Hemodialysis International 2014; ••:••–••

Anticoagulation, delivered dose and outcomes in CRRT: The program to improve care in acute renal disease (PICARD)

Rolando CLAURE-DEL GRANADO,[1] Etienne MACEDO,[1] Sharon SOROKO,[1] YeonWon KIM,[2] Glenn M. CHERTOW,[2] Jonathan HIMMELFARB,[3] T. Alp IKIZLER,[4] Emil P. PAGANINI,[5] Ravindra L. MEHTA[1]

[1]Medicine, University of California San Diego, San Diego, California, USA; [2]Medicine, Stanford University School of Medicine, Palo Alto, California, USA; [3]Medicine, Kidney Research Institute, University of Washington, Seattle, Washington, USA; [4]Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA; [5]Medicine, Cleveland Clinic Foundation, Cleveland, Ohio, USA

Abstract

Delivered dialysis dose by continuous renal replacement therapies (CRRT) depends on circuit efficacy, which is influenced in part by the anticoagulation strategy. We evaluated the association of anticoagulation strategy used on solute clearance efficacy, circuit longevity, bleeding complications, and mortality. We analyzed data from 1740 sessions 24 h in length among 244 critically ill patients, with at least 48 h on CRRT. Regional citrate, heparin, or saline flushes was variably used to prevent or attenuate filter clotting. We calculated delivered dose using the standardized Kt/V_{urea}. We monitored filter efficacy by calculating effluent urea nitrogen/blood urea nitrogen ratios. Filter longevity was significantly higher with citrate (median 48, interquartile range [IQR] 20.3–75.0 hours) than with heparin (5.9, IQR 8.5–27.0 hours) or no anticoagulation (17.5, IQR 9.5–32 hours, $P < 0.0001$). Delivered dose was highest in treatments where citrate was employed. Bleeding complications were similar across the three groups ($P = 0.25$). Compared with no anticoagulation, odds of death was higher with the heparin use (odds ratio [OR] 1.82, 95% confidence interval [CI] 1.02–3.32; $P = 0.033$), but not with citrate (OR 1.02 95% CI 0.54–1.96; $P = 0.53$). Relative to heparin or no anticoagulation, the use of regional citrate for anticoagulation in CRRT was associated with significantly prolonged filter life and increased filter efficacy with respect to delivered dialysis dose. Rates of bleeding complications, transfusions, and mortality were similar across the three groups. While these and other data suggest that citrate anticoagulation may offer superior technical performance than heparin or no anticoagulation, adequately powered clinical trials comparing alternative anticoagulation strategies should be performed to evaluate overall safety and efficacy.

Key words: Anticoagulation, citrate, continuous renal replacement therapy

Correspondence to: R. L. Mehta, MD, 200 W Arbor Drive, Mail Code 8342, San Diego, CA 92103, U S A. E-mail: rmehta@ucsd.edu

Disclosure:The work of Rolando Claure-Del Granado and Etienne Macedo was made possible through an International Society of Nephrology Fellowship award. Etienne Macedo is additionally supported by a training grant from the Conselho Nacional de Desenvolvimento Científico e Tecnologico. The study was supported by the National Institutes of Health (NIH-NIDDK RO1-DK53412, RO1-DK53411, and RO1-DK53413) and by the NIH-NIDDK O'Brien Center.

DOI:10.1111/hdi.12157

INTRODUCTION

Continuous renal replacement therapies (CRRT) require anticoagulation to prevent clotting in the extracorporeal circuit. Systemic unfractionated heparin and regional citrate are the two most commonly employed methods to prevent circuit clotting.[1,2] Systemic unfractionated heparin has traditionally been the most common form of anticoagulation in CRRT. Heparin has several advantages including relatively low cost, ease of administration, and wide availability. Monitoring of partial thromboplastin time is familiar to most physicians and nurses in the intensive care unit (ICU) and dialysis practice; moreover, heparin can be relatively easily reversed (with protamine) if required.[3] However, systemic use of unfractionated heparin has several drawbacks including most importantly bleeding complications, which if significant, requires transfusions. Relatively rare conditions, including heparin-induced thrombocytopenia (and arterial thrombosis), and heparin resistance[4–8] can also complicate its use. Regional citrate anticoagulation constitutes an alternative to systemic unfractionated heparin and has some advantages; however, regional citrate anticoagulation is more cumbersome to deliver, and requires more extensive monitoring to prevent or attenuate metabolic consequences such as hypocalcemia, metabolic alkalosis, and in some patients with advanced chronic liver disease, an anion gap metabolic acidosis.[9]

The efficacy of CRRT depends on circuit longevity, which is influenced by anticoagulation and several operational characteristics of the modality. Maintaining the patency of the extracorporeal circuit could reduce the difference between prescribed and delivered dialysis dose, mainly due to circuit downtime as shown by previous studies.[10–13] In this study, we evaluated the association of three alternative anticoagulation strategies (regional citrate, systemic unfractionated heparin and no anticoagulation (saline flushes alone) on CRRT safety and efficacy. We hypothesized that regional citrate anticoagulation would be associated with enhanced filter longevity and efficiency of solute clearance compared with unfractionated heparin or no anticoagulation. In addition, we hypothesized that after adjusting for comorbid conditions and severity of illness, in-hospital mortality rates would be lower in patients managed with citrate anticoagulation.

