

A Practical Citrate Anticoagulation Continuous Venovenous Hemodiafiltration Protocol for Metabolic Control and High Solute Clearance

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Obstacles to the widespread use of continuous renal replacement therapy (CRRT) include the need for anticoagulation, customized solutions, and complex protocols that carry an attendant risk for error, raise cost, and increase pharmacy and nursing workload. However, high solute clearance using CRRT with an effluent rate of 35 ml/kg per h has also recently been associated with improved survival in critically ill patients with acute renal failure. No published CRRT protocols using dilute regional citrate anticoagulation have achieved adequate metabolic control, effective anticoagulation, and high solute clearance in a practical, user-friendly, and economical manner. The safety and the efficacy of continuous venovenous hemodiafiltration at effluent rates of 35 ml/kg per h in critically ill acute renal failure patients were evaluated prospectively using a standardized bicarbonate-based dialysate; a systemic calcium infusion; and two separate trisodium citrate replacement solutions, a 0.67% solution and a 0.5% solution. All patients achieved adequate metabolic control, the desired effluent rate of 35 ml/kg per h, and high solute clearance. Use of the 0.67% citrate replacement solution resulted in mild alkalosis, whereas the 0.5% solution maintained appropriate acid–base balance. There was no difference in dialyzer survival between the 0.67 and 0.5% citrate groups (80 versus 82%; $P = 0.60$, Kaplan-Meier analysis). Dilute regional citrate as part of a CRRT protocol with a standard 25-mmol/L bicarbonate dialysate provides adequate metabolic control, high diffusive and convective clearance, and excellent dialyzer patency in a practical and cost-effective manner.

Clin J Am Soc Nephrol ●: ●●●–●●●, ●●●●. doi: 10.2215/CJN.00040505

Continuous renal replacement therapy (CRRT) has recently emerged as the dialysis technique of choice for critically ill patients with acute renal failure (ARF) and is superior to intermittent dialysis for fluid and metabolic control (1). In addition, high ultrafiltration rates (35 ml/kg per h) using CRRT, specifically continuous venovenous hemofiltration (CVVH), have been associated with improved patient survival (2). However, the widespread implementation of CRRT has been hindered by the lack of convenient protocols and standardized, economical solutions. In a recent international survey on the treatment of critically ill patients with ARF, the greatest concerns with CRRT included anticoagulation, dialyzer clotting, nursing workload, lack of standards, and cost (3).

The ideal CRRT protocol should provide volume control, metabolic (acid–base and electrolyte) control, and adequate solute clearance, without significant complications related to bleeding or clotting. It should be versatile to allow for independent adjustment of the above parameters and uncomplicated in terms of number of solutions, nursing protocols, and monitoring. CRRT should ideally run with little or no interruption.

Although the use of citrate for regional anticoagulation has been shown to be superior to heparin (4), it often complicates CRRT. A small number of regional citrate anticoagulation protocols offer high solute clearance but also require several customized solutions (5–10). Customization of solutions, with subsequent adjustments based on or determined by patient clinical status, expends pharmacy resources and increases the risk for error (11). In 2004, two patients who were receiving CRRT died after potassium chloride, rather than sodium chloride, was added mistakenly to a custom-made dialysate (12,13). Because the Food and Drug Administration does not presently require batch testing for quality control, potentially hazardous CRRT solution errors may be unrecognized.

At the University of Alabama at Birmingham, we exclusively use continuous venovenous hemodiafiltration (CVVHDF), a modality that provides both diffusive and convective solute clearance. CVVHDF, by combining diffusion and convection, easily maintains a filtration fraction <20% at low blood flow rates and high effluent rates, thereby decreasing the likelihood of filter clotting (14). The University of Alabama at Birmingham provides approximately 3000 CVVHDF days each year. To meet this clinical demand, it became necessary to simplify the CVVHDF process. Altering the composition of CRRT solutions for each patient proved to be costly, labor intensive, and error prone. As a result, we first devised a simplified citrate protocol using 2% trisodium citrate (TSC) delivered as replacement fluid at 250 ml/h (citrate 17.5 mmol/h), with a standardized normal

Received May 27, 2005. Accepted October 7, 2005.

Published online ahead of print. Publication date available at www.jasn.org.

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saline dialysate delivered at 1000 ml/h (15). However, this method could not provide higher effluent rates without also causing severe metabolic complications.

After a literature review, along with experience gained using several customized solutions, we hypothesized that a bicarbonate-based dialysate (Bicarbonate-25: 140 mmol/L sodium, 4 mmol/L potassium, 25 mmol/L bicarbonate, and 0.58 mmol/L magnesium) and a dilute citrate solution used for both anticoagulation and replacement fluid would provide adequate metabolic control, a high ultrafiltration rate, and effective regional anticoagulation. We initially planned to dilute the 2% TSC replacement fluid to a 0.5% solution (140 mEq/L sodium and 18 mmol/L citrate); however, because a 0.67% citrate solution (140 mEq/L sodium and 23 mmol/L citrate) was easier to prepare, we chose to evaluate the 0.67% solution first. Because the dialyzer removes as much as 30 to 50% of the citrate-calcium chelate, a bicarbonate-based dialysate was used to offset the citrate removed in the effluent (16,17). We surmised that both metabolic control and anticoagulation could be optimized by adjusting the dialysate and replacement fluid rates, without having to alter the basic composition of these solutions.

We herein describe the metabolic control and dialyzer patency in (1) 24 intensive care unit (ICU) patients with ARF using a 0.67% citrate replacement fluid, and (2) 32 ICU patients with ARF using a 0.5% citrate replacement fluid. Both groups were treated with Bicarbonate-25 dialysate and achieved effluent rates of 35 ml/kg per h.

