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ORIGINAL ARTICLE

Toward the optimal dose metric in continuous renal replacement therapy

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ABSTRACT

Purpose: *There is no consensus on the optimal method to measure delivered dialysis dose in patients with acute kidney injury (AKI). The use of direct dialysate-side quantification of dose in preference to the use of formal blood-based urea kinetic modeling and simplified blood urea nitrogen (BUN) methods has been recommended for dose assessment in critically-ill patients with AKI. We evaluate six different blood-side and dialysate-side methods for dose quantification.*

Methods: *We examined data from 52 critically-ill patients with AKI requiring dialysis. All patients were treated with pre-dilution CVVHDF and regional citrate anticoagulation. Delivered dose was calculated using blood-side and dialysis-side kinetics. Filter function was assessed during the entire course of therapy by calculating BUN to dialysis fluid urea nitrogen (FUN) ratios q/12 hours.*

Results: *Median daily treatment time was 1,413 min (1,260-1,440). The median observed effluent volume per treatment was 2,355 mL/h (2,060-2,863) ($p<0.001$). Urea mass removal rate was 13.0±7.6 mg/min. Both EKR ($r^2=0.250$; $p<0.001$) and K_D ($r^2=0.409$; $p<0.001$) showed a good correlation with actual solute removal. EKR and K_D presented a decline in their values that was related to the decrease in filter function assessed by the FUN/BUN ratio.*

Conclusions: *Effluent rate (mL/kg/h) can only empirically provide an estimated of dose in CRRT. For clinical practice, we recommend that the delivered dose should be measured and expressed as K_D. EKR also constitutes a good method for dose comparisons over time and across modalities.*

KEY WORDS: *Dialysis, Dose, Urea, Clearance, Acute kidney injury*

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INTRODUCTION

There is no consensus on the optimal method to measure dialysis dose in patients with acute kidney injury (AKI). While several techniques have been developed and utilized to quantify dose for intermittent hemodialysis (IHD), these have yet to be widely applied to continuous renal replacement therapies (CRRT). Moreover, studies of dose have used different expressions for solute clearance for different modalities. Studies in IHD generally use blood-side urea measurements (i.e., single-pool Kt/V_{urea}) as markers of dialysis dose, however, for several reasons its use may be inappropriate in patients with AKI (1). Another blood-side determination based on urea kinetic modeling (UKM) is the equivalent renal urea clearance (EKR) (2), a method not widely applied in CRRT. The EKR measurement may be an

alternative for dose quantification of intermittent and continuous modalities, allowing them to be compared. Most studies in CRRT exploring the relation between dose and outcomes have utilized a prescribed weight-based, hourly effluent rate, and measured effluent volume as a surrogate of solute removal (3-7). The use of direct dialysate-side quantification of dose in preference to the use of formal blood based UKM and simplified blood urea nitrogen (BUN) methods has been recommend (8, 9). One of the dialysate-side quantification methods is the solute removal index (SRI), proposed by Keshaviah and Star in 1994 as an approach to dialysis quantification based on urea removal (10). We hypothesized that dialysate-based kinetic methods provide a better method to assess delivered dialysis dose compared to blood-based kinetics in CRRT.

METHODS

Patients

The Program to Improve Care in Acute Renal Disease (PICARD) group included five academic medical centers in the United States: University of California San Diego (UCSD), Cleveland Clinic Foundation, Maine Medical Center, Vanderbilt University, and University of California San Francisco. Over a 31-month period (February 1999 to August 2001), all patients consulted for AKI in the ICU were evaluated by PICARD study personnel for potential study participation. Informed consent was required from all study participants or their proxy.

A detailed description of PICARD inclusion and exclusion criteria, data elements, data collection, and management strategies has been described elsewhere (11). AKI was defined as an increase in serum creatinine ≥ 0.5 mg/dL with baseline serum creatinine <1.5 mg/dL, or an increase in serum creatinine ≥ 1.0 mg/dL with baseline serum creatinine ≥ 1.5 mg/dL and <5.0 mg/dL. Patients with a baseline serum creatinine ≥ 5.0 mg/dL were not considered for study inclusion. Patients who were contacted by study personnel and who signed informed consents were enrolled in the study cohort. The Committees on Human Research at each participating clinical site approved the study protocol and informed consent. For this analysis, we included 52 patients from a single center (UCSD) who were treated with CVVHDF and had complete data for urea nitrogen concentration in the effluent.

All interventions were determined by the treating physicians and not influenced by the study personnel, including timing, modality, and intensity of dialysis. Reasons for starting dialysis were classified as follows: 1. Solute only (BUN ≥ 80 mg/dL and/or sCr ≥ 6 mg/dL); 2. Volume only (oliguria <400 cc/24 h or signs of volume overload); and 3. Combined (a combination of volume problems + solute problems + other indications including: electrolyte disturbances and pH).

Dialysis technique

CVVHDF was performed with a Prisma CRRT machine (Gambro, Lakewood, CO, USA), with a 0.7-1.8 m^2 AN69 membrane (MF-100 filter set for Prisma) or a Diapact machine (B. Braun, Melsungen, Germany) with a polysulfone synthetic high-flux filter (NR60; Fresenius, Bad Homburg, Germany). The essentials of the CVVHDF therapy setup have been described previously (12). Dual-lumen, 11 FR, temporary catheters and a prescribed blood flow rate (Qb) of 100 mL/min were used.

We used regional citrate anticoagulation to maintain filter patency using 4% tri-sodium citrate infused at the origin of the extracorporeal circuit (initially 170 mL/h, range 100-200 mL/h). Initial citrate flow rates prescribed were between 2% to 3% of Qb (e.g., for a Qb of 100 mL/min citrate flow rates ranged from 2-3 mL/min = 120-180 mL/h). Citrate flow rates were subsequently adjusted based on post-filter ionized calcium values, maintained within a range of 0.25 mmol/L to 0.4 mmol/L. These values were checked with a frequency ranging from every 6 to 12 hours. Citrate flow rates were adjusted within a range of 5 mL/h to 15 mL/h to achieve the post-filter ionized calcium values. No changes in Qb were done when citrate was adjusted (Fig. 1).

