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Solute clearance in CRRT: prescribed dose versus actual delivered dose

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Abstract

Background. Substantial efforts have been made toward defining the dose threshold of continuous renal replacement therapy (CRRT) associated with improved survival in critically ill patients with acute kidney injury. Published studies have used prescribed effluent rates, expressed as total effluent volume (TEV) per weight and unit time (mL/kg/h), as a surrogate for dose. The purpose of this study was to compare differences in CRRT dose based on prescribed effluent rate, measured TEV and direct measurement of urea and creatinine clearance.

Methods. We analyzed data that had been prospectively collected on 200 patients enrolled in a randomized trial comparing survival with a prescribed effluent rate of 20 mL/kg/h (standard dose) to 35 mL/kg/h (high dose) using pre-dilution continuous venovenous hemodiafiltration (CVVHDF). Filters were changed every 72 h. Blood urea nitrogen (BUN), serum creatinine (SCr), effluent urea nitrogen (EUN) and effluent creatinine (ECr) were collected daily. Actual delivered dose was calculated as: (EUN/BUN)*TEV for urea and (ECr/SCr)*TEV for creatinine. Data were available for 165 patients.

Results. In both groups, prescribed dose differed significantly from the measured TEV dose ($P < 0.001$). In the standard dose group, there was no difference between the measured TEV dose and actual delivered urea and creatinine clearances. However, in the high-dose group, measured TEV dose differed significantly from delivered urea clearance by 7.1% ($P < 0.001$) and creatinine clearance by 13.9% ($P < 0.001$).

Conclusions. Dose based on prescribed effluent rate or measured TEV is a poor substitute for actual CVVHDF creatinine and urea clearance.

Keywords: acute kidney injury; continuous renal replacement therapy; critical care nephrology; dialysis dose

Introduction

Acute kidney injury (AKI) occurs commonly in the intensive care unit (ICU) and is an independent predictor of mortality [1]. Despite improvements in dialysis technology over the past 50 years, the mortality rate of AKI in the ICU remains ~50% [2, 3]. Continuous renal replacement therapy (CRRT) is the most common dialytic therapy utilized in management of AKI in the ICU worldwide [4]. Consequently, substantial efforts have been made to establish a dose–response relationship for CRRT [5]. Seven randomized controlled studies have examined outcomes in patients with AKI requiring CRRT in the ICU. Two trials demonstrated a survival benefit following more intense dialysis [6, 7]. Five trials demonstrated no survival benefit [8–12].

Each of these studies utilized weight-based effluent rates in mL/kg/h as a surrogate for dialysis dose. However, none of these studies reported direct measures of solute clearance to compare the prescribed versus delivered dose. Many variables may contribute to reduced solute clearance in CRRT, including time off the machine for procedures, machine alarms, filter clotting and the use of prefilter replacement fluid [13]. We retrospectively analyzed data from a prior prospective dose study performed at our medical center to determine the relationship between prescribed dose, dose based on measured effluent rate and dose based on measured urea and creatinine concentrations.

Materials and methods

Patients

Over a 32-month period (August 2003 to March 2006), 200 patients were recruited from the medical and surgical ICUs at the University of

Alabama at Birmingham Hospital for a study designed to evaluate standard versus high dose continuous venovenous hemodiafiltration (CVVHDF) in patients who developed AKI. Patients were randomized to either standard dose (20 mL/kg/h) or high dose (35 mL/kg/h) CVVHDF. All patients had AKI in the ICU, as defined by having at least one of the following: (1) volume overload despite diuretics, (2) oliguria (urine output <200 mL/12 h) despite fluid resuscitation and diuretics, (3) anuria (urine output <50 mL/12 h), (4) azotemia [blood urea nitrogen (BUN) ≥ 80 mg/dL] or (5) hyperkalemia (K^+ ≥ 6.5 mmol/L) and/or an increase in serum creatinine > 2.5 mg/dL from normal values or a sustained rise in serum creatinine of ≥1 mg/dL over baseline. Exclusion criteria were end-stage renal disease, a history of having previously had intermittent hemodialysis, >24 h of CRRT at the time of enrollment or weight >125 or <50 kg due to limitations of the CRRT machine to deliver doses required for the study at those weights. CVVHDF was initiated at the discretion of the consulting nephrologist, without consideration of patient's eligibility for the study.

