Regional citrate anticoagulation in continuous venovenous hemofiltration in critically ill patients with a high risk of bleeding

RUNOLFUR PALSSON and JOHN L. NILES

Renal Unit and Department of Medicine and Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

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Background. Systemic heparinization is associated with a high rate of bleeding when used to maintain patency of the extracorporeal circuit during continuous renal replacement therapy (CRRT) in critically ill patients. Regional anticoagulation can be achieved with citrate, but previously described techniques are cumbersome and associated with metabolic complications.

Methods. We designed a simplified system for delivering regional citrate anticoagulation during continuous venovenous hemofiltration (CVVH). We evaluated filter life and hemorrhagic complications in the first 17 consecutive patients who received this therapy at our institution. Blood flow rate was set at 180 ml/min. Ultrafiltration rate was maintained at 2.0 liters/hr and citrate-based replacement fluid (trisodium citrate 13.3 mM, sodium chloride 100 mM, magnesium chloride 0.75 mM, dextrose 0.2%) was infused proximal to the filter to maintain the desired fluid balance. Calcium gluconate was infused through a separate line to maintain a serum-ionized calcium level of 1.0 to 1.1 mM.

Results. All patients were critically ill and required mechanical ventilation and vasopressor therapy. Systemic heparin anticoagulation was judged to be contraindicated in all of the patients. A total of 85 filters were used, of which 64 were lost because of clotting, with a mean life span of 29.5 ± 17.9 hours. The remaining 21 filters were discontinued for other reasons. Control of fluid and electrolyte balance and azotemia was excellent (mean serum creatinine after 48 to 72 hr of treatment was 2.4 ± 1.2 mg/dl). No bleeding episodes occurred. Two patients, one with septic shock and the other with fulminant hepatic failure, developed evidence for citrate toxicity without a significant alteration in clinical status. Nine patients survived (52.9%).

Conclusion. Our simplified technique of regional anticoagulation with citrate is an effective and safe form of anticoagulation for CVVH in critically ill patients with a high risk of bleeding.

Continuous renal replacement therapy (CRRT) has, in recent years, been increasingly employed for the management of acute renal failure in critically ill patients [1–6]. Although improvement in survival rates compared with intermittent hemodialysis (IHD) has not been proven, CRRT is frequently chosen for patients who do not tolerate IHD because of hemodynamic instability. Pump-assisted venovenous techniques such as continuous venovenous hemofiltration (CVVH) are now preferred over arteriovenous techniques because of significantly greater solute clearances and lower rates of vascular complications [7–9].

One of the main disadvantages with CRRT is the requirement for anticoagulation in order to prevent clotting of the extracorporeal circuit. Heparin has been the most frequently used anticoagulant, but is associated with a risk of life-threatening hemorrhagic complications as high as 25 to 30% [3, 10, 11]. In addition, heparin-induced thrombocytopenia may preclude the use of heparin in some cases (abstract; Chong and Jacques, *Intensive Care Med* 16:437, 1990) [13]. Although the use of frequent saline flushes without the use of anticoagulant has been reported by Paganini to increase the duration of the CRRT circuit patency [14], others have experienced frequent clotting of filters with this technique [3, 11]. Various alternative methods have been developed to confer anticoagulation of the extracorporeal circuit with reduced risk of bleeding, including regional heparinization [15], low molecular weight heparin [16], prostacyclin [17], and the serine proteinase inhibitor nafamostat [18], but these approaches have not been widely accepted because of their limitations.

The use of citrate as anticoagulant in hemodialysis (HD) was first described by Morita et al in 1961 [19], and a report by Pinnick et al in 1988 confirmed its usefulness [20]. In recent years, several reports have demonstrated the effectiveness of regional citrate anticoagulation in various forms of CRRT: continuous arteriovenous HD (CAVHD), continuous arteriovenous hemodiafiltration

(CAVHDF), and continuous venovenous hemodiafiltration (CVVHDF) (abstracts; Falkenhain et al, *J Am Soc Nephrol* 4:344, 1993; Mehta et al, *J Am Soc Nephrol* 4:368, 1993) [10, 11]. Citrate causes anticoagulation by chelation of ionized calcium in the extracorporeal circuit. However, systemic anticoagulation does not occur as the ionized calcium level is restored when blood returning from the extracorporeal circuit mixes with venous blood. Rapid metabolism of citrate to bicarbonate releases the calcium and maintains serum bicarbonate. However, patients with severe liver failure and lactic acidosis may have difficulties metabolizing citrate, which can accumulate and cause toxicity [21].