MATERIAL AND METHODS

Patients and data

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, 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 acute kidney injury (AKI) in the ICU were evaluated by PICARD study personnel for potential study participation. Informed consent was obtained from all study participants or their proxies.

We analyzed data from 1740 sessions 24 h in length among 244 critically ill patients with at least 48 h on CRRT (continuous venovenous hemofiltration, hemodialysis or hemodiafiltration [CVVH, CVVHD or CVVHDF]) (Figure 1). A detailed description of PICARD inclusion and exclusion criteria, data elements, data collection, and management strategies has been described elsewhere.[14] Acute kidney injury was defined as an increase in serum creatinine (sCr) ≥0.5 mg/dL with baseline sCr <1.5 mg/dL, or an increase in sCr ≥1.0 mg/dL with baseline sCr ≥1.5 mg/dL and <5.0 mg/dL. Patients with a baseline sCr ≥5.0 mg/dL were not considered for study inclusion. Patients who were contacted by study

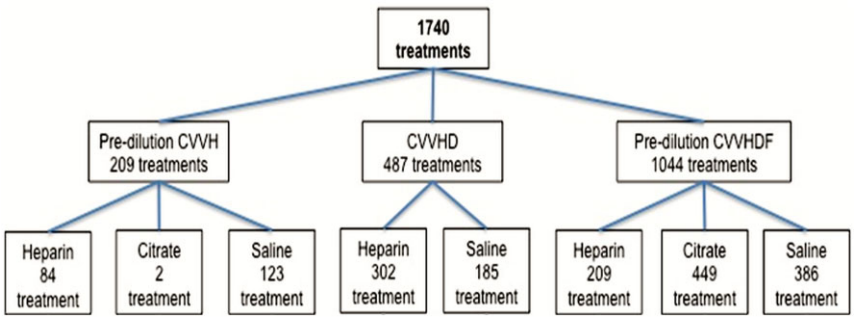

Figure 1 Distribution of type of CRRT and different anticoagulation strategies used. CRRT, continuous renal replacement therapies; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration.

personnel and who signed informed consent were enrolled in the study cohort. The Committees on Human Research at each participating clinical site approved the study protocol and informed consent.

We applied conventional definitions and reviewed medical records to define the presence or absence of chronic conditions. All interventions were determined by the treating physicians and not influenced by the study personnel including the timing, modality, and intensity of dialysis, and the type of anticoagulation if provided. The distribution of type of CRRT treatment and type of anticoagulation provided is shown in Figure 1.

Dialysis technique

Three types of CRRT were employed: pre-dilution CVVH, CVVHD, and pre-dilution CVVHDF. These modalities were performed with five different CRRT machines; almost half (48%) of treatments were performed using a Gambro PRISMA (Lakewood, CO, USA) CRRT machine, with a 0.7–1.8 m^2 AN69 membrane (MF-100 filter set for PRISMA); 26% of the treatments were performed using an Aquarius Baxter system (Edwards Lifesciencies, Unterschleissheim, Germany); 20% of the treatments were performed using a HOSPAL Gambro PRISMA machine and 5% were performed with a B. Braun Diapact machine, with a polysulfone synthetic high-flux filter (Fresenius NR60; Fresenius Medical Care Deutschland GmbH, Bad Homburg v. d. H., Germany); and other types of CRRT machines were employed in fewer than 1% of treatments.

By study protocol, the type of anticoagulation was determined by each center and each team of treating physicians. Patients generally received regional citrate anticoagulation, systemic heparin anticoagulation or no anticoagulation; with the latter, saline flushes were employed to prevent or ameliorate filter clotting.

The mean 24-hour heparin dose employed was 9681 ± 7102 IU. The 4% trisodium citrate (TSC) mean infusion rate was 180 mL/h and the mean TSC dose was 445 ± 161 mmol. TSC was added at the arterial catheter port and ionized calcium levels were 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.

Quantification of dose

Dose assessment was performed using *Std*Kt/V_{urea} as it allows comparing treatment efficacy among different renal replacement modalities and treatment schedules. Delivered *Std*Kt/V_{urea} were computed using the following equations:[15]

$$\textit{Std}\mathrm{Kt/V\ CVVH} = [(\mathrm{Qr} + \mathrm{Quf\ net}) \times (\mathrm{Qp}/\mathrm{Qp} + \mathrm{Qr})] \times 10.080/(\mathrm{W} \times 0.55) \times \mathrm{S}$$

$$\textit{Std}\mathrm{Kt/V\ CVVHD} = (\mathrm{Qd} + \mathrm{Quf\ net}) \times [10.080/(\mathrm{W} \times 0.55)] \times \mathrm{S}$$

$$\textit{Std}\mathrm{Kt/V\ CVVHDF} = [(\mathrm{Qd} + \mathrm{Qr} + \mathrm{Quf\ net}) \times (\mathrm{Qp}/\mathrm{Qp} + \mathrm{Qr})] \times 10.080/(\mathrm{W} \times 0.55) \times \mathrm{S}$$

