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Simplified citrate anticoagulation for continuous renal replacement therapy

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Simplified citrate anticoagulation for continuous renal replacement therapy.

Background. Regional anticoagulation with trisodium citrate is an effective form of anticoagulation for continuous renal replacement therapy (CRRT) for patients with contraindications to heparin. However, because of the metabolic complications of trisodium citrate, it is a complicated technique requiring specialized dialysis solutions. We have designed a simplified protocol for citrate regional anticoagulation for CRRT.

Methods. Two percent trisodium citrate was delivered at 250 mL/h via the prefilter port of a COBE PRISMA device, with the rate adjusted to maintain a postfilter ionized calcium (iCa^{++}) <0.5 mmol/L. A central calcium gluconate infusion was used to maintain a systemic iCa^{++} at 1.1 mmol/L. A standard dialysate solution consisting of 0.9% saline, KCl 3 mmol/L, and $MgSO_4$ 1 mmol/L was delivered at 1000 mL/h. We retrospectively reviewed the outcomes and complications associated with this protoco1 in 29 patients treated from July 1999 to October 1999, evaluating the frequency of clotting of the dialyzer, bleeding complications, citrate toxicity, and patient mortality.

Results. The Kaplan–Meier curve for dialyzer survival demonstrated a 61% survival rate at 48 hours. There were no episodes of significant bleeding or citrate toxicity. Seventy-two percent of patients died for reasons unrelated to CRRT.

Conclusions. A CRRT protocol using regional 2% trisodium citrate anticoagulation is not associated with significant bleeding complications or citrate toxicity, and represents a simplified approach compared with previous applications using 4% trisodium citrate.

Continuous renal replacement therapy (CRRT) is increasingly used in the United States to treat hemodynamically unstable patients with renal failure. Its major drawback is the need for anticoagulation. Many intensive care unit (ICU) patients cannot tolerate systemic anticoagulation with heparin, and regional anticoagulation with trisodium citrate is gaining acceptance. However, regional anticoagulation with citrate increases the complexity of CRRT by requiring customized low-sodium, bicarbonate-free dialysate solutions and/or replacement fluids to minimize metabolic complications. Moreover, a systemic intravenous calcium infusion is required to prevent systemic hypocalcemia from the citrate infusion. Unfortunately, no commercial dialysate or replacement solutions are available, making regional anticoagulation with citrate a labor-intensive therapy for physicians, nursing staff, and pharmacy.

We initiated a CRRT program at the University of Alabama at Birmingham (U.A.B.) two years ago and quickly became aware of the limitations of systemic anticoagulation with heparin. However, the published trisodium citrate protocols are complex. We sought to develop a simple, standard citrate protocol that could be used for most patients requiring CRRT and would minimize pharmacy time and error. A citrate protocol was instituted for continuous venovenous hemodialysis (CVVHD) using 2% trisodium citrate as a regional anticoagulant and normal saline with supplemental potassium and magnesium as the dialysate. We report herein our experience using this simple protocol.

METHODS

Continuous renal replacement therapy was performed using the COBE PRISMA M60 set with an AN69 dialyzer (effective surface area of 0.6 m^2). A double-lumen 12F catheter was inserted into either the internal jugular, femoral, or subclavian vein. The blood flow rate was initially 150 mL/h. The 2% trisodium citrate solution (citrate 70 mmol/L, sodium 210 mmol/L) consisted of 1500 mL of 5% dextrose and 1500 mL of 4% citrate (4% trisodium citrate solution; Baxter, McGaw Park, IL, USA). This was infused prefilter at a rate of 250 mL/h. The infusion rate was titrated to maintain postfilter ionized calcium (iCa^{++}) of less than 0.5 mmol/L. The standard dialysate,

Key words: trisodium citrate, acute renal failure, critical care medicine, dialysis, dialysate, bleeding complications, citrate toxicity.

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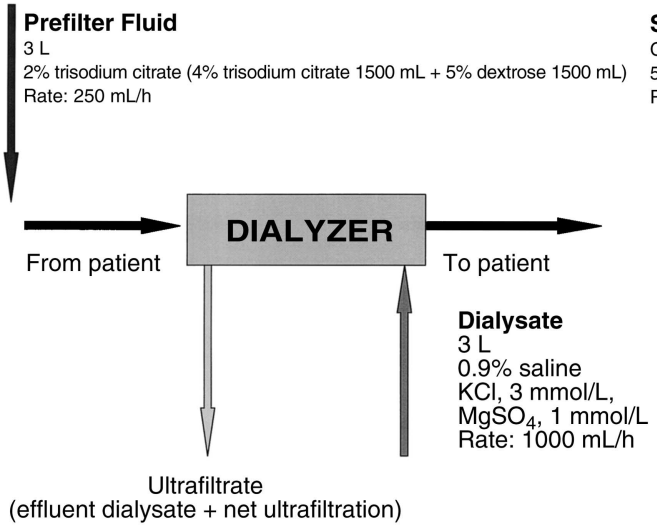