Materials and Methods

Patients

We prospectively evaluated 24 consecutive adult ICU patients who had ARF and received CVVHDF from August 2003 to February 2004 using 0.67% citrate replacement fluid and Bicarbonate-25 dialysate at an effluent rate of 35 ml/kg per h. We then prospectively studied 32 consecutive ICU patients who received CVVHDF from May 2004 to June 2005 using the same protocol except that 0.5% citrate was used as replacement fluid. Patients were eligible for inclusion when they were 19 yr of age or older and received at least 48 h of CRRT. Data that were collected upon enrollment included demographics, clinical parameters, Acute Physiology and Chronic Health Evaluation II score at initiation of CRRT, serum chemistries, arterial blood gas, and coagulation indices. CRRT data, including blood flow rate, dialysate rate, replacement fluid rate, fluid removal rate, and dialyzer patency, were also recorded daily.

Description of CVVHDF Technique

CVVHDF was performed using the COBE Prisma prepump M100 set with an AN69 dialyzer (effective surface area of 0.9 m²) through a double-lumen 12-French catheter inserted into the internal jugular, subclavian, or femoral vein. The prepump M100 infusion set is commercially available. It consists of a simple stopcock and extension line that allows a greater portion of the access line to be diluted by redirecting the replacement solution close to the blood access site and before the blood pump. This permits anticoagulation of virtually the entire extracorporeal circuit when citrate is delivered as prefilter replacement. Because the infusion set is routed through the prefilter replacement fluid port of the Prisma, the citrate infusion rate is accounted for by the Prisma device in calculations of net fluid removal. Hemodiafiltration was accomplished using a blood flow rate of 100 to

150 ml/min. On the Prisma machine, the total effluent rate in milliliters per hour is equal to the sum of the replacement fluid rate, dialysate rate, and fluid removal rate. Effluent rates of 35 ml/kg per h were prescribed and determined by the patient's body weight in kilograms at initiation of CVVHDF. We used effluent rate (ml/kg per h) as a surrogate for the dose of dialysis and calculated this value as follows: Effluent rate = [dialysate flow rate (ml/h) + replacement fluid flow rate (ml/h) + fluid removal rate (ml/h)]/patient weight (kg)

For example, a 70-kg patient would require a total effluent rate of 2450 ml/h (70 kg × 35 ml/kg per h). Rates for the replacement fluid, dialysate, and fluid removal then would be adjusted to achieve an effluent rate of 2450 ml/h. Replacement fluid and dialysate rates were set equally at initiation of CRRT and titrated according to the metabolic, anticoagulation, and fluid balance requirements of the patient. However, the total effluent rate remained constant.

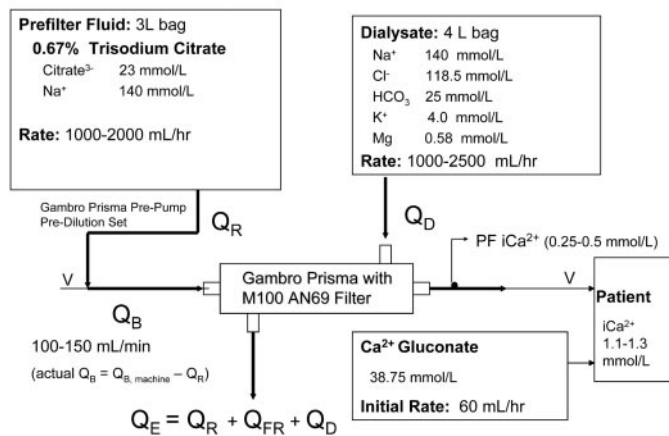
The 0.67% TSC solution was prepared by pooling the following into an empty 3-L bag: 2500 ml of 0.45% NaCl, 500 ml of 4% citrate (4% TSC Solution; Baxter, McGraw Park, IL), and 6 ml of concentrated NaCl (4 mmol/ml). The 0.5% citrate solution was prepared by pooling the following into an empty 3-L bag: 2250 ml of 0.45% NaCl, 325 ml of 4% citrate (4% TSC Solution; Baxter), and 15 ml of concentrated NaCl (4 mmol/ml). The Bicarbonate-25 solution was prepared by pooling the following into an empty 4-L bag: 4000 ml of sterile water for injection, 240 ml of Normocarb (Dialysis Solutions Inc., Toronto, Ontario, Canada), 36 ml of concentrated NaCl (4 mmol/ml), and 9 ml of concentrated KCl (2 mmol/ml). Normocarb contains 140 mmol/L sodium, 106.5 mmol/L chloride, 35 mmol/L bicarbonate, and 0.75 mmol/L magnesium. The final concentration of Bicarbonate-25 solution contained 140 mmol/L of sodium, 118.5 mmol/L of chloride, 0.58 mmol/L of magnesium, and 4 mmol/L of potassium. The calcium gluconate solution was prepared by adding 200 ml of 10% calcium gluconate solution to 1000 ml of 0.9% NaCl. Both citrate solutions and the dialysate were outsourced to Central Admixture Pharmacy Services, a nationwide network of state-licensed, Food and Drug Administration-registered pharmacies.

Both 0.67 and 0.5% TSC replacement solutions were delivered prefilter to maintain filter patency, and postfilter ionized calcium levels were measured from the postfilter blood sample port (blue in color) located on the return line of the Prisma device to guide the regional citrate dose. Calcium gluconate (38.75 mmol/L) was administered through a separate central venous line (or through the accessory infusion port of a large-bore multilumen central venous catheter) and initiated at 60 ml/h (Figure 1). The calcium gluconate infusion was titrated by 10-ml/h increments to maintain systemic ionized calcium levels between 0.9 and 1.3 mmol/L. The citrate replacement solutions were titrated by 100-ml/h increments to maintain postfilter ionized calcium levels between 0.25 and 0.5 mmol/L. Potassium, phosphorus, and magnesium were repleted separately, as needed.