Replacement solution (Qr) was comprised of 0.9% saline at a fixed rate of 500 mL/h at treatment initiation, but could be subsequently modified between a range of 250 mL/h to 700 mL/h. A custom dialysate (Qd) with low sodium (117 mEq/L), zero-alkali and zero calcium was infused at a rate of approximately 1 L/h (range 0.9-2.1 L/h). Net fluid removal (Qnet) was set at a fixed rate of 1000 mL/h at treatment initiation, but subsequently could be modified to a range of 700 to 2000 mL/h. Since the CRRT machines used in this study automatically set the effluent pump speed to include the replacement fluid (Qr), dialysate (Qd), and net fluid removal rate (Qnet), the total hourly effluent volume is derived from *dialysate (Qd) + ultrafiltrate (Quf = (Qr +*

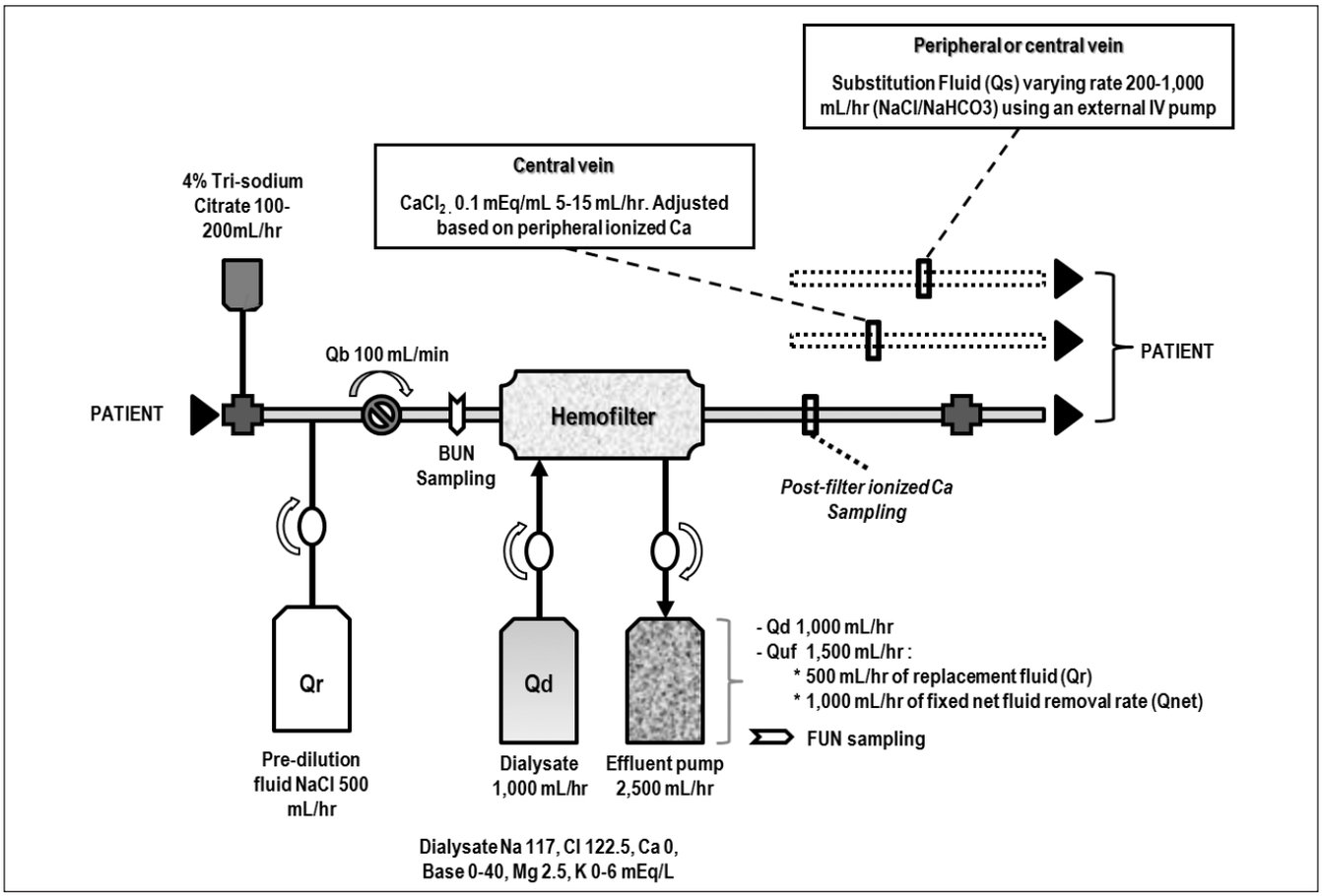

Fig. 1 - *CVVHDF circuit set-up and citrate anticoagulation protocol: CRRT dialysis circuit using regional citrate anticoagulation with the Gambro PRISMA machine. The 4% tri sodium citrate (TSC) mean infusion rate was 180 mL/h and Qb was 100 mL/min. TSC was added at the arterial catheter port and iCa levels sampled post-filter. Citrate flow rates were subsequently adjusted based on post filter ionized calcium values to be maintained within a range of 0.25-0.4 mmol/L. The pre-filter BUN value was measured after the infusion of TSC, and pre-dilution fluid (Qr) thereby accounting for the pre-dilutional effect of these solutions. Technique for fluid balance uses a fixed ultrafiltration rate (1,000 mL/h) to achieve target effluent volume; substitution fluid (Qs) is varied hourly to achieve a negative, zero, or positive fluid balance.*
Abbreviations: Qb = blood flow rate; Qd = dialysate flow rate; Qr = replacement fluid rate; Quf = total ultrafiltration rate; Qnet = net fluid removal rate; BUN = blood urea nitrogen; FUN = effluent urea nitrogen.