where W is patient weight; S is sieving coefficient; Qd is dialysate flow rate (mL/h); Qr is replacement flow rate; Quf net is net ultrafiltration rate; and Qp is plasma flow rate at the blood pump and is calculated by this formula:

$$\mathrm{Qp} = (1 - \mathrm{hematocrit}) \times \mathrm{Qb}$$

For prescribed *Std*Kt/V a total of 24-hour prescribed treatment time was considered; Qd, Qr, and Quf net were derived from original prescription and W was pre-dialysis body weight. For calculating delivered *Std*Kt/V observed Qd, Qr, and Quf net were used, these flow rates are adjusted for effective time of treatment (in a 24 h treatment period); W was post-dialysis body weight.

Filter monitoring

In 590 sessions in which effluent urea nitrogen (FUN) was available, we assessed filter efficiency by measuring FUN and blood urea nitrogen (BUN) levels every 12 hours and calculating FUN/BUN ratios for each 12-hour period of filter use.

Bleeding complications

We defined bleeding complications as follows: (1) a decrease in hemoglobin of ≥1.5 g/dL below the level of hemoglobin at initiation of CRRT; and (2) transfusion of one or more units of packed red blood cells.

Statistical analysis

Results are presented as means, medians, and interquartile ranges (IQRs) as appropriate. Baseline characteristics and outcome measures were compared using the *t*-test or the Wilcoxon's rank–sum test for quantitative variables, and the Pearson's χ^2 test or Fisher's exact test for proportions. Filter life hours was compared using Kruskal-Wallis test. $P < 0.05$ was considered statistically significant. Multivariable adjustment for variables including age, gender, etiology of AKI, and Sequential Organ Failure Assessment (SOFA) score was performed using a Poisson regression model. IBM SPSS statistical (v. 19.0, SPSS Inc., Chicago, IL, USA) was used for all analyses.

RESULTS

The mean age was 54.6 years; 60% were men; 43% were white; and 19% had chronic kidney disease. The mean sCr at CRRT initiation was 4.0 ± 2.1 mg/dL, median (IQR) daily urine output was 407 (150–1030) mL, and mean SOFA and Acute Physiology and Chronic Health Evaluation 3 scores were 8.2 ± 3.9 and 101.1 ± 24.7, respectively (Table 1). In 94% of the patients, the reason for starting dialysis was a combination of volume problems (oliguria < 400 cc/24 hours 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 6% of the cases, the indication for dialysis was exclusively volume related.

Compared with systemic unfractionated heparin, regional citrate was used more frequently in patients with liver disease (44% vs. 16%; P = 0.004). We found no significant differences between the use of unfractionated heparin or citrate with respect to baseline hemoglobin concentrations (10.1 g/dL vs. 10.6 g/dL; P = 0.58), platelet count (165 000/mcL vs. 118 000/mcL; P = 0.08), pH 7.34 vs. 7.34; P = 0.90), and bicarbonate concentration (21.3 mEq/L vs. 20.3 mEq/L; P = 0.37).

CVVHDF, CVVHD, and CVVH were employed in 60%, 28%, and 12% of the treatments respectively. The mean blood flows among the three different types of CRRT were: CVVHDF 110 ± 25 mL/min; CVVHD 160 ± 20 mL/min; and CVVH 151 ± 9 mL/min (P < 0.001). The mean dialysate fluid flow rate was higher in patients treated with CVVHD as compared with patients treated with CVVHDF (1566 ± 707 mL/h vs. 1084 ± 288 mL/h; P < 0.001). The mean replacement fluid flow rate was higher in patients treated with CVVH as compared with patients treated with CVVHDF (937 ± 244 mL/h vs. 582 ± 278 mL/h; P < 0.001). The mean ultrafiltration flow rate was different among the three types of CRRT (CVVHDF 941 ± 282 mL/h, CVVHD 175 ± 71 mL/h, and CVVH 115 ± 51; P < 0.001). The median (IQR) of prescribed and delivered dose (expressed as mL/kg/h) was