Fig. 1. Continuous venovenous hemodialysis (CVVHD) circuit diagram using 2% trisodium citrate as the regional anticoagulation. The 2% trisodium citrate is infused prefilter at an initial rate of 250 mL/h. Calcium gluconate (93 mEq in 1 L 5% dextrose) is infused systemically via a central venous line at initial rate of 60 mL/h. Dialysate (0.9% saline, KCl 3 mmol/L, $MgSO_4$ 1 mmol/L) is delivered at 1000 mL/h.

composed of 0.9% saline with KCl 3 mmol/L and $MgSO_4$ 1 mmol/L, was delivered at 1000 mL/h. Ninety-three milliequivalents of calcium gluconate in 1 L of 5% dextrose was infused into the patient through a separate central venous line at an initial rate of 60 mL/h (Fig. 1). Dialyzers were routinely changed at 48 hours.

Postfilter iCa^{++} levels were used to assess the adequacy of anticoagulation. Postfilter and systemic iCa^{++} levels were obtained at the initiation of CRRT, one hour after initiation, and then every six hours. The citrate infusion rate was titrated by increments of 10 mL/h to maintain the postfilter iCa^{++} between 0.25 and 0.5 mmol/L. The calcium gluconate infusion was titrated by the ICU nursing staff using a standardized protocol to maintain the systemic iCa^{++} between 1.0 and 1.1 mmol/L. Serum electrolytes, arterial blood gases, and complete blood counts were measured frequently and as needed by the nephrologist and the primary ICU team.

This study retrospectively evaluated the outcomes and complications during the first 48 hours of CRRT therapy using the 2% trisodium citrate protocol from July 1, 1999, to October 31, 1999. All adult ICU patients who were treated with CRRT using this protocol during this time period were screened for inclusion in the study. Patients who died within 48 hours of initiating CRRT (four patients) and patients with incomplete dialysis records (11 patients) were excluded. Twenty-nine patients were included in the final analysis.

Medical records were used to determine patient characteristics and demographics. Of the 29 patients included in the final analysis, 15 were female and 14 were male. The mean age was 54 ± 16 years, and the mean APACHE II score was 23 ± 6 at the time of initiation of CRRT. Six patients were diabetics. Twenty-three patients had acute renal failure and six had pre-existing end-stage renal disease (ESRD; Table 1). Baseline laboratory values are listed in Table 2.

We assessed the rates of dialyzer clotting, significant episodes of bleeding, citrate toxicity and mortality. Dialyzer clotting was defined as clotting of the dialyzer within 48 hours of initiating CRRT. Dialyzer survival was described using a Kaplan–Meier curve. Censored endpoints included disconnection of the dialyzer for reasons unrelated to clotting, bleeding, or citrate toxicity. Significant bleeding was defined as the documentation of an acute bleeding episode and/or the need for transfusion of more than two units of packed red blood cells within 48 hours. We detected citrate toxicity by monitoring changes in the serum pH, serum sodium, serum bicarbonate, and serum iCa^{++} levels. Mortality was defined as death at any point during the hospitalization.

RESULTS

Of the 29 patients, 6 (21%) were disconnected during the first 48 hours of CRRT for reasons unrelated to clotting, bleeding, or citrate toxicity. The Kaplan–Meier survival curve for dialyzer life is shown in Figure 2. Dialyzer survival was 61% at 48 hours. There was no difference in the mean maximum or mean minimum postfilter iCa^{++} levels between patients who had functional dialyzers (minimum iCa^{++} 0.41 ± 0.08 mmol/L, maximum iCa^{++} 0.55 ± 0.1 mmol/L) and those whose dialyzers clotted (minimum iCa^{++} 0.41 ± 0.12 mmol/L, maximum iCa^{++} 0.53 ± 0.07 mmol/L) within 48 hours of initiating CRRT.