Qnet)) and was prescribed and maintained at 2500 mL/h. In some patients, when additional clearance was required (to enhance solute removal and correction of hyperkalemia or acidemia), effluent volumes were increased by adjusting the dialysate flow rates from 1000 mL/h to a maximum of 2100 mL/h (range 1050-2100 mL/h) and in some instances net fluid removal was also adjusted to a maximum rate of 2000 mL/h (range 1100-2000 mL/h) for a temporary period (Fig. 1).

The fixed Qb and effluent volume resulted in the filtration fraction (Quf / Plasma flow ((1-hct) x Qb)) remaining roughly constant at 30%±6%. Targets for fluid balance (net negative, positive, or even) were individualized for each patient on an ongoing basis and the hourly fluid balance was achieved by varying the amount of substitution fluid (Qs), which was administered through a peripheral or central vein outside the CRRT circuit through a separate IV pump. We incorporated all measured intakes and outputs, including the CRRT circuit on an hourly basis, to calculate the volume of substitution fluid (Qs) required to maintain the desired fluid balance.

Blood and effluent samples of urea nitrogen were obtained at initiation of each CRRT treatment and every 12 hours thereafter. Pre-filter and post-filter BUN (mg/dL), effluent

urea nitrogen (mg/dL), effluent volume (mL), and blood flow (mL/min) were recorded for each treatment. Patient weight was measured immediately before treatment initiation and immediately after treatment discontinuation in order to calculate anthropometric volume of distribution (V, L). Effective time of treatment was measured (t) for each 24 hours of prescribed treatment and expressed in minutes.

Monitoring of filters

Filter efficacy was assessed by calculating FUN/BUN ratios for each 12 hour period of filter use.

Calculations

Steady state

Dialysate parameters and all dialysis dose expressions (blood-side and dialysate-side equations) were determined before and after a steady state were reached. The steady state of each patient was calculated at day of CRRT initiation using formula from Garred et al (13):

Days needed to achieved steady state = 2 x [(Volume of distribution (L) / K_{urea} (urea clearance, in L/d

Delivered dose of dialysis

Quantification of dose: Blood-side kinetics

• *Urea clearance (K_B)*

The following equation for urea clearance (K_{urea}) was used:

$K = Q_b$ (BUN_i [mg/dL] – BUN_f [mg/dL]) / BUN_i [mg/dL]

Where Q_b is the blood flow rate; BUN_i, is the inflow blood urea nitrogen concentration; BUN_f is the outflow blood urea nitrogen concentration. Blood fluid rate is expressed as mL/min.

• *Kt/V_B*

For each treatment, a delivered Kt/V_{urea} was calculated (Kt/V_B): K was derived from the equation shown above, from the dialysis actual treatment time (t), the post-treatment total body water (TBW) calculated as a fraction of the patient's weight (0.6 for males and 0.55 for females) (V, anthropometric) which was calculated based on weight changes every 24 hours (14).

• *Equivalent renal urea clearance*

For each treatment equivalent renal urea clearance (EKR) was calculated using the formula described by Marshall et al (1) as shown below:

$EKR = G- [(V_t \times BUN_t) - (V_0 \times BUN_0) / T] / TAC_{BUN}$

Where G is net urea generation rate (mg/min); V is urea volume of distribution; subcripts 0 and t refer to values at time 0 and t; T is the duration between 0 and t; and TAC_{BUN} is time-averaged urea concentration (mg/mL).

TAC_{BUN} was determined using the following formula (15):

TAC_{BUN} = [(preBUN + postBUN) t + (postBUN + postBUN) 60 + (pre2BUN) θ] / 2(t+60+θ)

Where preBUN = pre-treatment BUN; pre2BUN = pre-treatment BUN of the next treatment; postBUN = post-treatment BUN; t = effective time on dialysis; θ = interdialytic time.

Net urea generation rate (G) was calculated using the Leblanc et al formula (16) assuming no residual kidney function:

G = [UnMR / (60 * t)] – [BW * (BUN1 – BUN2)] / 10 *t – [BUN2 * (BW1 – BW2)] / 6 * t

Where UnMR = Urea mass removal rate in the effluent; t = effective time on dialysis; BW1 = pre-dialysis weight; BW2 = post-dilaysis body weight; BUN1 = pre-treatment BUN; BUN2 = post-treatment BUN.

Quantification of dose: Dialysate-side kinetics

• *Urea mass removal (UnM)*

UnM is the total amount of urea in the effluent that was removed over a given period of time in each treatment and is expressed in grams per day. Urea nitrogen eliminated in urine was not assessed.

• *Urea mass removal rate (UnMR)*

UnMR was calculated by multiplying effluent solute concentration by effluent volume for a given interval of analysis (mg/min).

UnMR = FUN concentration (mg/dL) * effluent volume (mL/min)

• *Urea Clearance (K_D)*

K_{urea} (mL/min) was derived from the ratio of mass removal rate to blood concentration and was calculated using the following formula:

K delivered = (FUN x EV) / BUN

Where, FUN is urea nitrogen in the effluent expressed in mg/dL; BUN is urea nitrogen in plasma expressed in mg/dL; and EV is the effluent volume expressed in mL/min.

• *Kt/V_D*

Because little to no rebound occurs in CVVHDF, it is expected that equilibrated Kt/V_{urea} ($eqKt/V_{urea}$) will be equal to single pool Kt/V_{urea} ($spKt/V_{urea}$). Dialysis-sided Kt/V_{urea} (Kt/V_D) was calculated using K_D, which in turn was derived from the ratio of mass removal rate to blood concentration as was shown previously. Total body water (TBW) was

determined from the patients' weight as described above (V, anthropometric) and *t* was determined from the actual treatment time.