Table 1 Baseline characteristics at continuous renal replacement initiation

Variable	All (n = 244)	None (n = 116)	Heparin (n = 71)	Citrate (n = 57)	P value
Mean age (years)	54.6	52.6	58.9	49.0	Sal/none vs. hep P = 0.02 Hep vs. cit P = 0.02
Male (%)	59.4	59.7	66.7	45.6	Hep vs. cit P = 0.03
Race/ethnicity: Caucasian (%)	78.1	74.6	90.5	57.9	Sal/none vs. hep P = 0.03 Hep vs. cit P < 0.0001
Etiology of AKI					
Acute tubular necrosis	76.1	81.5	76.0	70.2	ns
Infection	7.5	10.8	4.8	8.8	ns
Hepatic failure	17.7	24.6	13.5	17.5	ns
Congestive heart failure	8.8	13.8	9.6	1.8	Sal/none vs. cit P = 0.05
Nephrotoxicity	25.7	27.7	28.8	17.5	ns
Obstruction	0.4	0	1.0	0	ns
Volume depletion	17.3	26.1	11.5	17.5	Sal/none vs. hep P = 0.04
Vascular	17.7	13.8	27.9	3.5	Sal/none vs. hep P = 0.04 Hep vs. cit P = 0.03
Mean SOFA score	11.3	11.3	10.4	13.0	Sal/none vs. cit P = 0.05 Hep vs. cit P = 0.03
Mean APACHE 3 score	100.2	100.3	95.6	108.6	Hep vs. cit P = 0.03
Mean AM weight (kg)	93.5	91.1	98.8	80.5	Hep vs. cit P = 0.01
Median UO (mL)	400	490	515	226	Sal/none vs. cit P = 0.01
Mean creatinine (mg/dL)	4.0	3.8	4.2	3.8	ns
Mean BUN (mg/dL)	79.3	75.2	80.2	82.3	ns
Mean platelets (1000/mm^3)	135.6	106.8	164.8	117.6	Sal/none vs. hep P = 0.02 Hep vs. cit P = 0.02
Mean hemoglobin (g/dL)	10.1	9.6	10.1	10.6	Sal/none vs. cit P = 0.05

AKI, acute kidney injury; AM, ante meridiem; APACHE 3, acute physiology and chronic health evaluation; BUN, blood urea nitrogen; ns, not significant; SOFA, sequential organ failure assessment; UO, urine output.

significantly different among the three different types of CRRT employed: *prescribed* 25 mL/kg/h (20–25) and *delivered* 21.1 mL/kg/h (12.3–21.6) for CVVH; *prescribed* 22 mL/kg/h (20–25) and *delivered* 19.3 mL/kg/h (15.0–24.2) for CVVHD; and *prescribed* 30 mL/kg/h (25–35) and *delivered* 27.5 mL/kg/h (20.1–28.3) for CVVHDF. Expressed as *Std*Kt/V_{urea} the median (IQR) of delivered dose was also higher in patients who were treated with CVVHDF 9.1 (7.1–11.5) as compared with patients who were treated with either CVVH 6.5 (3.9–8.1) or CVVHD 5.8 (4.6–7.4) ($P < 0.001$ for both comparisons).

As shown in Figure 2, delivered *Std*Kt/V was highest in treatments where citrate was employed as an anticoagulant. Notably, the delivered *Std*Kt/V was significantly lower in treatments where systemic unfractionated heparin was used than in treatments in which filter was managed with saline flushes.

Table 2 shows filter life and delivered *Std*Kt/V by type of CRRT and anticoagulation. Among modalities CVVHDF had the highest delivered dose when regional citrate was used as the anticoagulant. Filter longevity was significantly lower with unfractionated heparin and among filters where no anticoagulant was used.

Finally, in those treatments where FUN was available, higher filter efficiency (FUN/BUN ratio) was found in treatments where regional citrate was used to prevent filter clotting (Figure 3). As shown with delivered *Std*Kt/V, the FUN/BUN ratio was higher (more efficient clearance) when using saline flushes than with unfractionated heparin (Figure 3).

Seventy (28.6%) patients had a decline in hemoglobin concentration ≥1.5 g/dL below the level of hemoglobin at CRRT initiation. Rates of declines in hemoglobin concentration >1.5 g/dL were observed in 43%, 39%, and 19% in the systemic unfractionated heparin, regional citrate, and no anticoagulation groups, respectively ($P = 0.0009$). There was no difference in the variation of daily hemoglobin levels in the systemic unfractionated heparin, regional citrate, and no anticoagulation groups, respectively (delta hemoglobin of –0.03 ± 1.9, –0.07 ± 1.9, and +0.05 ± 2.2;