Each of the 200 patients enrolled had their hematocrit, BUN, serum creatinine (SCr), effluent urea nitrogen (EUN) and effluent creatinine (ECr) checked daily. Total CVVHDF effluent volume and total time of actual CVVHDF treatment (min/24-h period) were measured daily as well. Complete data were available for 1237 days from a total of 165 patients. The standard-dose arm yielded 587 observations from 83 patients. The high-dose arm yielded 650 observations from 82 patients.

CRRT technique

CVVHDF was performed with COBE Prisma (Lakewood, CO) M100 set and AN69 dialyzer (effective surface area 0.9 m^2) through a double-lumen 12F catheter inserted into the internal jugular, subclavian or femoral vein. Hemodiafiltration was accomplished using blood flow rates of 100–150 mL/min and predilution replacement fluid. Regional citrate or no anticoagulation was used according to the consulting nephrologist's clinical decision, with regional citrate anticoagulation employed ~95% of the time and no anticoagulation in the remainder. Dialyzers were changed due to circuit failure from clotting, after 72 h of use or when the patient was off CVVHDF for >2 h due to a procedure or imaging study.

The patients were randomized to each arm based on the prescribed effluent rate. The prescribed effluent rate (mL/h) is the sum of the replacement fluid rate, dialyzate rate and fluid removal rate. For example, a 70-kg patient assigned to the high-dose arm would require an effluent rate of 2450 mL/h (70 kg × 35 mL/kg/h). The replacement fluid rate, dialyzate rate and fluid removal rate for that patient would be adjusted to achieve an effluent rate of 2450 mL/h/day for the study duration. Dose was calculated only once per patient and based on the patient's actual body weight on the day of CVVHDF initiation. This dose remained constant throughout the treatment period and was not adjusted for body weight changes. Every attempt was made to divide the effluent rate equally between the replacement fluid and dialyzate.

Calculations

Urea clearance (K_U, mL/kg/h) and creatinine clearance (K_C, mL/kg/h) were calculated for prescribed, estimated and delivered doses. Units of mL/kg/h were utilized rather than mL/min because mL/kg/h is the most widely accepted method of measuring CRRT dose.

Prescribed K (K_P). Prescribed K (K_P) was calculated from the programmed effluent rate from the initial prescription. It was corrected for the effect of pre-dilutional replacement fluid. All clearance formulas are demonstrated below [14–17].

$$K_P = Q_E * [Q_{BW}/(Q_{BW} + Q_{RF})]/W(\text{mL/kg/h}),$$

$$Q_E = Q_{RF} + Q_D + Q_{RR}(\text{mL/h}),$$

$$Q_{BW} = (1-\text{HCT}) * Q_B(\text{mL/h}),$$

where K_P is the prescribed clearance corrected for predilutional replacement fluid, Q_E is the prescribed effluent rate (mL/h), Q_{RF} is the prefilter replacement fluid flow rate (mL/h), Q_D is the dialyzate flow rate (mL/h), Q_{RR} is the fluid removal rate (mL/h), W is the patient's weight at initiation of CVVHDF (kg), Q_{BW} is the blood water flow rate (mL/h), Q_B is the blood flow rate (mL/h) and HCT is the hematocrit.

Estimated clearance (K_E). Estimated clearance was calculated from the measured effluent volume over 24 h, adjusted for the effect of predilutional replacement fluid.

$$K_E = \text{TEV} * [Q_{BW}/(Q_{BW}+Q_{RF})]/W(\text{mL/kg/h}),$$

where K_E is the estimated clearance and TEV is the measured effluent volume in a given 24-h period.

Solute clearance (K_U and K_C). Solute clearance was calculated from the measured effluent rate over 24 h and the effluent to BUN ratio for urea clearance and the effluent to serum creatinine ratio for creatinine clearance.

$$K_U = \text{TEV} * (\text{EUN}/\text{BUN})/W(\text{mL/kg/h}),$$

$$K_C = \text{TEV} * (\text{ECr}/\text{SCr})/W(\text{mL/kg/h}),$$

where K_U is the measured urea clearance and K_C is the measured creatinine clearance.