There were no significant bleeding events or episodes of serious citrate toxicity. Five patients (17%) had a systemic iCa^{++} <0.9 mmol/L, with a lowest iCa^{++} value of 0.7 mmol/L. Three of these patients had a low iCa^{++}

Table 1. Patient characteristics

Patient	Diagnosis	Age	Sex	APACHE II[a]	ESRD	Diabetes	Albumin *g/dL*	Survived
1	Pre-eclampsia, abruptio placentae	34	F	17	N	N	Unknown	Y
2	Sepsis	57	F	26	Y	N	1.4	N
3	Heart transplant with sepsis	44	M	14	N	N	2.4	Y
4	AML with sepsis	49	M	16	N	N	2.1	N
5	Congestive heart failure	35	M	25	N	N	2.3	Y
6	Sepsis s/p bone marrow transplant	41	F	24	N	N	1.4	N
7	Hepatorenal syndrome	50	M	23	N	N	2.7	N
8	Rhabdomyolysis	32	M	28	N	N	2.1	Y
9	Acute renal failure s/p AAA repair	71	M	22	N	N	1	N
10	Sepsis	74	F	18	N	N	1.4	N
11	Endocarditis	56	F	25	Y	Y	2.6	N
12	Toxic epidermal necrolysis	87	F	23	N	Y	2.2	N
13	Acetaminophen overdose	28	F	29	N	N	2.7	N
14	Hypotension due to arrhythmia	67	F	36	Y	Y	Unknown	N
15	Retroperitoneal bleed s/p PTCA	69	M	27	N	N	4.3	N
16	Sepsis s/p bone marrow transplant	36	F	15	N	N	2.4	Y
17	Tamponade s/p coronary bypass surgery	60	M	21	Y	Y	3.2	N
18	Sepsis from suppurative mediastinitis	70	F	37	N	N	1.4	N
19	Ischemic bowel	60	M	22	N	N	1.4	N
20	Cirrhosis with pseudomonas sepsis	51	M	21	N	N	1.1	N
21	PTLD s/p bone marrow transplant	51	F	30	N	N	1.8	N
22	Ischemic bowel	76	F	36	Y	N	2.1	N
23	Sepsis s/p bone marrow transplant	52	M	22	N	N	1.4	N
24	Motor vehicle accident	60	M	29	N	N	0.8	Y
25	Ventricular tachycardia	27	F	14	N	N	2.1	N
26	Sepsis with alcohol abuse	72	M	27	N	N	1.6	N
27	Thrombotic thrombocytopenic purpura	64	F	18	N	N	2.8	Y
28	Sepsis with heart transplant	51	M	14	Y	Y	2.7	Y
29	Fournier's gangrene	56	F	22	N	Y	1.6	N

Abbreviations are: AML, acute myelogenous leukemia; AAA, abdominal aortic aneurysm; ESRD, end-stage renal disease; APACHE II, acute physiology and chronic health evaluation; PTCA, percutaneous transluminal coronary angioplasty; PTLD, post-transplant lymphoproliferative disorder.

[a] APACHE II score at initiation of continuous renal replacement therapy

prior to citrate infusion. Hypocalcemia was corrected in two of the five patients using the protocol calcium infusion; the others required additional intravenous calcium. No patient developed symptomatic hypocalcemia. The highest serum sodium recorded was 150 mEq/L in one patient. Four patients had an initial serum sodium level of less than 130 mEq/L, with a lowest level of 125 mEq/L. None of these patients had a rise in the serum sodium of greater than 9 mEq/L in 24 hours after CRRT with 2% trisodium citrate was initiated. Two patients had a serum pH >7.50, with a maximum recorded pH of 7.53. Only one patient developed a serum bicarbonate >30 mEq/L (33 mEq/L). Twenty-one patients (72%) died during their hospitalization; these deaths were related to the patients' underlying disease processes and not CRRT complications.

DISCUSSION

Recent advances in CRRT have led to an increase in its use for treating acute renal failure in critically ill patients. Systemic anticoagulation with heparin is associated with a high incidence of hemorrhagic complications in these patients, many of whom have had recent surgery, trauma, or bleeding [1, 2]. Contraindications to systemic anticoagulation preclude use of CRRT in many patients.

Regional trisodium citrate is an alternative to heparin. It provides effective regional anticoagulation by chelating calcium in the extracorporeal circuit. The anticoagulation is reversed by systemic infusion of calcium. The metabolism of citrate to CO_2 and H_2O by the liver, kidneys, and skeletal muscle generates bicarbonate [3]. While effective, trisodium citrate administration can cause significant metabolic complications. When used as a 4% solution, trisodium citrate is hypertonic (560 mOsm/L) and hypernatremic (420 mmol/L) and can result in hypernatremia and metabolic alkalosis. Hypocalcemia can result from chelation of calcium by citrate. Systemic iCa^{++} levels below 0.8 mmol/L can cause potentially fatal arrhythmias [4], and the use of concentrated trisodium citrate solutions has been proscribed by the Food and Drug Administration [5].