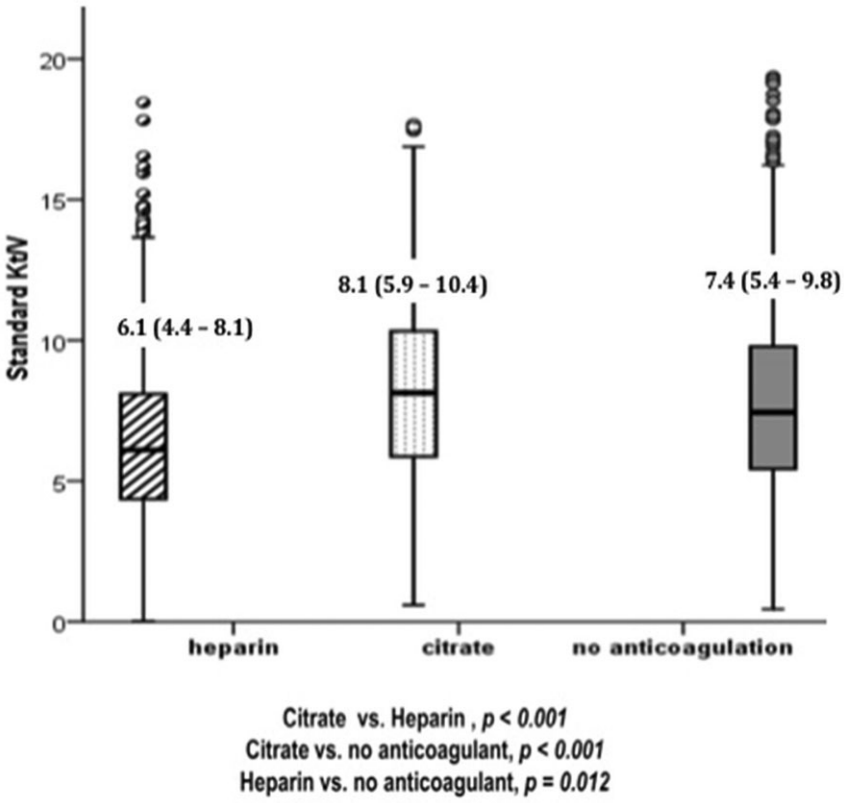

Figure 2 Delivered dose of dialysis measured as Standard Kt/V_{urea} in CRRT sessions using unfractionated heparin, regional citrate and no anticoagulation. A higher proportion of regional citrate was employed on CVVHDF treated patients, as compared with other modalities (CVVHD and CVVH). CRRT, continuous renal replacement therapies; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration.

Table 2 Comparisons of the delivered dose with use of heparin, citrate or no anti-coagulation among different types of CRRT

		Median (IQR) delivered Standard Kt/V by type of therapy		
Type of anticoagulant	Mean filter life hrs (number of filters)	CVVH [number of sessions]	CVVHD [number of sessions]	CVVHDF [number of sessions]
Citrate	54.5 (173)	1.7 (0.59–2.9) [n = 2]	[n = 0]	8.2 (5.9–10.4) [n = 467]
Heparin	21.1 (824)	2.85 (1.8–4.1) [n = 84]	5.6 (4.6–7.4) [n = 288]	8.31 (5.8–10.8) [n = 196]
No anticoagulant	23.1 (403)	7.3 (5.3–9.0) [n = 105]	5.9 (4.5–7.3) [n = 189]	8.5 (6.3–11.2) [n = 399]
P value	<0.001	<0.001	0.584	0.062

CRRT, continuous renal replacement therapies; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; IQR, interquartile range.

P = 0.262). Packed red blood cell transfusions were required in 44%, 25%, 31% in the systemic unfractionated heparin, regional citrate, and no anticoagulation groups, respectively (P = 0.06). No difference in in-hospital mortality was found between the use of systemic unfractionated heparin and regional citrate (48% vs. 58%; P = 0.21). After adjusting for age, gender, etiology of AKI and SOFA score, compared with no anticoagulation, the odd of death was higher with the use of UFH (odds ratio [OR] 1.82, 95% confidence interval [CI] 1.02–3.32; P = 0.033) but not with citrate (OR 1.02 95% CI 0.54–1.96; P = 0.53).

DISCUSSION

Maintaining circuit patency during CRRT is a key factor for providing adequate volume control and solute clearance in patients with severe, dialysis-requiring AKI. The impact of filter clotting on the delivered dose of CRRT is greater than the impact of filter clotting in intermittent hemodialysis as the lower solute clearance of CRRT requires a continuous or nearly continuous treatment without interruptions to achieve a prescribed dialysis dose.[16] Several studies have shown that one of the major barriers for delivering a prescribed dose is filter clotting or

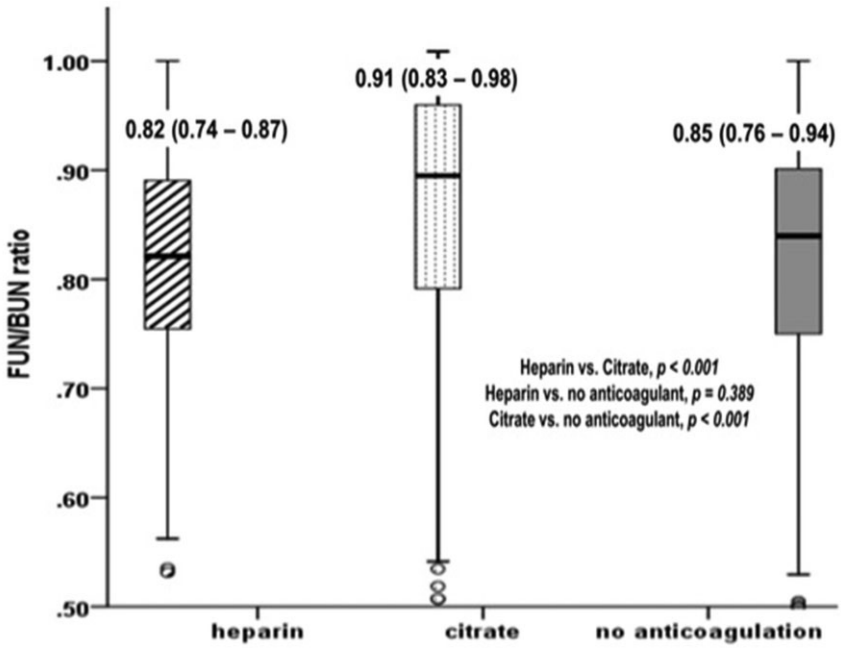

Figure 3 Shows filter efficiency measure as FUN/BUN ratio and type of anticoagulation used (systemic unfractionated heparin and regional citrate). Filters in which regional citrate was used showed a higher FUN/BUN ratio. FUN, effluent urea nitrogen; BUN, blood urea nitrogen.