Kt/V_D = K delivered x t / V

• *Solute Removal Index*

The solute removal index *(SRI)* was determined by a modification of the formula of Keshaviah and Star (9). The amount of urea present in the dialysate was determined by multiplying the total volume of dialysate for that treatment by the urea concentration in the collected dialysate. The total body concentration of urea was determined by multiplying the pre-treatment BUN level by the TBW. The TBW was determined anthropometrically as previously described.

SRI = FUN / pre-BUN x TBW x 100%

Where FUN is total urea nitrogen in effluent expressed in mg/dL; pre-BUN is pre-treatment blood urea nitrogen; and TBW is total body water (anthropometrically).

We assessed the degree of the correlation of each of the blood-side and dialysis-side dose expressions with the UnMR as the gold standard of solute removal.

RESULTS

The mean age was 49 (±14) years; 55% were female, 43% were non-white, and 10% had a history of chronic kidney disease. The mean serum creatinine concentration at CRRT initiation was 1.64±1.2 mg/dL, median daily urine output was 80 mL (IQR 25–278 mL) and mean SOFA and APACHE III scores were 9.9±3.6 and 111.1±24.8, respectively (Tab. I). In 49 (94%) patients the reason for starting dialysis was a combination of volume problems (oliguria <400 cc/24 hrs or signs of volume overload) and solute problems (e.g., BUN ≥ 80 mg/dL and/or sCr ≥ 6 mg/dL, electrolyte disturbances, and pH). In 3 (6%) of the 52 patients the indication for dialysis was exclusively volume related (oliguria <400 mL/24 h and/or signs of volume overload).

CRRT parameters of the 420 treatments included in the analysis are described in Table II. The median observed treatment time was 1413 minutes (IQR 1368 to 1440 min), with a median down time per day of 120 minutes (60-240 minutes). The median prescribed and observed effluent volume per treatment were 2500 mL/h (2413-2500) and 2355 mL/h (2060-2863) (p<0.001), respectively (Tab. II). Seventy three percent (73%) of the prescribed dose was actually delivered (median [interquartile range] prescribed clearance was 41 mL/min [40.2 to 41.7] versus 29.7 mL/min [25.3 to 33.6] of delivered clearance; p<0.001).

The Qd, Qr, and Qnet flow rates on the initial prescription (day 1 of CRRT = 56 of 420 total treatments) were as follows: 46 patients started with a Qd of 1000 mL/h; 51 patients started with a Qr of 500 mL/h; and 37 patients started with a Qnet of 1000 mL/h. In 8 patients the Qd (day 1 CRRT) was between 1100-1500 (mL/h); in 5 patients the Qr was between 600-700 mL/h; and in 6 patients the Qnet was between 1200-1500 mL/h. In the consecutive 364 treatments (after day 1 of CRRT), the Qd was 1,000 mL/h in 76%; Qr was 500 mL/h in 85%; and Qnet was 1,000 mL/h in 68%. In 75 (23.9%), 55 (15%), and 62 (32%) of consecutive treatments Qd, Qr, and Qnet were increased when additional clearance was required (range 1050-2100 mL/h; 550-800 mL/h; 1100-2000 mL/h; respectively).

TABLE I - BASELINE CHARACTERISTICS OF THE PATIENTS AT INITIATION OF CRRT (N=52)

Parameter	Means (SD)
Age (years)	49±14
Gender:	
F (%)	31 (55.4%)
Race/Ethnicity	
Caucasian	32 (57.1%)
African-American	2 (3.6%)
Hispanic	15 (26.8%)
Asian/Pacific Islander	6 (10.7%)
Other	1 (1.8%)
Weight (kg)	78.8±29.5
Height (cm)	168.9±10.5
BMI (kg/m2)	27.3±8.3
Urine output (mL/day)	80 (24.5-278)*
Urea nitrogen levels (mg/dL)	64.7±37.8
Creatinine levels (mg/dL)	1.64±1.2
Fluid accumulation from admission (liters)	4.5±2.1
Severity of illness scores:	
SOFA	9.9±3.6
APACHE 3	111.1±24.8

SOFA = Sequential Organ Failure Assessment Score; APACHE 3 = Acute Physiology and Chronic Health Evaluation 3.
*Median and Interquartile range