Several protocols using trisodium citrate have been described (Table 3). A direct comparison of the efficacy and complications of the four protocols is difficult, as they have not been evaluated in a randomized clinical trial. Furthermore, they vary not only in the amount of citrate delivered, but also in the type of CRRT modality,

Table 2. Patient baseline labs

Patient	Total Ca^{++} *mg/dL*	iCa^{++} *mmol/L*	pH	Hct	Platelet	PT/INR	PTT
1	7.1	1.03	7.35	28	140	16.1/1.2	38
2	12	1.3	7.42	25	112	18.9/1.6	47
3	7.4	0.86	7.43	32	229	22.1/1.8	32
4	8	1.14	7.47	23	180	16.1/1.3	44
5	N/A	1.05	7.36	26	247	17.2/1.4	29
6	7.7	1.09	7.41	34	14	17.1/1.4	41
7	7.8	0.98	7.45	34	79	21.4/1.8	38
8	6.9	0.77	7.36	44	346	28.1/2.6	200
9	5.2	1	7.33	30	100	81.6/10.3	128
10	9.3	1.21	7.35	34	114	22.3/1.8	40
11	7.9	1.14	7.32	20	61	17.6/1.3	27
12	6.7	0.98	N/A	33	119	24.2/2.0	36
13	6	0.82	7.38	29	90	50/5.2	62
14	9.4	1.1	7.09	35	201	81/9.6	61
15	N/A	1.07	N/A	32	44	14.6/1.1	29
16	8.8	1.25	7.29	29	67	N/A	199
17	N/A	1.17	7.36	29	265	14.7/1.1	35
18	8.2	1.24	7.21	29	38	30.7/2.8	48
19	N/A	1.21	7.34	29	75	19.2/1.5	30
20	8.1	1.1	7.3	26	115	20.5/1.6	89
21	8.1	1.01	7.21	16	156	28.7/2.5	200
22	8.7	1.03	7.14	31	42	24.7/2.1	46
23	9.3	1.2	7.4	27	52	17.5/1.3	24
24	7.8	1.24	N/A	26	166	15.5/1.1	39
25	6.5	0.93	N/A	23	118	23.4/1.9	31
26	N/A	0.91	7.3	29	360	N/A	N/A
27	6.9	N/A	7.55	28	28	14.9/1.1	37
28	10.3	1.39	N/A	28	171	N/A	N/A
29	7.2	1.14	7.32	25	213	20.8/1.7	77

Abbreviations are: Hct, hematocrit; PT, prothrombin time; INR, international normalized ratio; PTT, partial thromboplastin time; N/A, not available; Ca^{++}, calcium; iCa^{++}, ionized calcium.

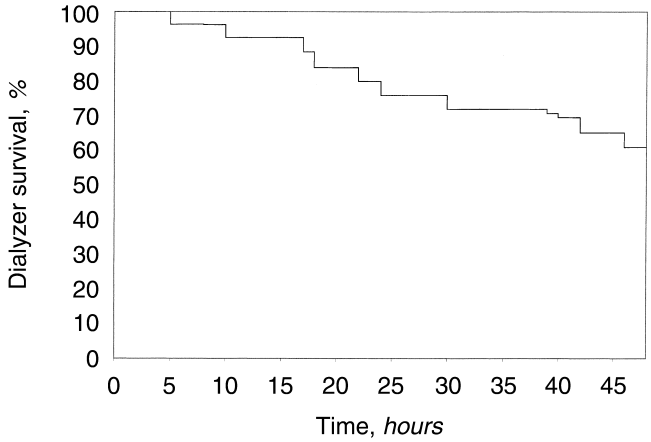

Fig. 2. Kaplan–Meier curve for dialyzer survival.

the blood flow rate, and the assessment of adequate anticoagulation. These factors may affect dialyzer patency and clotting. However, Kaplan–Meier curves in two studies [1, 6] can be used to compare dialyzer survival at 48 hours. A comparison of these curves reveals an approximate 48-hour survival rate of 50% in the study by Mehta et al [1] and 70% in the study by Kutsogiannis et al [6], compared with 61% with the 2% trisodium citrate protocol in this study.