Monitoring of Therapy

Serum and postfilter ionized calcium levels were measured 1 h after initiation of CRRT and then every 6 h thereafter. Arterial blood gases were measured at least daily. Serum electrolytes, including magnesium, calcium, and phosphorous, coagulation parameters, and complete blood count were monitored at least once daily. Nursing staff were instructed to call for serum pH <7.20 or >7.45, bicarbonate <15 or >35 mmol/L, or systemic ionized calcium <0.9 or >1.3 mmol/L. When the systemic ionized calcium was <0.9 mmol/L, the calcium infusion was increased by 20 ml/h, and a level was rechecked in 1 h. When the systemic ionized calcium was >1.3 mmol/L, the calcium infusion was decreased by 10-ml/h increments until a therapeutic level was obtained. Any changes to the fluid removal rate, replacement fluid

A 0.67% Citrate



B 0.5% Citrate

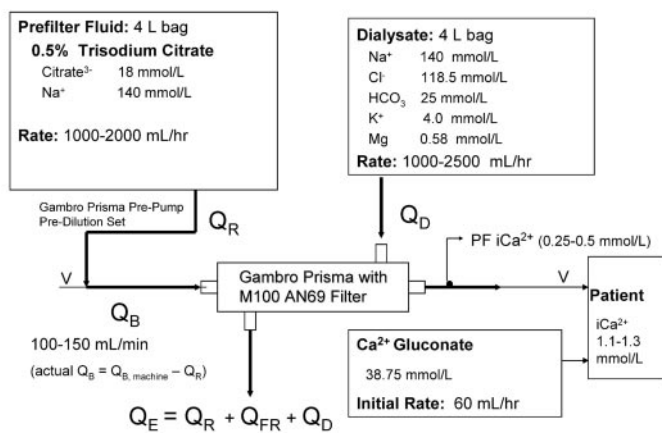


Figure 1. University of Alabama at Birmingham continuous venovenous hemodiafiltration (CVVHDF) protocol for 0.67 and 0.5% citrate. Schematic representation of flow rates, dialysate, prefilter replacement fluid, calcium infusion, and dialyzer membrane.

Q_R indicates replacement fluid rate; Q_D , dialysate rate; Q_B , blood flow rate; V , vein; PF, postfilter; iCa , ionized calcium; Q_{FR} , fluid removal rate; Q_E , effluent rate.

rate, or dialysate flow rate resulted in reciprocal adjustments to ensure a constant effluent rate of 35 ml/kg per h. Dialyzer filters were changed routinely every 72 h per the manufacturer's recommendations. Monitoring for citrate toxicity was performed as described previously (18).

Statistical Analyses

Results are presented as means, medians, and interquartile ranges. Baseline characteristics and outcome measures were compared using the *t* test or the Wilcoxon rank sum test for quantitative variables, and the Pearson χ^2 test or Fisher exact test for proportions. Filter survival was compared using Kaplan-Meier survival statistics and the log rank test. $P < 0.05$ was considered statistically significant.

Results

Patient Clinical Characteristics at Initiation of CRRT

The baseline characteristics of the 24 ICU patients who were treated with 0.67% citrate and the 32 ICU patients who

were treated with 0.5% citrate replacement fluid are shown in Table 1. Metabolic and CRRT parameters are also summarized. At the initiation of CRRT, 15 (56%) of 24 patients in the 0.67% citrate group had sepsis, 13 (54%) were oliguric, 21 (88%) were intubated, and 14 (58%) required pressors for hemodynamic support. In the 0.5% citrate group, 13 (41%) of 32 patients had sepsis, 19 (59%) were oliguric, 26 (81%) were intubated, and 16 (50%) required pressors. There were no significant differences among baseline characteristics between the two groups.

Patient Metabolic and Acid-Base Control on CRRT

Acid-base and electrolyte control for the first 10 d of CRRT are shown for both the 0.67 and 0.5% citrate groups in Figure 2. The box plot diagrams display median values for pH, pCO_2 , serum bicarbonate, sodium, and potassium for each day of CRRT, along with interquartile ranges and extreme values. In the 0.67% citrate group, median pH ranged from 7.40 to 7.45. Median serum bicarbonate and pCO_2 ranged from 21 to 27 mmol/L and 30 to 38 mmHg, respectively. In the 0.5% citrate group, median pH ranged from 7.36 to 7.43. Median serum bicarbonate and pCO_2 ranged from 21 to 25 mmol/L and 31 to 39 mmHg, respectively. Metabolic alkalosis during CRRT occurred more frequently in the 0.67% citrate group, compared with the 0.5% citrate group ($P = 0.001$, χ^2). Eighteen of 24 patients in the 0.67% citrate group had a pH ≥ 7.50 (maximum pH 7.62) at some point during CRRT, whereas only nine of 32 patients in the 0.5% citrate group had a pH ≥ 7.50 (maximum pH 7.55). Alkalosis was mitigated by adjusting the rates of the replacement fluid and dialysate rather than by altering the composition of CRRT solutions. For example, to correct metabolic alkalosis in a patient who was on CRRT with a dialysate rate of 1500 ml/h and replacement fluid rate of 1500 ml/h, one would increase the dialysate flow rate to 1800 ml/h and decrease the replacement fluid rate to 1200 ml/h. Such changes notably maintain a constant effluent rate. Decreasing the replacement fluid rate reduces citrate delivery (and subsequent bicarbonate production); increasing the rate of the dialysate (where the bicarbonate concentration is 25 mmol/L) enhances bicarbonate removal, thus lowering the serum bicarbonate.