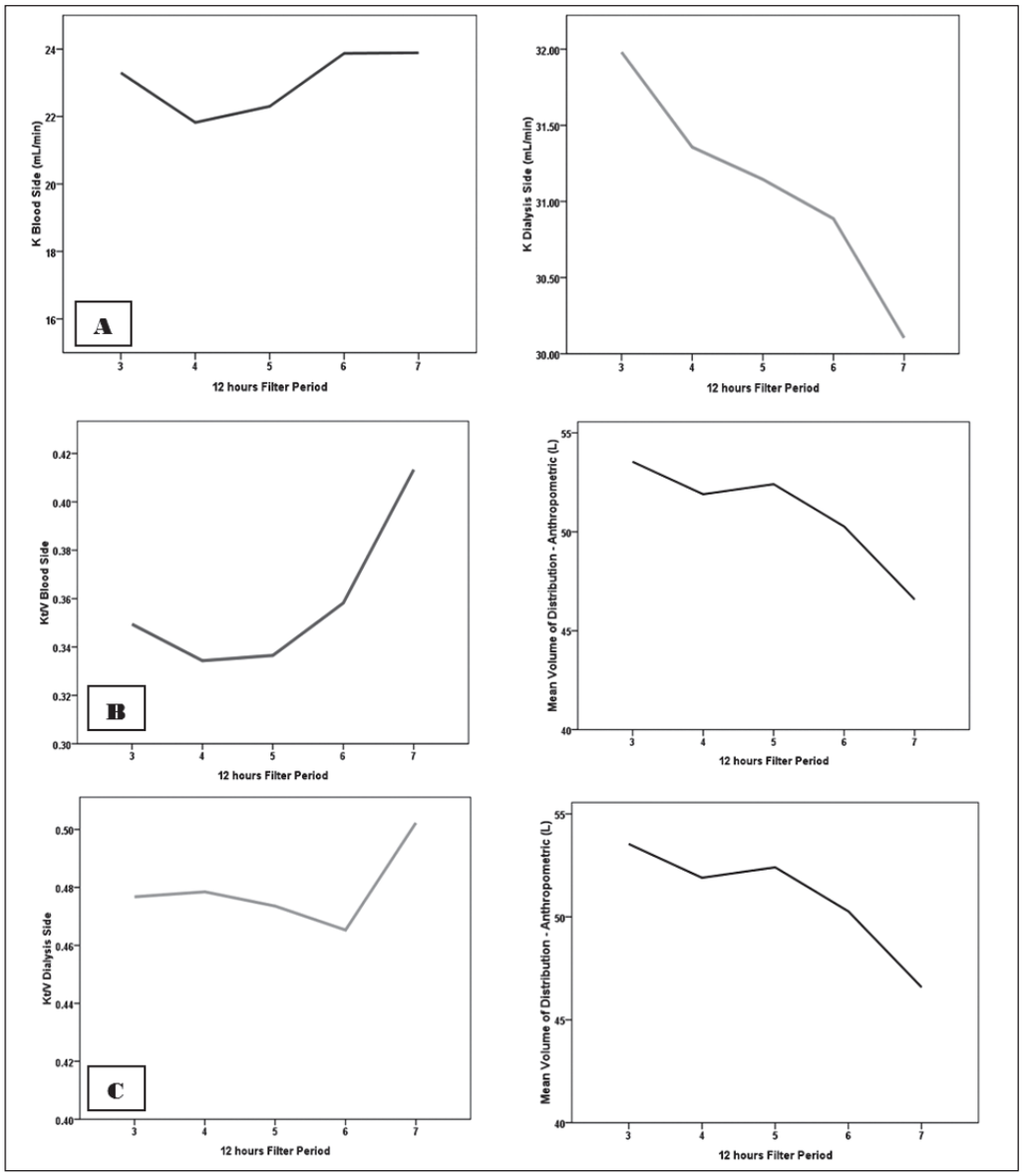

Fig. 2 - *Blood-side and dialysis-side clearance (K) and Kt/V_{urea} across 12-h periods of filter use.* ***(A)*** *Shows blood-side and dialysis-side clearance (K_B and K_D) across 12-h consecutive periods of filter use, only K_D values declines with consecutive periods of filter use.* ***(B)*** *Shows blood-side Kt/V_{urea}, its value increases after the fifth period of filter use this is related to a decrease urea volume of distribution.* ***(C)*** *Shows dialysis-side Kt/V_{urea}, the same phenomenon of increasing values related to decreasing urea volume of distribution is observed.*

TABLE II - PRESCRIBED AND OBSERVED TREATMENT CHARACTERISTICS OF 52 PATIENTS DURING CRRT

Median (IQR)	†Prescribed	‡Observed
Mean number of treatments per patient		7.5±7
Median treatment days		5 (3-12)
Treatment time (min)	1,440	1,413 (1,260-1,440)
Blood Flow rate (Qb; mL/min)	100 (100-100)	100 (100-100)
Dialysis flow rate (Qd; mL/h)	1,000 (1,000-1,000)	1,000 (958-1,000)
Replacement fluid rate (Qr; mL/h)	500 (500-500)	441 (342-500)
Net fluid removal rate (Qnet; mL/h)	1,000 (1,000-1,000)	809 (677-1,000)
Total effluent (mL/h)	2,500 (2,412.5-2,500)	2,280 (2,035-2,558)

Table III shows dialysate parameters, at CRRT initiation and after a steady state was reached (usually at 48 hours). As expected, blood and effluent urea nitrogen and anthropometric volume of distribution were lower after reaching steady state.

Dose quantification

Table IV shows "adequacy" indices used to express delivered dose on the first day of dialysis, and before and after the steady state was reached. As shown in Figure 2A, a decline in delivered dialysis dose is noted in consecutive 12-hour periods of CRRT therapy if it is assessed using dialysate-side clearance; when blood-side clearance is employed, the values did not show the same decline. We compared both K_{urea} with actual solute removal expressed as a rate (UnMR, mg/min); K_D has a better correlation (r^2=0.409; p<0.001) with actual solute removal than K_B (r^2=0.071; p=0.06).

Once a steady state was reached, almost no variation in Kt/V_B and Kt/V_D was observed across 12-hour periods of CRRT treatment; nevertheless, after 72 hours of treatment higher values of Kt/V_B as well as values of Kt/V_D were observed. This decline in both parameters correlates with a decline in the volume of distribution that begins after day 1 of CRRT treatment (Figs. 2B and C). Both dialysis dose

TABLE III - METABOLIC PARAMETERS OF THE 52 PATIENTS AT INITIATION OF CRRT AND AFTER REACHING STEADY STATE

Parameters	At initiation of CRRT	After steady state was reached	*P* value
Pre filter BUN mg/dL	59.5 (36.7-77.3)	39.0 (25-54)	<0.01
Effluent UN mg/dL	59.5 (39.5-77.5)	35.0 (24-51.5)	<0.01
Urea Mass Removal (mg/day)	12,810.8 (6,765.5-16,370.3)	15,636.3 (9,870.8-22,638.0)	0.03
Urea Mass Removal Rate (mL/min)	13.3 (9.5-21.2)	11.0 (7.4-15.9)	0.13
nPCR (g/kg/day)	1.62 (1.21-2.15)	1.75 (1.09-2.87)	0.01
UnA (mg/min)	9.9 (4.9-12.7)	10.5 (6.5-17.4)	0.28
Anthropometric V (L)	48.8 (41.1-55.5)	44.1 (39.8-53.5)	0.08

CRRT = continuous renal replacement therapy; BUN = blood urea nitrogen; UN = urea nitrogen; nPCR = normalized protein catabolic rate; UnA = ura nitrogen appearance; V = urea volume of distribution.