Statistical analyses

Continuous variables were expressed as mean ± SD and analyzed using the unpaired *t*-test or Wilcoxon rank sum test, as indicated. Nonparametric variables were expressed as median and 25th–75th percentiles and analyzed using the Mann–Whitney test. Categorical variables were expressed as absolute (n) and relative (%) frequency and were analyzed using Chi-square or Fisher's Exact, where indicated. All statistical tests were two-tailed and $P < 0.05$ was considered significant. Analyses were performed using JMP 8.0.1 Statistical Software (Cary, NC) and GraphPad InStat 3.0 (San Diego, CA).

Results

Baseline patient characteristics were similar between dose groups (Table 1). Mean (SD) age for the standard dose group was 62 ± 14 years, while that for the high-dose group was 59 ± 15 years. Approximately 60% of the study subjects in both groups were men. Roughly 95% of the study subjects in each arm received citrate anticoagulation, with the remainder receiving no anticoagulation. There was no significant difference in filter clotting between both dose groups. Mean (SD) serum creatinine was 4.2 ± 2.2 mg/dL in the standard-dose group and 4.2 ± 1.6 mg/dL in the high-dose group at time of CRRT initiation. Acute physiology and chronic health evaluation (APACHE) II scores at initiation of CRRT were similar for both groups.

Table 2 shows the prescribed clearance, estimated clearance and measured urea and creatinine clearances for the standard-dose and high-dose groups. Mean prescribed clearance was lower than the prescribed 20 versus 35 mL/kg/h dose due to the effect of predilutional replacement fluid. The standard and high dose cohorts differed significantly for each calculated clearance ($P < 0.001$ for all comparisons), demonstrating separation of dose between

Table 1. Baseline patient characteristics at initiation of CVVHDF

Characteristic	Standard dose (20 mg/kg/h)	High dose (35 mg/kg/h)	P
Patients (n)	83	82	
Citrate anticoagulation	95	97	0.41
Age (years)	62 ± 14	59 ± 15	0.22
Male gender (%)	60	63	0.68
Weight (kg)	91 ± 18	94 ± 18	0.27
Creatinine (mg/dL)	4.2 ± 2.2	4.2 ± 1.6	0.92
BUN (mg/dL)	76 ± 40	77 ± 36	0.82
Urine output (mL/day)	611 ± 792	522 ± 574	0.40
APACHE II	26.0 ± 6.3	26.3 ± 5.9	0.76

both groups for prescribed dose, estimated effluent dose and actual measured urea and creatinine clearance.

For the standard dose cohort, K_P was 17.62 ± 0.96 mL/kg/h, K_E was 15.79 ± 2.47 mL/kg/h, K_U was 15.55 ± 3.07 mL/kg/h and K_C was 15.67 ± 3.88 mL/kg/h. K_P differed significantly from K_E, K_U and K_C ($P < 0.001$ for all comparisons). K_P over-estimated K_U and K_C by 11.7 and 11.1%, respectively. There was no statistically significant difference between K_E, K_U and K_C (Figure 1).

For the high dose cohort, K_P was 28.10 ± 1.44 mL/kg/h, K_E was 25.10 ± 3.16 mL/kg/h, K_U was 23.32 ± 5.30 mL/kg/h and K_C was 21.62 ± 5.50 mL/kg/h. K_P, K_E, K_U and K_C all differed significantly from each other ($P < 0.001$ for all comparisons). K_E overestimated K_U and K_C by 7.1 and 13.9%, respectively. K_P overestimated K_U and K_C by 17.0 and 23.1%, respectively (Figure 1).

Table 2. CVVHDF clearance comparisons

	Standard dose (20 mg/kg/h)	High dose (35 mg/kg/h)	P
Prescribed clearance (K_P)	17.62 ± 0.96	28.10 ± 1.44	<0.001
Estimated clearance (K_E)	15.79 ± 2.47	25.10 ± 3.16	<0.001
Urea clearance (K_U)	15.55 ± 3.07	23.31 ± 5.30	<0.001
Creatinine clearance (K_C)	15.67 ± 3.88	21.62 ± 5.5	<0.001