Although citrate anticoagulation has been shown to be effective and safe in CRRT, previously described systems are cumbersome and have been associated with metabolic complications [10, 11]. It has been widely claimed that citrate cannot be used safely with hemofiltration alone (CVVH) because of insufficient clearance of sodium citrate from the blood, resulting in derangements of serum sodium and bicarbonate concentrations. It has been felt that dialysis (diffusive clearance) is necessary for adequate removal of citrate, as well as the sodium load caused by the hypertonic trisodium citrate [4, 11, 22, 23]. However, we have designed a simple and safe system for delivering regional citrate anticoagulation during CVVH. To investigate the efficacy and safety of our technique, we evaluated extracorporeal circuit patency and hemorrhagic complications in the first 17 consecutive patients with renal failure and a high risk of bleeding who received this form of therapy in the intensive care units (ICUs) at our institution. We found our technique of regional citrate anticoagulation to be simple, effective, and safe in this high-risk population.

METHODS

Patients

We retrospectively studied the first 17 adult patients with renal failure who were treated with a new method of regional citrate anticoagulation with CVVH in the ICUs at the Massachusetts General Hospital from August 1995 through May 1996. The modality of renal replacement therapy (RRT) was selected by the attending nephrologist. In addition to CVVH, many patients also received IHD at other times during their hospitalization. Fourteen patients also received heparin anticoagulation with RRT (including IHD) at other times during their ICU course. Medical records were reviewed to obtain information on demographic factors, diagnosis, etiology of renal failure, APACHE II illness severity score [24] at the time of ICU admission, contraindication to heparin, hemofilter life span, metabolic and coagulation parameters, hemorrhagic episodes, other complications of CVVH, and survival.

Citrate continuous venovenous hemofiltration system

A diagram of our system of regional citrate anticoagulation with CVVH is shown in Figure 1A. The previously reported design of regional citrate anticoagulation with CAVHD by Mehta et al is illustrated in Figure 1B for comparison [10].

Vascular access was established by insertion of a double-lumen 14 F catheter (Quinton Instruments, Seattle, WA, USA) into either the femoral, subclavian, or internal jugular vein. We used a Baxter BM 11 CVVH blood pump (Baxter Healthcare Corporation, Deerfield, IL, USA) and Renaflo II HF700 polysulfone hemofilters (Renal Systems, Minneapolis, MN, USA). The filters were primed with two liters of isotonic saline containing 10,000 U/liter of heparin. In patients with heparin-induced thrombocytopenia, priming was performed without heparin. Blood flow rate was maintained at 180 ml/min as measured after dilution with the replacement fluid. A Travenol 6300 volumetric infusion pump (Baxter Healthcare) was set to maintain a constant ultrafiltration rate at 2 liter/hr. The ultrafiltrate was measured hourly and replaced by continuous infusion with a citrate-based replacement fluid to maintain the desired fluid balance. The replacement fluid contained trisodium citrate 13.3 mmol/liter (40 mEq/liter), sodium chloride 100 mmol/liter, magnesium chloride 0.75 mmol/liter (1.5 mEq/liter), and 0.2% dextrose (Table 1). The replacement fluid was infused proximal to the filter at a rate dependent on the volume of other parenteral solutions administered and the net fluid removed. Filters were flushed every four hours with 200 ml of 0.9% saline. Filters were changed for suspected clotting if the ultrafiltration rate decreased to approximately 1500 ml/hr for more than two consecutive hours.

The serum-ionized calcium level was checked prior to initiation of CVVH, and if necessary, calcium gluconate was infused until the ionized calcium was greater than 1.0 mmol/liter. During CVVH, calcium was infused through a separate line at a rate determined by a sliding scale. Twenty grams of calcium gluconate in one liter of D5W was infused at 70 ml/hr for an ionized calcium of 0.9 to 1.0 mmol/liter, 60 ml/hr for an ionized calcium of 1.0 to 1.1 mmol/liter, and 50 ml/hr for an ionized calcium of 1.1 to 1.3 mmol/liter. The median rate of calcium infusion was 60 ml/hr, which provided 2.8 mmol/hr (5.6 mEq/ hr). Three patients received an equivalent sliding scale using calcium chloride instead of calcium gluconate. Potassium and magnesium were supplemented as needed.