TABLE IV - BLOOD-SIDE AND DIALYSIS-SIDE ADEQUACY PARAMETERS AT 1ST DAY OF DIALYSIS, BEFORE AND AFTER REACHING STEADY STATE

Adequacy parameter (median [IQR])	First day of dialysis	Before reaching steady state	After reaching steady state	*P* value
KB (mL/min)	18.5 (16.4-22.9)	19.0 (15.4-21.5)	21.3 (18.2-25.5)	0.04
KD (mL/min)	24.7 (18.1-31.3)	30.1 (25.2-33.6)	33.8 (25.9-33.9)	0.04
Kt/V_B	0.85 (0.56-1.1)	0.58 (0.55-0.63)	0.75 (0.62-0.94)	0.001
Kt/V_D	0.52 (0.38-0.75)	0.47 (0.38-0.72)	0.91 (0.70-1.2)	0.001
EKR	17.7 (13.4-24.6)	19.1 (12.9-25.1)	20 (15.4-25.1)	0.08
SRI	36.7 (24.6-49.5)	25.7 (17.9-35.1)	47.5 (39.1-58.4)	0.001

K_B = clearance blood-side determination; K_D = clearance dialysis-side determination; Kt/V_B = blood-side Kt/V_{urea}; Kt/V_D = dialysis-side Kt/V_{urea}; EKR = estimated urea clearance; SRI = solute removal index; IQR = interquartile range.

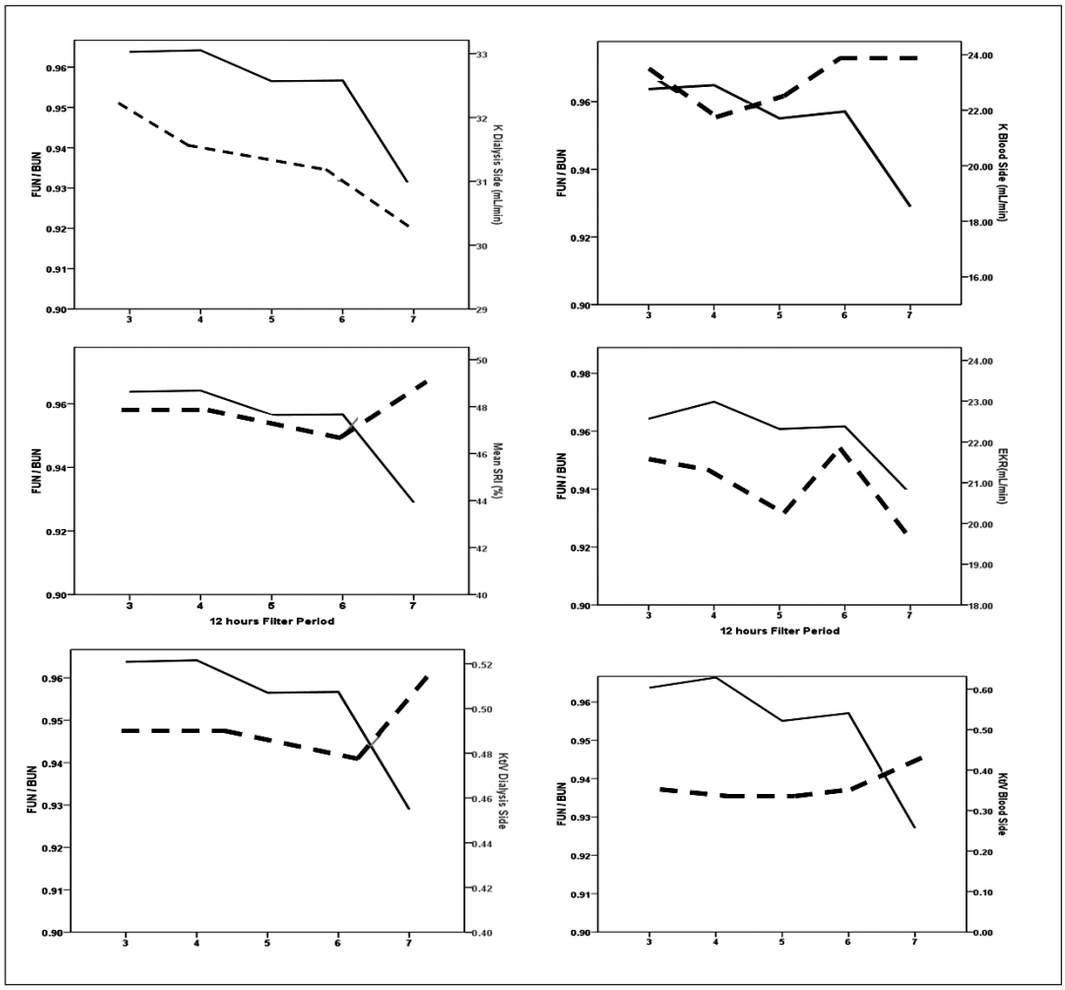

Fig. 3 - *Shows the relationship between different dialysis-adequacy parameters and filter function (FUN/BUN ratio). Only K_D and EKR dose adequacy expression show a decline in their values as filter efficacy reduces.*
K_B = Clearance blood-side determination;
K_D = Clearance dialysis-side determination;
Kt/V_B = Blood-side Kt/V_{urea};
Kt/V_D = Dialysis-side Kt/V_{urea};
EKR = estimated urea clearance;
SRI = solute removal index.

expressions showed no correlation with the actual solute removal ($Kt/V_{B,}$ r^2=0.134; p=0.85 and $Kt/V_{D,}$ r^2=0.045; p=0.49).