fouling.[10,17–20] Recently, we showed that filter function affects the likelihood of delivering a prescribed dose; we assessed filter efficiency by calculating FUN/BUN ratios for each 12-hour period of filter use. The median FUN/BUN ratio at the time of filter change was 0.96 (0.94–0.98) in non-clotted filters compared with 0.87 (0.77–0.95) in low sieving or clotted filters.[21] We further demonstrated that the mean prescribed/delivered dose ratio was higher in treatments where the FUN/BUN ratio was greater than 0.9 (0.84 ± 0.12 vs. 0.79 ± 0.11).[21]

In the analyses presented here, we evaluated the use of two alternative anticoagulation strategies on delivered dialysis dose of CRRT in critically ill patients with AKI. We assessed delivered dose by computing *Std*Kt/V, as it allows us to compare the relative efficiency of alternative CRRT modalities and treatment schedules. Previous studies that have compared systemic unfractionated heparin and regional citrate focused on the effects of these two anticoagulants on filter patency but failed to explore how these distinct anticoagulation strategies affect filter efficiency and consequently the delivered dialysis dose, bleeding complications and transfusions. However, a more recent study that evaluate, in critically ill patients with severe AKI following cardiac surgery, the efficacy and safety of regional citrate anticoagulation using a low concentration citrate solution have also shown that delta of prescribed vs. delivered dose was $4.7 \pm 12.1\%$ when citrate was used as compared with $13 \pm 20.5\%$ when heparin was used.[22]

Our finding of the superiority of regional citrate over systemic unfractionated heparin in terms of filter life is consistent with some previous studies. In our study, the mean filter life in treatments where regional citrate was used (54.5 h) was longer than some previous reported studies. In the study of Palsson and Niles who used a simplified citrate system for delivering regional citrate anticoagulation during CVVH, the reported mean filter life span was 29.5 ± 17.9 hours in 85 filters that were used, of which 64 were lost because of clotting.[23] Bagshaw et al. reported a median filter life span with regional citrate anticoagulation of 40 hours (IQR 14–72 hours) in a prospective cohort study in which the effects of regional citrate with CVVHDF and of systemic unfractionated heparin with CVVH were compared.[2] In a more recent study, Betjes et al. randomized 48 critically ill patients at low risk for bleeding to either CVVH with regional citrate or systemic unfractionated heparin anticoagulation and reported a median circuit survival time in the citrate group of 36 hours.[24] Moreover, two recent studies have supported the notion that citrate is superior to heparin; however, filter life span in circuits where citrate was used was longer than what we have reported. In the first study, Monchi et al.[25] analyzed data from 20 patients, and using a cross-over design patients were randomized to either systemic unfractionated heparin or regional citrate. In total, 49 circuits were analyzed (heparin = 23 and citrate = 26). The authors found a significantly longer filter life in circuits where citrate was used (70 hours [IQR 44–140] vs. 40 hours [IQR 17–48]; P = 0.0007). They also found a reduced risk of bleeding with regional citrate anticoagulation; 0.2 units of packed red blood cells were transfused per day vs. 1-unit circuits where anticoagulation was managed with systemic unfractionated heparin.[25] In the second study, Kutsogiannis et al. reported a median citrate circuit survival time of 124.5 hours (95% CI 95.3–157.4) and a median heparin circuit survival time of 38.3 hours (95% CI 24.8–61.9).[26] In addition, after adjustment for antithrombin-III levels and illness severity score, the relative risk of hemorrhage with regional citrate anticoagulation was significantly lower than with systemic unfractionated heparin, although the confidence limits were wide owing to the small sample size (RR 0.14; 95% CI 0.02–0.96, P = 0.005).[26] Our study confirms and extends these findings in a larger critically ill cohort using a diverse array of modalities and devices.

If we look to the treatments where CVVHDF was used, no significant difference was found in terms of delivered *Std*Kt/V comparing regional citrate, systemic unfractionated heparin or saline flushes. However, the number of filters used to achieve that delivered dose was lower in the regional citrate group (Table 2). We have also provided evidence that *Std*Kt/V could be used as a unified dose expression to assess and compare treatment efficacy of different CRRT modalities and among different treatment frequencies, and could be used as standard method to monitor dose delivered. This is an unresolved issue as there are no established metrics for monitoring the dose delivered or ensuring the quality of renal replacement therapy we are providing to critically ill patients with AKI.[27] Kleger and Fassler recently explored the concept of using circuit longevity as quality indicator in CRRT. These authors showed that in addition to monitoring the complication rates of alternative anticoagulation strategies, the evaluation of circuit longevity using survival analysis (i.e., time to access or system failure) is a simple feasible means of assessing the quality of CRRT in the ICU.[28] Our findings confirm those of Uchino et al., who analyzed data from 48 critically ill patients treated with CVVH using 266 filters. The authors reported a significant inverse correlation between down time and percentage of delta creatinine and urea over each 24-hour cycle; the most common reason for down time was filter clotting.[10]