Because the dialysate is isotonic, problems with significant hypo- or hypernatremia were avoided. None of the 0.67% citrate patients and 3% of the 0.5% citrate patients developed hypernatremia (sodium > 150 mmol/L), with the maximum sodium of 153 mmol/L, as compared with 23% of patients who previously received 2% citrate at our center ($P < 0.01$ for both groups, Fisher exact test) (19). Potassium levels were normalized using a dialysate potassium bath of 4 mmol/L. Median serum sodium and potassium levels for both groups ranged from 134 to 138 mmol/L and from 3.6 to 4.2 mmol/L, respectively. Because Bicarbonate-25 dialysate does not contain phosphorous, supplementation sometimes was necessary.

Clotting and Ionized Calcium Data on CRRT

In the 0.67% citrate group ($n = 24$), the mean number of CRRT days per patient was 9.3 ± 8 . A total of 111 filters were used. After initiation of CRRT, 92% of filters were patent at

Table 1. Clinical characteristics of patients on CVVHDF^a

	0.67% Citrate	0.5% Citrate
Patients	<i>n</i> = 24	<i>n</i> = 32
Mean age (yr)	63 ± 15	59 ± 16
Male:female	11:13	22:10
Cause of ARF		
sepsis	15	14
surgery	5	1
cardiogenic/others	4	17
Mean APACHE II ^b	26 ± 6	26 ± 6
Mean weight (kg)	95 ± 15	90 ± 19
Mean BUN (mg/dl) ^b	91 ± 37	73 ± 35
Mean creatinine (mg/dl) ^b	4.2 ± 1.4	4.3 ± 1.6
Mean pH ^b	7.33 ± 0.1	7.34 ± 0.09
Mean pCO ₂ (mmHg) ^b	33 ± 11	34 ± 9
Mean HCO ₃ (mmol/L) ^b	19 ± 5	19 ± 5
Mean Na (mmol/L) ^b	139 ± 7	137 ± 7
Mean K (mmol/L) ^b	4.5 ± 1.0	4.4 ± 0.8
CRRT characteristics		
mean days of CRRT/patient	9.3 ± 8	7.8 ± 8
mean CRRT effluent rate (ml/kg per h)	35	35
mean blood flow (ml/min)	117 ± 12	116 ± 13
mean replacement fluid rate (ml/h)	1200 ± 229	1211 ± 240
mean fluid removal rate (ml/h)	186 ± 57	129 ± 64
mean dialysate rate (ml/h)	1919 ± 437	1775 ± 542

^aValues are presented as means ± SD. For all comparisons between groups, *P* = NS. ARF, acute renal failure; APACHE II, Acute Physiology and Chronic Health Evaluation II; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy.

^bAt initiation of CRRT.

24 h, 80% at 48 h, and 69% at 72 h (Figure 3). In the 0.5% citrate group (*n* = 32), the mean number of CRRT days per patient was 7.8 ± 8. A total of 137 filters were used. Eighty-nine percent of filters were patent at 24 h, 82% at 48 h, and 80% at 72 h. There was no significant difference in filter patency between groups.

Systemic ionized calcium levels ranged from 0.73 to 1.45 mmol/L and from 0.78 to 1.54 mmol/L for the 0.67 and 0.5% citrate groups, respectively. For each abnormal systemic ionized calcium value, adjustment to the calcium infusion rate per protocol resulted in normalization of the ionized calcium level within 1 h. There were no instances of clinically significant hypocalcemia, and further adjustments to the infusion rate were minimal once a steady state was achieved. Most adjustments to the systemic calcium infusion occurred within 24 h of CRRT initiation. Despite varying the replacement fluid rate from 900 to 2000 mL/h, postfilter ionized calcium levels remained <0.5 mmol/L for both groups, except for one instance that corrected by increasing the replacement fluid rate. Postfilter ionized calcium levels ranged from 0.17 to 0.56 mmol/L and from 0.16 to 0.47 mmol/L in the 0.67 and 0.5% citrate groups, respectively. There were no bleeding episodes or instances of clinically significant citrate toxicity. The maximum total calcium to ionized calcium ratio was 2.8 in the 0.67% citrate group and 2.7 in the 0.5% citrate group. Overall, both citrate groups received 80% of prescribed CRRT therapy as compared with 68% as described by Venkataram *et al.* (20). Transportation for

procedures and patient care issues, rather than subtherapeutic anticoagulation, mostly contributed to lost treatment time.