The values of *SRI* remained constant after reaching steady state; however, after 72 hours of CRRT treatment values of *SRI* increased. The increment in *SRI* values correlates with a decrease in the volume of distribution after 72 hours of CRRT treatment. The *SRI* showed no correlation with actual solute removal (r^2=0.032; p=0.49)

Finally, *EKR,* a dose expression that utilize blood-side kinetics, showed lower values during the first four 12-hour periods, and thereafter its values seem to have less variation. Thus, the *EKR* expression does not seem to be affected by the decline in volume of distribution. *EKR* showed a good correlation with actual solute removal (r^2=0.250; p<0.001).

Filter operational characteristics affecting dialysis dose measurement

Parameters to compute FUN/BUN ratio were available for 159 of the 175 filters used. The median [IQR] FUN/BUN at the time of filter change was higher in those patients where reasons for stopping treatment were not filter clotting, concentration polarization, or filter leak (0.96 [0.94-0.98] vs. 0.87 [0.77-0.95]; p<0.0001). The median filter duration was 75 hours (48.5-115.6), with a minimum duration of 1.3 hours and a maximum duration of 183.3 hours. The median filter life was lower in the group with reduced filter efficacy (68.1 h [44.3-96.6] vs. 87.0 h [61.9-119]; p=0.01). We assessed filter function (FUN/BUN ratio) as a factor that could influence dialysis dose measurement. As shown in Figure 3, only *ERK*, a blood-side kinetic measurement, and K_{urea} derived from dialysate-side measurements showed a decline in their values as filter function decreased.

DISCUSSION

"Dose" in CRRT is a broad concept and its measurement and expression constitutes a real challenge. The ideal dose expression in CRRT should have some essential characteristics. It should be numerically comparable across all modalities and treatment schedules; it should relate to patient outcomes, since dose by definition does not represent a clinical end point per se (17); it should relate to the technical process of solute removal; and it should be simple to interpret and useful to guide therapy. In recent years, dose in CRRT has been expressed using the dose metric mL/kg/h; this dose expression can be related to patient outcomes, to the technical process of solute removal, and can be easily used to prescribe and to adjust CRRT (3, 5-7, 18-20). This dose expression operates well only at a steady state with respect to BUN concentrations in patients with a constant protein catabolic rate (nPCR). In this ideal scenario, and as long filter function remains constant, K_{urea} and UnMR will be constant and parallel to each other along treatment time. However, most of the previous assumptions cannot be made in critically-ill patients with AKI. Finally, the mL/kg/h dose expression cannot be used to compare dose in intermittent methods (e.g., IHD, SLED), for which the common approach is to express dose as single pool Kt/V_{urea}. This approach is not correct since AKI is associated with catabolism, which alters urea generation and will have a profound influence on clearance data based on pre-dialysis and post-dialysis BUN (21). It might be more accurate to use direct-dialysate urea nitrogen collection and compute urea clearance expressing delivered dose as mL/min; this would allow the dose between different types of RRT to be compared.

In the present study we evaluated six different methods of assessing and expressing delivered dose in CRRT; we employed three equations derived from blood-side kinetics, and three equations derived from dialysate-side kinetics. The first parameter compared was clearance (K, mL/min) calculated using blood-side for dialysate-side measurements; we compare both of these parameters with actual mass removal expressed as a rate (UnMR; mg/min), because this value adequately involves the process of solute removal across time. A significant correlation was found between dialysate-side clearance (K_D, mL/min) and UnMR; conversely, we did not find any correlation when blood-side clearance (K_B, mL/min) was compared. Blood-side clearance measurements are affected by the compartmentalization phenomenon, which occurs within the dialyzer and within the patient's body. Compartmentalization of solute during dialysis can result in overestimation of the amount of solute removed when this is done by using blood-side kinetics (pre- and post-dialysis blood samples) (22). As we have shown, K_D provides more accurate mass transfer information than a blood-side determination, although it is important to recognize that clearance is not a measure of actual mass removal of a particular solute by dialysis. K_D more clearly demonstrates the effect of some operational treatment characteristics (e.g., filter fouling and filter clotting) on actual solute removal. We have previously shown that clotting and protein fouling of the filter reduces its efficacy (FUN/BUN ratio) across time and this in turn can decrease the amount of solutes removed by dialysis (UnMR, mg/min) (23); this reduction in the amount of solutes removed is better correlated with K_D than with K_B. This observation also highlights two important aspects of acute dialysis: the importance of the measuring dose in AKI; and the continuous assessment of the factors that influence delivering a prescribed dose, such as filter efficiency, type of catheter used and site, and type of anticoagulation used. Recent studies have highlighted the difference between the prescribed dose and the delivered dose; we have found a gap that ranges from 15% to 32% (5, 7, 24). Several patient- and treatment-related factors could prevent the prescribed dose from being delivered. Among treatment-related factors, the influence of filter efficacy on achieving a prescribed dose needs to be emphasized, as has been shown previously by other investigators. Uchino et al showed a significant inverse correlation between circuit down-time, and creatinine and urea percentage reduction; the main cause of circuit down-time was filter clotting (25). We have previously shown that there is a gap between the prescribed dose and the delivered dose that usually ranges between 20% and 30%, and that by using the total effluent volume as a surrogate of delivered dose, the delivered dose of dialysis will be overestimated (23). The influence of filter efficacy on delivered dose could only be accounted for by K_D and not by K_B. The influence on solute clearance of some operational characteristics like frequent filter clotting was also emphasized by the authors of the RENAL study (20), and is a factor that must be considered in future clinical trials.

