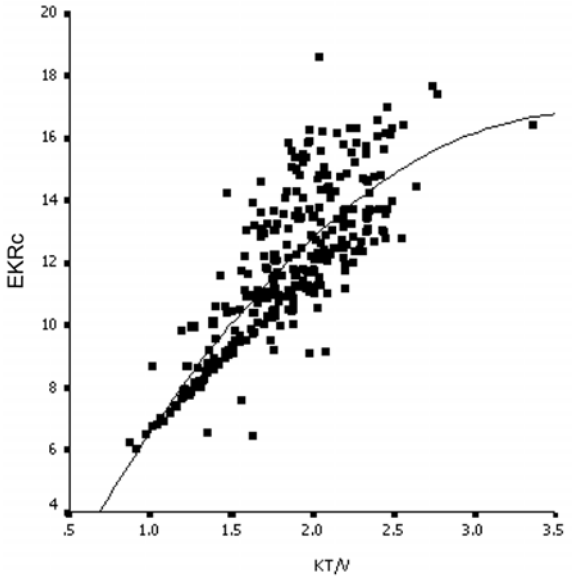
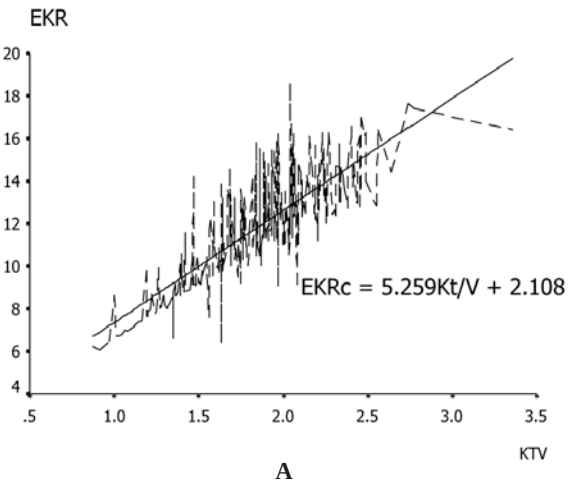


Fig. 1 Correlation between EKRc and Kt/V persession in twice-weekly HD patients

Discussion

Assessment of dialysis dose by means of urea removal is well established[9]. Although urea was non-toxic by itself, urea removal has demonstrated a strong correlation to dialysis outcome[11-13]. Two most popular methods to measure urea elimination are Kt/V and URR. K/DOQI guidelines have stated the target goal of these two parameters, Kt/V > 1.2 and URR > 65% per session[1]. These settled targets are supported by many large scale studies[11,12,14,15]. Unfortunately, most of the supporting data come from thrice-a-week HD. Furthermore, these two parameters represent only the dialytic period and do not include the interdialytic duration. Taken together, the target values of both Kt/V and URR in thrice-a-week HD could not be used in other modalities of HD. New urea removal index, EKR, which determines urea removal in the continuous fashion, is very interesting[3]. By assuming that the patient's urea nitrogen is in a steady state, which is approximately equal to TAC. For any given urea generation rate (G), supposed to be stable, urea clearance, or EKR is then simply calculated as: EKR = G/TAC. This concept would



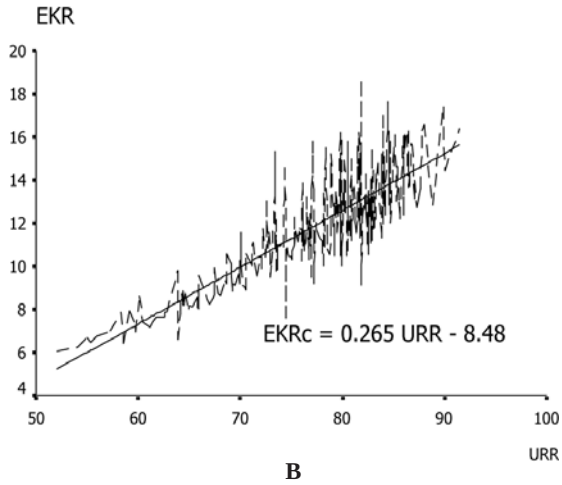


Fig. 2 Curve estimation analysis in linear model
A) EKRc and Kt/V
B) EKRc and URR