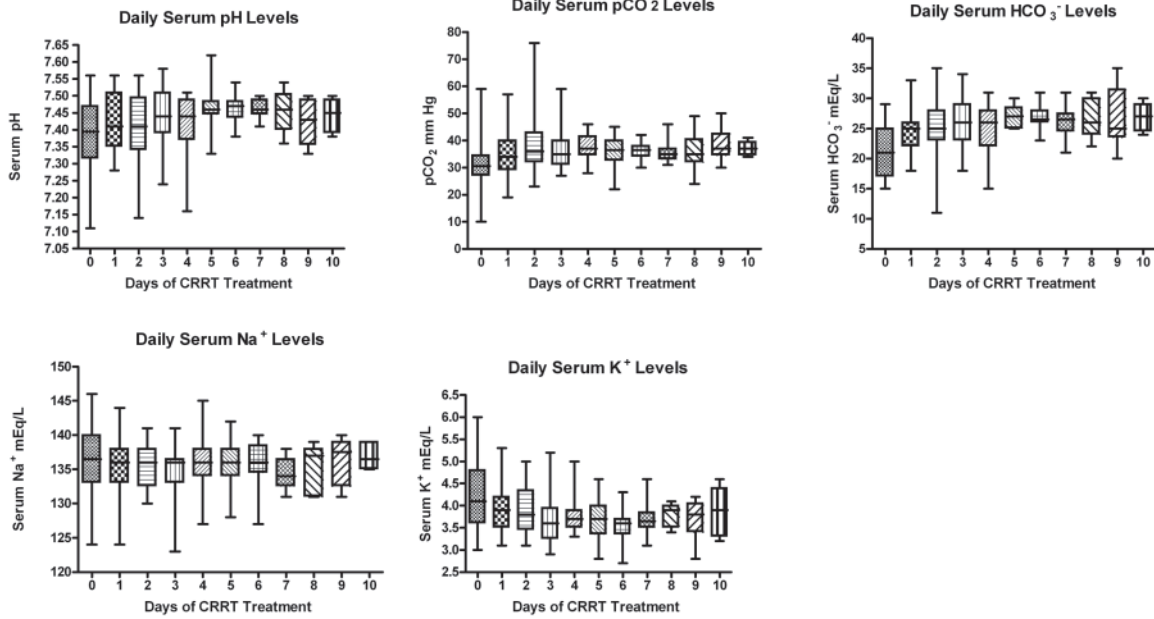
Discussion

This protocol, which uses standardized Bicarbonate-25 dialysate and dilute TSC as replacement fluid, is practical and a notable improvement over currently published citrate protocols. Table 2 (5–10) describes the most recent CVVHDF protocols using citrate for regional anticoagulation. The distinctive feature of this protocol is the use of only three standardized solutions, which together allow for high solute clearance and anticoagulation. Other citrate protocols use customized solutions, which often then require further adjustments in pharmacy to meet metabolic and electrolyte requirements. This protocol uses standardized solutions and achieves metabolic control as well as a constant effluent rate simply by altering solution flow rates, rather than by changing their composition.

The main advantages of this citrate protocol, compared with other citrate protocols, are as follows:

1. It consistently provides high solute clearance. Recent data suggest that higher dialysis doses lead to improved clinical outcomes. Schiffl *et al.* (21) demonstrated this finding for intermittent hemodialysis, and Ronco *et al.* (2) confirmed this using CVVH. Even when weight-based dosing is not used with our protocol, starting the replacement fluid and dialy-

A 0.67% Citrate



B 0.5% Citrate

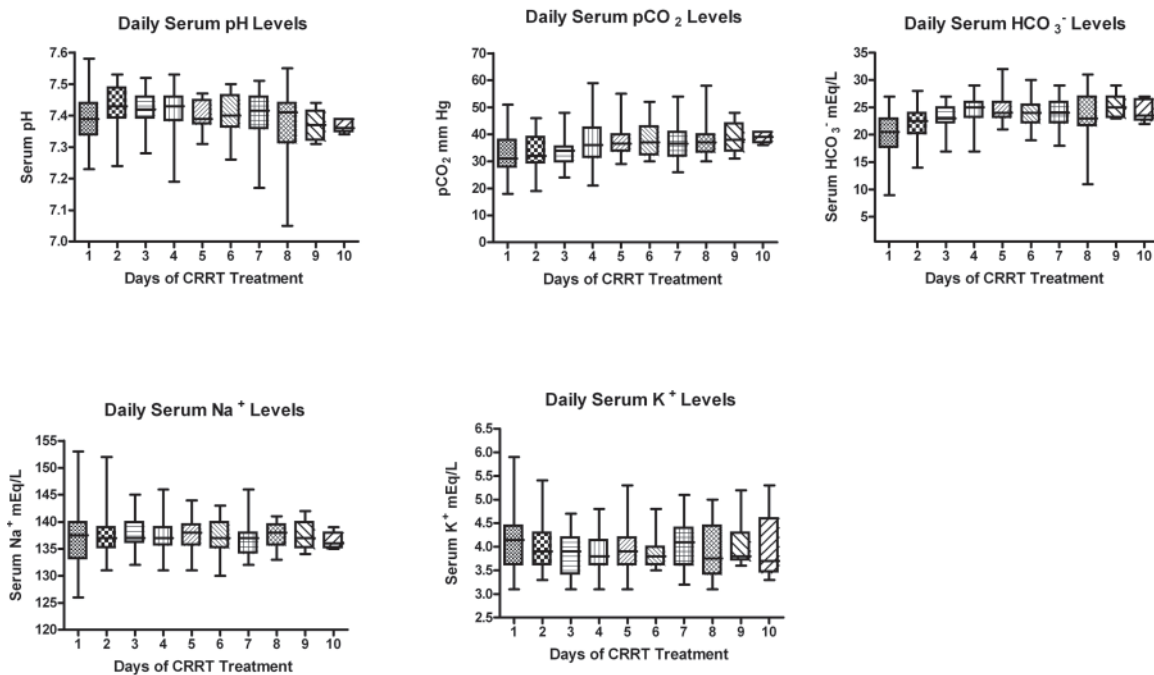


Figure 2. Metabolic and electrolyte control on CVVHDF for patients who received 0.67 and 0.5% citrate (results are presented as medians and interquartile ranges).

sate rates at 1000 to 1500 ml/h, with any fluid removal rate, achieves high solute clearance. Solution rates were adjusted in this study primarily to compensate for changes in the fluid removal rate and thereby maintain an effluent of 35 ml/kg per h. As not all nephrologists use a weight-based protocol or maintain a constant effluent rate, our standard orders initiate the replacement fluid ≥ 1000 ml/h and dialysate ≥ 1000 ml/h. As a result, the

only changes usually required on a daily basis, depending on desired volume status, are to the fluid removal rate. Even without a weight-based dose, excellent metabolic control and high solute clearance are achieved. Unlike the 0.67% protocol, rate changes were not required for metabolic control using 0.5% TSC; adjustments were made to keep the effluent rate constant as the fluid removal rate changed.