In addition to improving circuit longevity, reducing the incidence of bleeding complications, and enhancing the delivered dialysis dose, regional citrate may offer additional advantages over heparin or no anticoagulation strategies. Citrate may improve membrane biocompatibility; compared with heparin, citrate anticoagulation attenuates the release of myeloperoxidase, elastase, interleukin-1β, and platelet factor 4.[29–32] Citrate also down regulates the inflammation induced by foreign material by causing deep hypocalcemia in the filter-modulating intracellular calcium signaling. These beneficial effects could possibly be linked to increased rates of the recovery of kidney function and decrease in mortality rates as shown by Oudemans van Straaten et al. in a randomized controlled trial comparing regional citrate to low-molecular weight systemic anticoagulation for CVVH.[33]

Data from PICARD do not show significant differences in terms of a large decline in hemoglobin, transfusion or mortality. However, compared with patients on no anticoagulation, the odds of death associated with systemic unfractionated heparin was significantly higher as compared with the use of regional citrate anticoagulation.

Our study has several strengths. We included patients from five tertiary care academic medical centers across the United States with different demographics and clinical conditions, increasing the generalizability of our results. In contrast to many other studies where information was collected upon initial review or around the time of initiation of dialysis, data from patients enrolled in PICARD were collected from 3 days preceding the day of AKI diagnosis throughout their ICU course. PICARD affords us with extraordinarily detailed clinical data on a relatively large cohort whose population is reasonably representative of critically ill patients with AKI. Our multicenter prospective study also provides important information on efficacy of the filter and delivered dialysis dose that were not addressed by previous studies; the effect of the type of anticoagulation being used on delivered dose and filter patency highlights the importance of continuously monitoring filter patency in order to ensure that the prescribed dose, or something close to it, is delivered. We have detailed data regarding the rates of bleeding complications and transfusions among different anticoagulation strategies.

The main limitations of the study, as an observational study, is that groups were not randomized for anticoagulation strategy, and as the physicians determined the modality and the intensity of dialysis, according to the patients' clinical condition and local habits and facilities, there would be unavoidable bias in the inclusion of study participants and the treating prescriptions, so we cannot assume a causal relation between the use of regional citrate and outcomes.

In conclusion, the use of regional citrate as an anticoagulant strategy in CRRT is associated with prolonged filter life compared with the use of systemic unfractionated heparin. Regional citrate improves filter patency and the efficiency of solute clearance, which translates into a higher delivered dialysis dose, as defined using *Std*Kt/V. While randomized trials conducted to date have shown no difference in the effect of higher vs. standard dialysis dose, the type of anticoagulation should be considered and accounted for in future studies, as we aim to refine and improve CRRT for all treated patients.

ACKNOWLEDGMENTS

The study was made possible through an International Society of Nephrology Fellowship award, and the support of the UAB—UCSD O'Brien Center.

Manuscript received October 2013; revised January 2014.

REFERENCES

1 Mehta RL, Letteri JM. Current status of renal replacement therapy for acute renal failure. A survey of US nephrologists. The National Kidney Foundation Council on Dialysis. *Am J Nephrol*. 1999; **19**:377–382.
2 Bagshaw SM, Laupland KB, Boiteau PJ, Godinez-Luna T. Is regional citrate superior to systemic heparin anticoagulation for continuous renal replacement therapy? A prospective observational study in an adult regional critical care system. *J Crit Care*. 2005; **20**:155–161.
3 Tolwani AJ, Wille KM. Anticoagulation for continuous renal replacement therapy. *Semin Dial*. 2009; **22**:141–145.
4 van de Wetering J, Westendorp RG, van der Hoeven JG, Stolk B, Feuth JD, Chang PC. Heparin use in continuous renal replacement procedures: The struggle between filter coagulation and patient hemorrhage. *J Am Soc Nephrol*. 1996; **7**:145–150.
5 Oudemans-van Straaten HM, Wester JP, de Pont AC, Schetz MR. Anticoagulation strategies in continuous renal replacement therapy: Can the choice be evidence based? *Intensive Care Med*. 2006; **32**:188–202.
6 Menajovsky LB. Heparin-induced thrombocytopenia: Clinical manifestations and management strategies. *Am J Med*. 2005; **118**(Suppl 8A):21S–30S.
7 Davenport A. Management of heparin-induced thrombocytopenia during continuous renal replacement therapy. *Am J Kidney Dis*. 1998; **32**:E3.