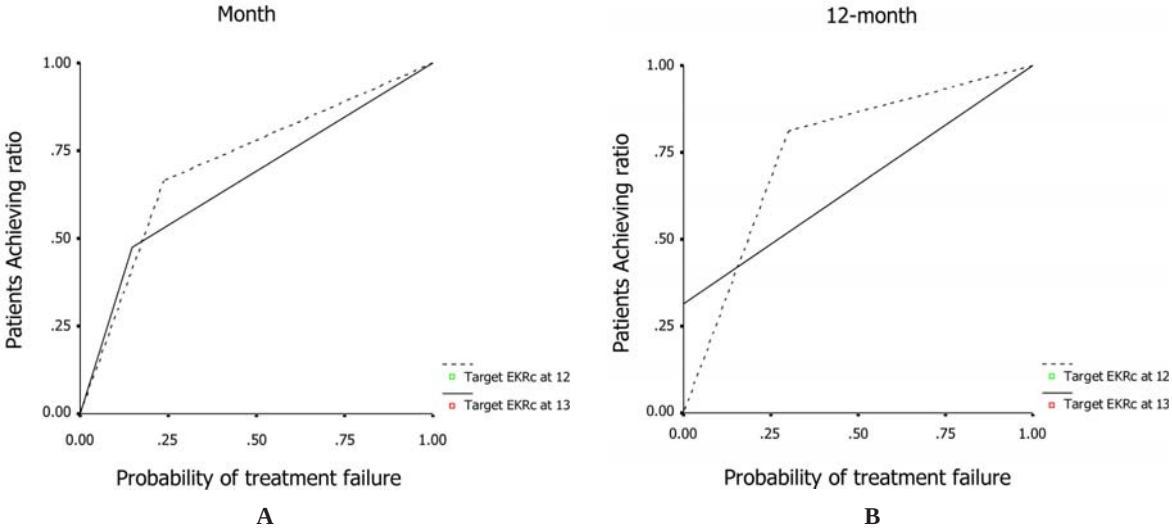


Fig. 3 ROC analysis of EKRc and treatment failure

universally correct no matter how G or TAC is derived. Since EKRc has been introduced by Casino-Lopez, the target EKRc has been established based on the K/DOQI target[1,3,7]. Barreneche et al showed that EKRc had predictive index of mortality in their patients in comparable with serum albumin and advocated to use EKRc as the adequacy parameter[16]. Apart from being a dialysis measuring parameter, EKRc also provides two additional implications. Firstly to compare dialysis dose among various modalities. Secondly, to extract the target dose and to transform valuable data from one regimen to another. However, EKRc has limitations since its value does not allow the nephrologists to adjust dialysis dose and time as in the case of Kt/V. Dialysis dose expression in the term of Kt/V is still essentially required.

In the present study, both implications of measured EKRc have been verified. By using twice-a-week hemodialysis, as a model, first, the authors confirmed that the actually measured EKRc had very high correlation to the measured Kt/V as well as URR (Table1 and Fig. 1). Thus, it is capable to convert among these three parameters in the studied patients, EKRc = 5.26 Kt/V $\pm$ 2.11 and EKRc = 0.27URR – 8.48. This correlation between Kt/V and actual EKRc was in a log scale, as previously demonstrated by computer simulation curve in Casino-Lopez expectation[3].

Of interest, the present study revealed that it was possible for twice-a-week dialysis to reach target EKRc > 13 mL/mim/40L even in the patients with no residual renal function (Table 1). This might be because the presented patient's volume was relatively small. Furthermore, the values of TAC were measured by the three blood sample analysis method, not by extrapolating from UKM. The authors believed this calculating method can lessen the error occurring when both parameters were utilized in the same equation. Considering if G was employed from UKM and TAC was also extrapolated from UKM. The equation of G/TAC is all UKM extent in its nature. The correlation between Kt/V, which was derived from the UKM, and EKRc as well as the limitation of the curve, may exist because of the same set of the equation. If there were any errors in this kind of calculation, the magnitude of error might be amplified. Admittedly, twice-a-week dialysis is inevitably to have a high difference between the peak and the minimum levels of BUN and also have more fluctuating of body volume when compared with more frequent dialysis.