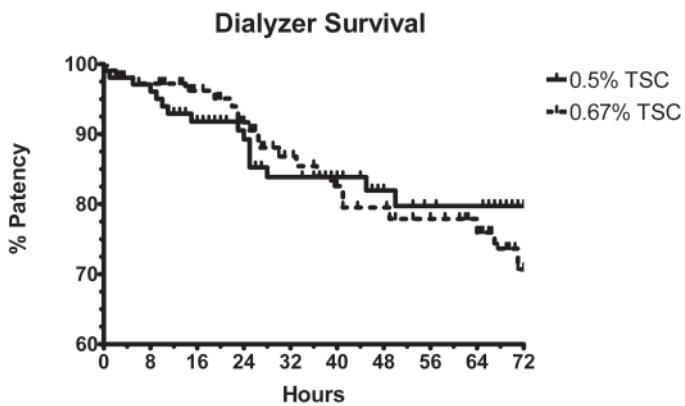


Figure 3. Dialyzer survival time for both 0.67 and 0.5% citrate groups by Kaplan-Meier analysis. TSC indicates trisodium citrate.

2. It uses standardized solutions that require no additional modifications. Although some protocols use commercial solutions, additives are often adjusted according to an individual's metabolic needs, and sometimes customization is necessary. Our protocol, in contrast, uses standard compositions for the citrate replacement fluid, the dialysate (which is now commercially available), and the calcium gluconate infusion. After initiation of CRRT, the composition of each fluid remains unchanged. This has allowed for batch preparation of solutions and batch testing by an admixture pharmacy unit. If CRRT is discontinued, then unused solutions are available for other patients and not discarded. As we currently manage 17 Prisma devices and treat >300 patients per year, this protocol has clearly been practical and cost-effective.
3. Because electrolytes are at physiologic concentrations, the risk for metabolic catastrophe is minimized. Imagine the metabolic consequences of inadvertently substituting concentrated citrate, in which the sodium concentration in commercially available solutions may be as high as 408 mmol/L, for the dialysate solution and then increasing the flow rate from 200 ml/h (a common rate for 4% TSC) to 1000 ml/h (a common rate for dialysate). We have also encountered metabolic problems using concentrated citrate for anticoagulation and a low-sodium dialysate, as per Mehta's protocol. If the citrate solution is omitted or the low-sodium dialysate is substituted mistakenly for citrate, then the resulting hyponatremia may be fatal. With our protocol, any accidental interchanges of the dialysate and replacement solutions or their respective rates results in negligible metabolic consequences as a result of the dilute citrate concentration and physiologic content of electrolytes.
4. Only three solutions are required, reducing the risk for error. Even with three solutions, we have been humbled by how often CRRT solutions and rates are set incorrectly. One can only imagine the escalation of errors that may occur when additional solutions are used, as required with other protocols.
5. Citrate 0.5% provides a blood citrate concentration of 2 to 6 mmol/L with replacement fluid rates ranging from 1 to 2

L/h. It was demonstrated previously that a blood citrate concentration of 3 to 6 mmol/L corresponds to a systemic ionized calcium level <0.35 mmol/L (22). Table 3 illustrates the blood citrate concentration for varying blood flow and replacement fluid rates using the 0.5% citrate protocol. For ranges in blood flow rates between 100 and 180 ml/min and replacement fluid rates between 1 and 2 L/h, ionized calcium levels are easily maintained at <0.5 mmol/L.

Four citrate protocols use a three-way stopcock or Y-connector (5,8–10). This device is placed at the end of the arterial limb of the venous access for the citrate infusion, whereas replacement fluid is given as usual through the prefilter replacement fluid port. Because the stopcock is outside the CRRT circuit, net fluid removal measured by the CRRT device does not include the citrate infusion rate. Thus, nursing staff become responsible for including the amount of citrate infused when net fluid balance is calculated. Only two protocols use dilute citrate and a total of three solutions. In 2003, Dorval *et al.* (7) prospectively evaluated 14 patients over 72 h using a citrate anticoagulation regimen for CVVHDF. Although they showed that citrate as replacement fluid simplified CRRT, only four of 14 patients actually received a dialysate (and thus CVVHDF), and the rest received CVVH. Potassium and phosphorus were added to the replacement fluid as needed, according to patient requirements. In addition, the ultrafiltration rate was limited to 2 L/h, as a result of the risk for citrate toxicity. Gabutti *et al.* (6) evaluated 12 patients using dilute citrate as both replacement fluid and dialysate. In their approach, the compositions of the dialysate and/or replacement fluid were titrated on the basis of systemic pH. Although their protocol simplified citrate use with CVVHDF, it was limited by having to reduce the dialysate and ultrafiltration rates at high pH, because both solutions contained citrate. As a result, some patients with a high pH received only replacement fluid and no dialysate. Furthermore, five patients were switched from citrate to heparin for uncertain reasons, and the ultrafiltration rate for all patients was limited to 2 L/h. Finally, filter survival was only 15% at 48 h. The remaining citrate protocols shown in Table 2 are more complicated, require additional solutions and mixtures, and have lower filter survival rates.

Some patients who received 0.67% citrate developed mild alkalosis and required adjustment to the replacement fluid rate and dialysate rate for correction. Alkalosis later was mitigated in the second patient cohort by dilution of the citrate replacement solution to 0.5%. With 0.5% citrate, changes to the dialysate rate or replacement fluid rate occurred only when the fluid removal rate was altered, to keep the effluent rate at 35 ml/kg per h. Because acid–base status was controlled adequately with the 0.5% solution, further rate adjustments were unnecessary.