Asymptomatic hypocalcemia occurred with all four protocols [1, 6, 7]. In Mehta et al's study, recorded systemic iCa^{++} levels were between 0.61 and 1.44 mmol/L [1]. While no episodes of symptomatic hypocalcemia or bleeding were reported, three episodes of metabolic alkalosis occurred [1]. Palsson and Niles observed two patients with asymptomatic hypocalcemia (lowest iCa^{++} level of 0.7 mmol/L) and reported no bleeding episodes [7]. Kutsogiannis et al reported three episodes of metabolic alkalosis, no symptomatic episodes of hypocalemia, and a definite bleeding rate of 0.045 events per person-day [6].

The major metabolic complication of the 2% citrate protocol was asymptomatic hypocalcemia, although none of the five affected patients had clinically significant arrhythmias. Systemic ionized calcium levels were corrected to normal in all five patients by administration of intravenous calcium. This underscores the importance of close monitoring of iCa^{++} levels, particularly in critically ill patients with initial ionized hypocalcemia. These patients, especially those who cannot metabolize citrate, may require even more aggressive calcium monitoring and repletion than described by the present protocol.

Trisodium citrate should be used cautiously in patients with liver impairment. Ineffective citrate removal by impaired hepatic metabolism can result in systemic hypercalcemia, hypercitric acidemia, and ionized hypocalcemia, despite large amounts of calcium [8]. These patients may require a reduced infusion rate of citrate than provided by this protocol. Because of the increased risk, total calcium levels should be measured daily in these patients to detect an increased ionized to total calcium ratio, indicating citrate toxicity. In addition, rapid turnaround of serum citrate measurements should become available at tertiary care centers that utilize regional citrate anticoagulation for CRRT.

There were no significant complications due to hypernatremia or the rate of change in serum sodium concentration, despite using a normal saline bath. The maximum serum sodium level was 150 mEq/L. Hypernatremia was treated by increasing free water administration to the patient. It is important to consider the contribution of concomitant fluids administered to the serum sodium level in the management of these patients. We recommend obtaining serum electrolytes at least every eight hours in patients undergoing CRRT with citrate anticoagulation.

There were no bleeding complications observed during this study. However, we only assessed complications during the first 48 hours of therapy, and this makes it difficult to compare the bleeding rate of the 2% citrate protocol to other citrate protocols. A more important comparison of bleeding complications would be between

Table 3. Comparison of citrate protocols

	N	Modality	Blood flow rate	Citrate delivery	Dialysate	Replacement fluid	Patency at 48 hours
Mehta et al [1]	11	CAVHD	52–125 mL/min	23.8 mmol/h[a]	Na^+ 117 mEq/L Cl^- 122.5 mEq/L K^+ 4 mEq/L Mg^{++} 1.5 mEq/L Dextrose 2.5%	0.9% Saline	~50%
Palsson et al. [7]	17	CVVH	180 mL/min	18.6 mmol/h[b]	N/A	Na^+ 140 mEq/L Cl^- 101.5 mEq/L Mg^{++} 1.5 mEq/L Citrate 40 mEq/L Dextrose 0.2%	N/A
Kutsogiannis et al. [6]	9	CVVHDF	125 mL/min	25 mmol/h[a]	Na^+ 110 mEq/L Cl^- 110 mEq/L Mg^{++} 1.5 mEq/L	Na^+ 110 mEq/L Cl^- 110 mEq/L Mg^{++} 1.5 mEq/L Varied $NaHCO_3^-$	~70%
Tolwani et al. (current study)	23	CVVHD	125–150 mL/min	17.5 mmol/h[a]	0.9% Saline K^+ 3 mEq/L Mg^{++} 2 mEq/L	N/A	61%

Abbreviations are: CAVHD, continuous arteriovenous hemodialysis; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; CVVHD, continuous venovenous hemodialysis; N/A, not available.

[a] Initial citrate infusion rate

[b] Average citrate infusion rate

an optimized citrate regional anticoagulation protocol and traditional systemic heparin anticoagulation.

The main advantage of the protocol described in this article is its simplicity. Other trisodium citrate protocols require customized dialysis solutions to avoid the metabolic complications of citrate [1, 6, 7]. By using 2% trisodium citrate, a standard dialysate solution made of normal saline can be used without undue risk of significant hypernatremia. The definition of a standard glucose-free dialysate based on normal saline has allowed our hospital pharmacy to prepare dialysate bags in advance that can be stored for up to 30 days and used for any patient on CRRT with citrate anticoagulation. This removes the need to prepare individually the bags for specific patients and reduces pharmacy workload, direct expense, and wastage of unused bags. By simplifying and standardizing the dialysate solution, there also should be a reduction in physician, pharmacy, and nursing errors.

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