In attempting to certify dose-measuring property of EKRc for twice-a-week HD, none of the patients in the present study met the clinical failure criteria during the 12-month observation. Previous studies indicated that serum albumin is positively correlated to the dialysis dose[15] and that hypoalbuminemia (< 4.0 gm/dL) had predictive power to the treatment failure and mortality[17-19]. By using hypoalbuminemia as a surrogate marker for the treatment failure, EKRc expressed an excellent ability to measure dialysis dose (Table 2). The mean monthly EKRc as well as URR of the success group was significantly higher than the failure group. When extending the ob-

servation to 12 month period, the mean 12-month EKRc in the success group was still higher than the failure group whereas the statistically significant value in terms of Kt/V and URR were decreased (Table 2). This finding would underscore the superiority of EKRc over Kt/V and URR in measuring dialysis dose.

As seen in Table 1 when Kt/V was 1.8 per session, only 30% of the data had EKRc above 13 mL/min. Thus, for twice-a-week HD, to achieve the target EKRc by ROC analysis, at 90% confidence, the target Kt/V and URR per session must be above 2.11 and 82.89%, respectively. At 95% confidence to do so, Kt/V and URR per session must exceed 2.25 and 84.5% respectively. These targets seem possible for high flux/high efficiency system but are hard to achieve by conventional dialysis. Although new dialysis systems offer a very high clearance (K), it still needs relatively long dialysis time to attain this target (should be not less than 4 to 5 hrs per session). Another benefit from extending the dialysis time is the increase of the diffusive clearance of middle molecule and lessen the multiple pool effect[20]. This topic needs further study.

In conclusion, the present study proves that EKRc has dose-exchanging properties. One can figure out the target goal for their regimens, supported by data from this large scale study by exchanging the values in terms of EKRc.

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การใช้ค่าอีเคอาร์ในการกำหนดปริมาณเป้าหมายสำหรับการฟอกเลือดสัปดาห์ละสองครั้ง

กฤษณพงศ์ มโนธรรม, ขจร ตีรณธนากุล, เกื้อเกียรติ ประดิษฐ์พรศิลป์, สมชาย เอี่ยมอ่อง

วัตถุประสงค์: *ในปัจจุบันยังไม่มีการกำหนดค่าความพอเพียงในการฟอกเลือดสัปดาห์ละสองครั้ง ในการฟอกเลือดรูปแบบต่าง ๆ มีผู้นำค่าอีเคอาร์ซึ่งวัดค่าการขจัดยูเรียในรูปแบบต่อเนื่องมาใช้เป็นค่ามาตรฐานกลางกล่าวคือ ให้สูงกว่า 13 มล./นาที*

วัสดุและวิธีการ: *ทำการวัดค่าอีเคอาร์ เคทีโอเวอร์วี ยูอาร์อาร์ และซีรัมอัลบูมิน ทุกเดือนเป็นเวลา 12 เดือนในผู้ป่วย 26 รายที่รับการรักษาด้วยการฟอกเลือดสัปดาห์ละสองครั้ง*

ผลการศึกษา: ค่าอีเคอาร์เฉลี่ยจากการวัด 294 ครั้งเท่ากับ 11.68 $\pm$ 0.16 มล./นาที ค่าอีเคอาร์มีความสัมพันธ์อย่างสูงกับค่าเคทีโอเวอร์วีและยูอาร์อาร์ ค่าอีเคอาร์ที่สูงกว่า 13 มล./นาที มีโอกาสร้อยละ 90 และร้อยละ 100 ในการคงระดับค่าซีรัมอัลบูมินของแต่ละเดือนและทุก 12 เดือนให้สูงกว่า 4 ก./ดล.

สรุป: ในการฟอกเลือดสัปดาห์ละ 2 ครั้ง เพื่อให้ได้ค่าอีเคอาร์สูงกว่า 13 มล./นาที จะต้องได้ค่าเคทีโอเวอร์วีสูงกว่า 2.2 และค่ายูอาร์อาร์สูงกว่าร้อยละ 85