The protocol described here results from extensive experience and appraisal of our CRRT records. It became evident in dealing with various ICU environments and personnel that a streamlined, standard CRRT protocol was necessary to reduce errors in prescription, formulation, and administration (23). Detailed records of the preparation and delivery of CRRT at our center have been maintained since 1999. The majority of errors

Table 3. Blood citrate concentration for varying BFR and replacement fluid rates using 0.5% citrate replacement fluid^a

BFR (ml/min)	Citrate ^b (mmol/L) at RF 1 L/h	Citrate (mmol/L) at RF 1.5 L/h	Citrate (mmol/L) at RF 2 L/h
100	3	4.5	6
120	2.5	3.75	5
150	2	3	4
180	1.7	2.5	3.3
200	1.5	2.25	3

^aRF, replacement fluid rate.

^bA blood concentration of citrate of 3 to 6 mmol/L corresponds to a systemic ionized calcium concentration <0.35 mmol/L (22).

were in administration, namely either using improperly formulated solutions or inadvertently substituting replacement fluid for dialysate, or *vice versa*. Fortunately, established safety measures identified most errors quickly, and there have been no adverse outcomes or fatalities. Errors of calcium administration have also been reported (23), and color-coded bags were subsequently developed to minimize the risk for such errors. Close monitoring with paired serum and postfilter ionized calcium levels every 6 h ensured no hypo- or hypercalcemia.

Our protocol has permitted significant cost curtailment in the delivery of CRRT. This has largely resulted from standardization of solutions, less waste, and fewer dialyzer changes for clotting. The solution cost for CRRT at our center, per patient per day, has declined from \$370 to \$290 between 1999 and 2005, mainly from reduced pharmacy costs and the commercial availability of PrismaSate B25GK4/O (5-L bag: 140 mmol/L sodium, 120.5 mmol/L chloride, 4.0 mmol/L potassium, 0.75 mmol/L magnesium, 3 mmol/L lactate, 22 mmol/L bicarbonate, and 110 mg/dl dextrose; Gambro, Lakewood, CO).

Conclusions

By using dilute citrate and a bicarbonate-based dialysate, this protocol provides effective metabolic control, high ultrafiltration rates, and adequate anticoagulation of the CRRT circuit, without increasing the risk for citrate toxicity. Compositional solution changes are avoided, thereby containing cost, reducing workload, and minimizing errors. The bleeding risk is also negligible. These solutions are uncomplicated and yet highly versatile. They are safe, effective, and practical and represent a significant step toward the more widespread acceptance of CRRT as the modality of choice for renal replacement in critically ill patients with ARF.

Appendix 1: University Alabama at Birmingham CVVHDF Protocol

Device. Cobe Prisma Machine, M100 prepump infusion set, AN69 dialyzer membrane

MD to Nurse/Pharmacy. Patient is to be started on CRRT with Bicarbonate-25 as dialysate and TSC 0.5% as the replacement fluid

Instructions for dialysis nurse:

- Prisma Warmer to be used if patient's core temperature is $\leq 94^{\circ}\text{F}$.
- Heparin (10,000 units/ml) is to be instilled to each dialysis catheter port if patient becomes disconnected from CRRT machine, with 5000 units heparin mixed with 1 ml of normal saline (for a total of 1.5 ml to each port). For patients with heparin-induced thrombocytopenia, Alteplase is to be used as alternative agent.
- Dialysis catheter care: Sterile dressing change daily with mask per hospital policy.
- Normal saline 0.9% 20 ml per syringe pump.
- If blood flow through the dialysis catheter is <120 ml/min and the access pressure is >150 mm Hg, then notify the dialysis nurse to perform assessment of catheter flow or catheter function.

Priming, as Determined by Nephrology

Heparinized prime solution: Dialysis nurse to administer 2000 units of heparin in 1 L of normal saline 0.9% as flush. Prime pump with two bags of solution and discard.

Or

Unheparinized prime solution: Dialysis nurse to administer 1 L of normal saline 0.9%. Prime pump with two bags of solution and discard.

Citrate Protocol

Blood flow rate: 150 ml/min (100 to 150 ml/min).

Fluid removal rate: As determined by nephrology, in ml/min.

- Check chemistry 10 profile from patient before initiation of CRRT and every 6 h thereafter. Notify renal fellow if bicarbonate is <15 mmol/L or >35 mmol/L.
- Check ionized calcium from blue port of CRRT machine (postfilter) at 1 h after initiation of CRRT and every 6 h thereafter. Notify renal fellow if postfilter ionized calcium is >0.5 mmol/L.
- Check serum ionized calcium from patient 1 h after initiation of CRRT and then every 6 h thereafter. Notify renal fellow if serum ionized calcium is outside designated range of 0.9 to 1.3 mmol/L.
- ICU nurse to obtain both serum ionized calcium and postfilter ionized calcium simultaneously.
- Check arterial blood gasses before initiation of CRRT and notify renal fellow if pH >7.45 or <7.20 and/or bicarbonate >30 or <15 mmol/L.

Replacement Fluid Orders

- Use TSC 0.5% as replacement solution.
- Final concentration: 140 mmol/L Na, 89 mmol/L Cl, 18 mmol/L citrate.
- Flow rate (ml/h) of TSC to be determined by nephrology, *e.g.*, 1000 ml/h.