We compared the different dose metrics with the process of solute removal. In the case of Kt/V_{urea}, one might expect a better correlation between Kt/V_D and the process

of solute removal, since K_{urea} was derived from urea mass removal; however, neither of the parameters showed a significant correlation with UnMR (Kt/V_D and Kt/V_B) and also showed increasing values after 72 hours of therapy, coinciding with a decrease in urea volume of distribution. The latter observation shows that the use of Kt/V_{urea} as an expression in acute dialysis is not free of difficulties and does not adequately reflect solute removal, mainly because of the uncertainty about the determination of urea volume of distribution.

The use of TBW as a surrogate of urea volume of distribution constitutes another problem, since TBW determined by anthropometric measurements yield significantly lower measures compared to TBW determined by physiological formulae or by bioelectrical impedance analysis, as pointed out by Himmelfarb et al (26). Kt/V_B and Kt/V_D could not account for the effect of filter efficacy on delivered dose either (Fig. 2). The use of Kt/V for dose assessment in patients with AKI requires potentially unreasonable assumptions about V and UKM that cannot be made in patients with AKI (21, 27).

Since *SRI* is calculated using direct urea dialysate quantification, which most experts consider a gold standard for assessing dialysis dose (1), one would expect it to be a better parameter for assessing the delivered dialysis dose. However, we did not find a direct correlation between *SRI* and UnMR. This could be due to the reliance of *SRI* on peak BUN concentrations, which in critically-ill patients with AKI are very asymmetrical and variable before a steady state is reached (28, 29). The peak urea concentration hypothesis that was validated in patients with ESRD cannot be extrapolated (28). We also demonstrated that although we only considered *SRI* measurements for the analysis after a steady state was reached in order to abrogate the effect of peak BUN on *SRI*, the delivered dialysis dose increased, contrary to what one would expect (effect of operational characteristics in delivered dose) (Fig. 3). The effect of decreasing the values for the volume of distribution in the *SRI* calculation could explain this observation. Finally, as pointed out by Marshall (28) *SRI* does not express CRRT dose in a manner that is easy to relate to patient outcomes, to the process of solute removal, or to residual kidney function.

A better correlation was found between *EKR* and UnMR. *EKR* has some advantages over *SRI*; *EKR* is calculated using time average urea concentrations (TAC) as opposed to the peak urea concentrations used for calculating SRI. Ratanarat et al consider *EKR* a poor indicator of dialysis dose because the key assumption of this parameter is that urea generation rate is equal to the urea removal rate: an assumption that fails to hold in hypercatabolic states (15). We considered that calculating *EKR* after a steady state is reached could solve this problem and *EKR* could became a valid method to quantify delivered dialysis dose. The reduction in volume of distribution (V) during consecutive days did not affect *EKR* since V is not used for these calculations. *EKR* also correlates with filter efficacy as its values decrease as filter function declines (Fig. 3). Another advantage of *EKRc* is that it is expressed in mL/min, which can be easily correlated with parameters like residual renal function and actual solute removal (30).

From a practical standpoint, dose measurements should guide prescriptions to match patient need. This requires an assessment of the delivered dose and the effects of the dose on patient parameters. Dialysate-side methods focus on the operational aspects of the therapy to show that the procedure is clearing solutes as intended. Blood-side methods capture the effects of the therapy on patient solute level. Consequently, the utilization of the two methods is for different purposes: dialysate-side measurements ensure delivery of the dose, while blood-side measurements help define if changes need to be made to the prescription. Additionally, dialysate-side methods quantify each session, while blood side methods also capture the changing renal function and equate it to patient need. In AKI, as renal function is changing, EKR will give an accurate assessment of the patient needs, and K_D provides an estimate of the filter performance; while FUN/BUN ratio permits a dynamic assessment to compute the delivered clearance as filter efficacy decreases. All these measurements thus provide different information and together can help guide therapy. At steady state, EKR could be used to modify the dose, and K_D and FUN/BUN could be used to ensure that the filter is working.

CONCLUSIONS

In summary, delivered dose expressed as clearance (K_D, mL/min) and calculated using dialysate-side measurements constitutes an excellent method for assessing and expressing delivered dose in CRRT. K_D has a strong correlation with the urea mass removal and can account for some important operational characteristics that influence delivered dose such as filter function, filter duration, and

effective time of treatment. K_D is also easy to understand, and the units in which it is expressed (mL/min) are compatible with those of residual kidney function. *EKR* also provides a good estimate of delivered dialysis dose in CRRT since it is a true mass balance parameter and also provides a tool to compare different types of therapies. EKRc (EKR corrected to a urea volume of distribution of 40 L) can be determined from single pool Kt/V_{urea} using monograms (2, 31), and its value could be numerically transformed to effluent rate if one choses to express dose as mL/h/kg by multiplying *EKR* by 0.975, as was first described by Marshall et al (28, 32). Kt/V_{urea} and *SRI* are dose expressions that in our opinion do not fit many of the characteristics that an ideal dose expression should have (i.e., the calculation of Kt/V_{urea} is based on assumptions that cannot be made in patients with AKI).

Expressing dose as mL/kg/h requires that a complete saturation of effluent has occurred; however, there are some common situations where this is not true, for instance, when pre-dilution is used and when filter function is compromised. Effluent rate (mL/kg/h) can only empirically provide an estimate of the dose in CRRT. For clinical practice, we recommend that the delivered dose should be measured and expressed as K_{urea} using dialysate-side measurements, and that filter function should be closely monitored using the FUN/BUN ratio. *EKR* also constitutes a good method for dose comparisons over time and across modalities. We believe that these parameters would provide a more accurate quantification of dose in CRRT and increase the quality of therapy delivered.

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