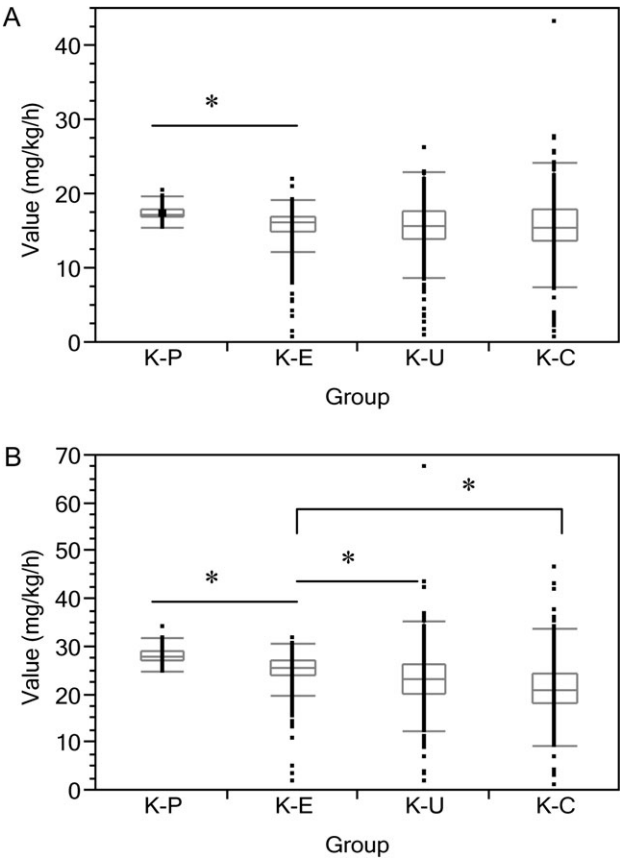

Fig. 1. Distribution of prescribed and measured clearance values for the (**A**) 20 mg/kg/h cohort and the (**B**) 35 mg/kg/h cohort. Value denotes serum measurement in mg/kg/h. K_P = prescribed clearance. K_E = estimated clearance. K_U = measured urea clearance. K_C = measured creatinine clearance. Each box and whisker plot shows the median value (line in the middle of each box) and 25th–75th quantile (box). Whiskers include 95% of measures. *$P < 0.001$ for designated comparison groups.

Discussion

In all CRRT modalities, the 'effluent' represents the end product of filtration and comprises the ultrafiltrate in convective therapies, the spent dialyzate in diffusive therapies and the sum of both in combined therapies. CRRT solute clearance is determined by the ratio between the concentration of the solute in the effluent and in the plasma multiplied by the effluent rate. Because urea is a small molecular weight solute, it reaches complete equilibrium in the effluent; thus, the ratio of the concentration of urea in the effluent to plasma side of the dialysis membrane should be 1. Urea clearance becomes equal to the effluent rate, provided that the replacement fluid is given post-filter. For the published randomized trials regarding dose, utilization of TEV to estimate CRRT dose is based on this assumption that urea and other small solutes diffuse freely across the dialysis membrane.

For both dose cohorts in this study, the above assumption did not hold true; K_P (accounting for the predilution effect of replacement fluid) overestimated K_E, K_U and K_C. For the standard dose cohort, K_E (accounting for the predilution effect of replacement fluid) was no different from K_U or K_C. However, for the high dose cohort, K_E significantly overestimated both actual urea and creatinine clearance. The creatinine clearance was overestimated by an even larger margin than urea clearance. These results demonstrate that prescribed dose based on effluent rate significantly overestimates actual delivered dose based on measured solute clearances, even when correcting for predilution effect and time on therapy. As one would expect from previous research, this discrepancy increases with larger solute size and higher prescribed effluent rates [18].

Since the CRRT machine maintains a constant effluent generation rate, the reduced efficiency of solute removal must result directly from compromised filter permeability. One possible mechanism of compromised filter permeability is clotting of the filter due to insufficient anticoagulation. However, ~95% of patients in each arm received citrate anticoagulation, with the remaining 5% receiving no anticoagulation. Other proposed mechanisms involve protein layering on the membrane, which would effectively reduce pore size and lead to preferential reduction in the clearance of larger molecules [19]. Over 15 years ago, Langsdorf and Zydney [20] showed a reduction in middle molecule clearance using the AN69 membrane attributed to a layer of plasma proteins on the membrane. The thickness of the protein layer increases with time, leading to further reduction in solute clearance, particularly those >10 000 D [21]. Messer *et al.* [22] recently demonstrated a reduction in middle molecule clearance in CRRT *in vitro* when convective clearance and higher ultrafiltration rates are utilized. Since the molecular weight of creatinine is almost twice that of urea (113.1 versus 60.1 D), the further reduction in creatinine clearance relative to urea clearance in the higher dose arm of our study suggests this protein layering as a possible mechanism despite the use of

citrate anticoagulation and changing of filter every 72 h routinely.