Dialysate Fluid Orders

- Use Bicarbonate-25 solution as dialysate.
- Final concentration: 140 mmol/L Na, 4 mmol/L K, 118.5 mmol/L Cl, 25 mmol/L HCO₃, 0.58 mmol/L Mg.
- Flow rate (ml/h) to be determined by nephrology, *e.g.*, 1000 ml/h.

Calcium Fluid Orders

- Calcium gluconate, 38.75 mmol/L (1 amp: 4.65 mEq or 90 mg elemental calcium) in 1 L of normal saline 0.9%.
- Start rate of calcium gluconate drip at 60 ml/h. Check serum ionized calcium level from patient every 6 h. For serum ionized calcium >1.3 mmol/L, decrease rate by 10 ml/h; 0.9 to 1.3 mmol/L, no change; 0.8 to 0.9 mmol/L, increase rate by 10 ml/h; <0.8 mmol/L, increase rate by 20 ml/h and call nephrology fellow.

- All changes to dialysis orders (e.g., fluid removal rates, adjustment of flow rates) must be confirmed by nephrology.
- Nephrology must be notified immediately if patient becomes disconnected from CRRT machine (specific contact numbers for dialysis RN and renal fellow are provided for full 24-h period).

Acknowledgments

We acknowledge the input of Anupam Agarwal, MD, Ruth Campbell, MD, Philip O'Reilly, MD, and Ms. Cyndi Calhoun in the preparation of this manuscript.

References

- Clark WR, Murphy MH, Alaka KJ, Mueller BA, Pastan SO, Macias WL: Urea kinetics during continuous hemofiltration. *ASAIO J* 38: M664–M667, 1992
- Ronco C, Zanella M, Brendolan A, Milan M, Canato G, Zamperetti N, Bellomo R: Management of severe acute renal failure in critically ill patients: An international survey in 345 centres. *Nephrol Dial Transplant* 16: 230–237, 2001
- Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, La Greca G: Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: A prospective randomized trial. *Lancet* 355: 26–30, 2000
- 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* 30: 260–265, 2004
- Cointault O, Kamar N, Bories P, Lavayssiere L, Angles O, Rostaing L, Genestal M, Durand D: Regional citrate anticoagulation in continuous venovenous haemodiafiltration using commercial solutions. *Nephrol Dial Transplant* 19: 171–178, 2004
- Gabutti L, Marone C, Colucci G, Duchini F, Schonholzer C: Citrate anticoagulation in continuous venovenous hemodiafiltration: A metabolic challenge. *Intensive Care Med* 28: 1419–1425, 2002
- Dorval M, Madore F, Courteau S, Leblanc M: A novel citrate anticoagulation regimen for continuous venovenous hemodiafiltration. *Intensive Care Med* 29: 1186–1189, 2003
- Tobe SW, Aujla P, Walele AA, Oliver MJ, Naimark DM, Perkins NS, Beardsall M: A novel regional citrate anticoagulation protocol for CRRT using only commercially available solutions. *J Crit Care* 18: 121–129, 2003
- Kutsogiannis D, Mayers I, Chin WD, Gibney RT: Regional citrate anticoagulation in continuous venovenous hemodiafiltration. *Am J Kidney Dis* 35: 802–811, 2000
- Mehta RL, McDonald BR, Aguilar MM, Ward DM: Regional citrate anticoagulation for continuous arteriovenous hemodialysis in critically ill patients. *Kidney Int* 38: 976–981, 1990
- Mueller BA: Pharmacy aspects of continuous renal replacement therapies. 2004 Midyear Clinical Meeting, College of Pharmacy, Anne Arbor, University of Michigan. Available: <http://ashp.omnibooksonline.com/2004/papers/PI-009.pdf>. Accessed October 6, 2005
- External Patient Safety Review*, Calgary, Alberta, Canada, Calgary Health Region, 2004
- Canada News Wire Group: Health Quality Council of Alberta releases recommendations for safe handling of potassium chloride containing products and preparation of continuous renal replacement therapy dialysis solutions in hospitals, 2004. <http://www.newswire.ca/en/releases/archive/July2004/07/c1242.html>. Accessed October 6, 2005
- Mehta R: Continuous renal replacement therapy in the critically ill patient. *Kidney Int* 67: 781–795, 2005
- Tolwani A, Campbell R, Schenk M, Allon M, Warnock DG: Simplified citrate anticoagulation for continuous renal replacement therapy. *Kidney Int* 60: 370–374, 2001
- Swartz R, Pasko D, O'Toole J, Starmann B: Improving the delivery of continuous renal replacement therapy using regional citrate anticoagulation. *Clin Nephrol* 61: 134–143, 2004
- Chadha V, Garg U, Warady BA, Alon US: Citrate clearance in children receiving continuous venovenous renal replacement therapy. *Pediatr Nephrol* 17: 819–824, 2004
- Meier-Kriesche HU, Finkel KW, Gitomer JJ, DuBose TD Jr: Unexpected severe hypocalcemia during continuous venovenous hemodialysis with regional citrate anticoagulation. *Am J Kidney Dis* 33: 1–4, 1999
- Walker LJ, Campbell RC, O'Reilly PJ, Tolwani AJ: Continuous renal replacement therapy using 2% trisodium citrate regional anticoagulation: A prospective study [Abstract]. *Blood Purif* 19: 333, 2001
- 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* 17: 246–250, 2002
- Schiff H, Lang SM, Fischer R: Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med* 346: 305–310, 2002
- Flanigan MJ, Pillsbury L, Sadewasser G, Lim VS: Regional hemodialysis anticoagulation: Hypertonic trisodium citrate or anticoagulation citrate dextrose. *Am J Kidney Dis* 27: 519–524, 1996
- Mehta R: Acid–base and electrolyte management in continuous renal replacement therapy. *Blood Purif* 20: 262–268, 2002