8 Cutts MW, Thomas AN, Kishen R. Transfusion requirements during continuous veno-venous haemofiltration: The importance of filter life. *Intensive Care Med*. 2000; **26**:1694–1697.
9 Oudemans-van Straaten HM. Citrate anticoagulation for continuous renal replacement therapy in the critically ill. *Blood Purif*. 2010; **29**:191–196.
10 Uchino S, Fealy N, Baldwin I, Morimatsu H, Bellomo R. Continuous is not continuous: The incidence and impact of circuit "down-time" on uraemic control during continuous veno-venous haemofiltration. *Intensive Care Med*. 2003; **29**:575–578.
11 Tolwani AJ, Campbell RC, Stofan BS, Lai KR, Oster RA, Wille KM. Standard versus high-dose CVVHDF for ICU-related acute renal failure. *J Am Soc Nephrol*. 2008; **19**:1233–1238.
12 Palevsky PM, Zhang JH, O'Connor TZ, et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med*. 2008; **359**:7–20.
13 Bellomo R, Cass A, Cole L, et al. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med*. 2009; **361**:1627–1638.
14 Mehta RL, Pascual MT, Soroko S, et al. Spectrum of acute renal failure in the intensive care unit: The PICARD experience. *Kidney Int*. 2004; **66**:1613–1621.
15 Diaz-Buxo JA, Loredo JP. Standard Kt/V: Comparison of calculation methods. *Artif Organs*. 2006; **30**:178–185.
16 Marshall MR. Current status of dosing and quantification of acute renal replacement therapy. Part 1: Mechanisms and consequences of therapy under-delivery. *Nephrology (Carlton)*. 2006; **11**:171–180.
17 Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: A prospective randomised trial. *Lancet*. 2000; **356**:26–30.
18 Mehta RL, McDonald B, Gabbai FB, et al. A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. *Kidney Int*. 2001; **60**:1154–1163.
19 Venkataraman R, Kellum JA, Palevsky P. Dosing patterns for continuous renal replacement therapy at a large academic medical center in the United States. *J Crit Care*. 2002; **17**:246–250.
20 Kumar VA, Yeun JY, Depner TA, Don BR. Extended daily dialysis *versus* continuous hemodialysis for ICU patients with acute renal failure: A two-year single center report. *Int J Artif Organs*. 2004; **27**:371–379.
21 Claure-Del Granado R, Macedo E, Chertow GM, et al. Effluent volume in continuous renal replacement therapy overestimates the delivered dose of dialysis. *Clin J Am Soc Nephrol*. 2011; **6**:467–475.
22 Morabito S, Pistolesi V, Tritapepe L, et al. Regional citrate anticoagulation in cardiac surgery patients at high risk of bleeding: A continuous veno-venous hemofiltration protocol with a low concentration citrate solution. *Crit Care*. 2012; **16**:R111.
23 Palsson R, Niles JL. Regional citrate anticoagulation in continuous venovenous hemofiltration in critically ill patients with a high risk of bleeding. *Kidney Int*. 1999; **55**:1991–1997.
24 Betjes MG, van Oosterom D, van Agteren M, van de Wetering J. Regional citrate versus heparin anticoagulation during venovenous hemofiltration in patients at low risk for bleeding: Similar hemofilter survival but significantly less bleeding. *J Nephrol*. 2007; **20**:602–608.
25 Monchi M, Berghmans D, Ledoux D, Canivet JL, Dubois B, Damas P. Citrate *versus* heparin for anticoagulation in continuous venovenous hemofiltration: A prospective randomized study. *Intensive Care Med*. 2004; **30**:260–265.
26 Kutsogiannis DJ, Gibney RT, Stollery D, Gao J. Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients. *Kidney Int*. 2005; **67**:2361–2367.
27 Mehta RL. Comparing dialysis modalities for critically ill patients: Are we barking up the wrong tree? *Clin J Am Soc Nephrol*. 2007; **2**:413–414.
28 Kleger GR, Fassler E. Can circuit lifetime be a quality indicator in continuous renal replacement therapy in the critically ill? *Int J Artif Organs*. 2010; **33**:139–146.
29 Bohler J, Schollmeyer P, Dressel B, Dobos G, Horl WH. Reduction of granulocyte activation during hemodialysis with regional citrate anticoagulation: Dissociation of complement activation and neutropenia from neutrophil degranulation. *J Am Soc Nephrol*. 1996; **7**:234–241.
30 Bos JC, Grooteman MP, van Houte AJ, Schoorl M, van Limbeek J, Nube MJ. Low polymorphonuclear cell degranulation during citrate anticoagulation: A comparison between citrate and heparin dialysis. *Nephrol Dial Transplant*. 1997; **12**:1387–1393.
31 Gabutti L, Ferrari N, Mombelli G, Keller F, Marone C. The favorable effect of regional citrate anticoagulation on interleukin-1beta release is dissociated from both coagulation and complement activation. *J Nephrol*. 2004; **17**:819–825.
32 Gritters M, Grooteman MP, Schoorl M, et al. Citrate anticoagulation abolishes degranulation of polymorphonuclear cells and platelets and reduces oxidative stress during haemodialysis. *Nephrol Dial Transplant*. 2006; **21**:153–159.
33 Oudemans-van Straaten HM, Bosman RJ, Koopmans M, et al. Citrate anticoagulation for continuous venovenous hemofiltration. *Crit Care Med*. 2009; **37**:545–552.