In our dose study, despite the discrepancy in the prescribed dose and actual delivered dose, there was still a significant difference in small solute clearance in the standard-dose group versus the high-dose group. However, given that the measured creatinine clearance had a greater reduction in the high dose cohort as compared to the standard dose cohort, it is possible that the dose prescriptions in our dose study and the Acute Renal Failure Trial Network (ATN) study [10] and Randomized Evaluation of Normal versus Augmented Level Replacement Therapy (RENAL) study [11] may have delivered similar clearances for solutes larger than creatinine despite achieving nearly perfect dose separation in small solute clearance. This was seen in the *in vitro* study published by Hofman and Fissell [23]. They analyzed dialyzate-side clearances of tracer molecules from 10 to 100 KD molecular weights in an *in vitro* simulation of bovine blood using CVVHDF at 20 and 35 mL/kg/h effluent. Their results demonstrated that middle molecule clearance differed by <2 mL/min between the two dosing arms. They inferred from their results that the CRRT prescription used in our trial and the ATN study achieved dose ranging for small molecules while holding middle molecule clearance nearly constant due to protein polarization. This suggests that we may not yet know what the 'ideal' CRRT dose is to improve outcome. It is possible that higher clearances of middle molecular weight solutes may have a survival benefit.

Claure-Del Granado *et al.* [24] recently published a similar study to ours by comparing measured urea clearance to the prescribed CRRT dose based on effluent rate. Their results demonstrated that for urea clearance, even after accounting for the effects of predilution, the prescribed and estimated clearance overestimated the delivered dose by 26 and 25.7%, respectively. This is a much larger discrepancy than seen in our study. This discrepancy may be due to several reasons. Firstly, their study population had overall higher prescribed effluent rates (mean 30 mL/kg/h). Our study had two dosing arms: 20 versus 35 mL/kg/h. We noticed that the reduction in clearances for both urea and creatinine were greater in our high-dose arm at effluent rates comparable to the study by Claure-Del Granado. Secondly, we changed our filters every 72 h, while Claure-Del Granado *et al.* let their filters run much longer, allowing for more protein layering to occur. Finally, 18% of all their treatments were done with a Braun Diapact machine with a Fresenius NR60 filter. The rest of the treatments were done with a Prisma using an M100 filter. It is possible that the membrane characteristics of the NR60 differ from the M100 and result in differences in actual solute clearances.

Despite the published randomized dose trials in CRRT, controversy remains about the best way to measure and what constitutes optimal dose of CRRT for patients with AKI. The methods used for CRRT dose quantification in AKI have several limitations and have not been fully validated in this specific population. They have focused on urea clearance as the target clearance molecule for outcome. Even though adequate separation between small molecule clearance (as with urea) should be achieved in the dose studies, this does not necessarily apply to larger molecular weight molecules. Over the past few years, several articles have been published regarding the clearance of middle molecular weight molecules. Given our results regarding creatinine clearance, which is only a slightly larger molecule than urea, it becomes apparent that clearance of any larger molecules between the high- and standard dose cohorts is similar, without a dose separation. Since we do not know which molecule to target clearance for better outcomes, it is important to measure other molecules and design studies that look at other parameters for dose and ensure a dose separation with other solutes.

Our study has several limitations. It involves only a single center. Data were analyzed retrospectively. Thirty-five patients enrolled in the initial study had incomplete data and therefore were excluded from this analysis.

In conclusion, prescribed effluent rates overestimate solute removal in predilutional CVVHDF when utilizing doses commonly used today. Therefore, direct measurements of solute clearance are indicated if one is targeting a specific CRRT dose. Further research should focus on determining the optimal dose parameter in CRRT for AKI, including clearance of larger molecular weight solutes in AKI and its effect on outcomes. Furthermore, additional studies are needed to determine how different membrane properties affect solute clearance in CRRT.

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Conflict of interest statement. None declared.

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