Monitoring of therapy

Serum electrolytes and arterial blood gases were monitored every 6 to 12 hours or more frequently if needed. Serum-ionized calcium was measured every six hours or more often if indicated, and serum total calcium was measured daily. The nephrology coverage was notified
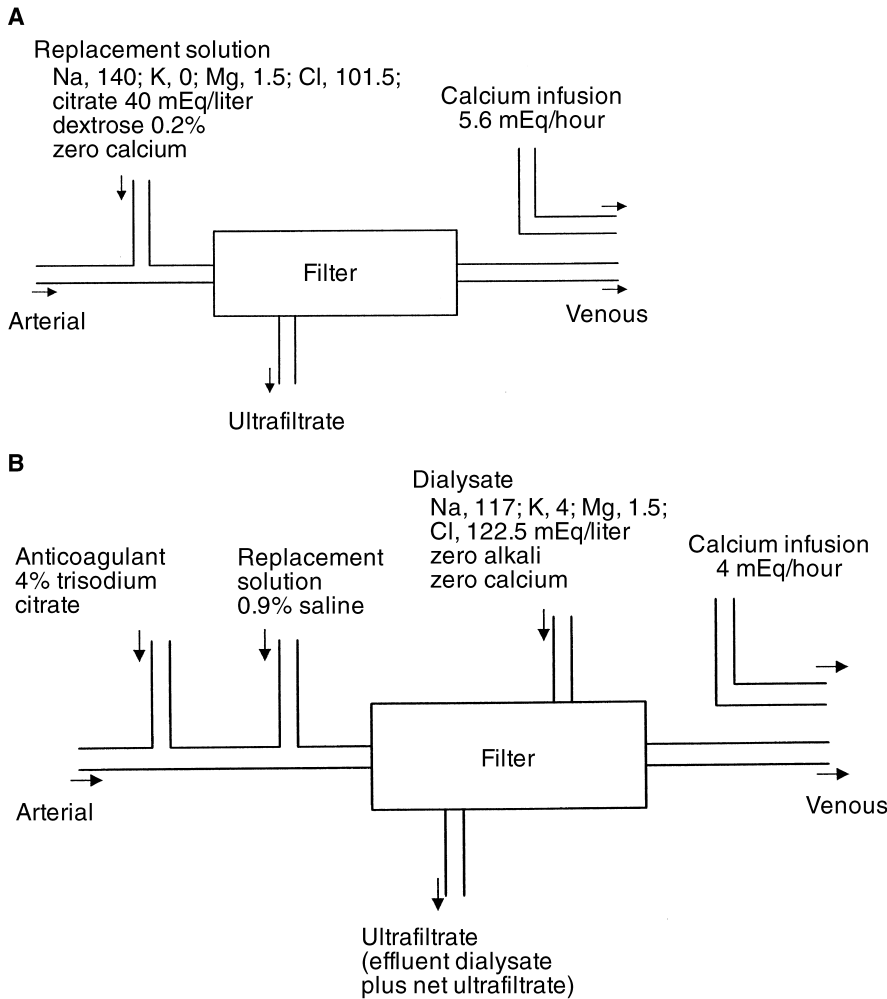
A

Replacement solution
Na, 140; K, 0; Mg, 1.5; Cl, 101.5;
citrate 40 mEq/liter
dextrose 0.2%
zero calcium

Calcium infusion
5.6 mEq/hour

Filter

Arterial

Venous

Ultrafiltrate

B

Dialysate
Na, 117; K, 4; Mg, 1.5;
Cl, 122.5 mEq/liter
zero alkali
zero calcium

Anticoagulant
4% trisodium
citrate

Replacement
solution
0.9% saline

Calcium infusion
4 mEq/hour

Filter

Arterial

Venous

Ultrafiltrate
(effluent dialysate
plus net ultrafiltrate)

Fig. 1. **Comparison of our citrate-CVVH system (A) and the citrate-CAVHD system of Mehta et al (B).** This was taken from Ravindra L. Mehta, Brian R. McDonald, May M. Aguilar, and David M. Ward: Regional citrate anticoagulation for continuous arteriovenous hemodialysis in critically ill patients. *Kidney Int* 38:976–981, 1990 (used with permission).

Table 1. Composition of citrate replacement fluid

Trisodium citrate	13.3 mmol/liter
Sodium chloride	100 mmol/liter
Magnesium chloride	0.75 mmol/liter
Dextrose	0.2%

for an ionized calcium below 0.9 or greater than 1.3 mmol/liter. A complete blood count, coagulation parameters, phosphate, blood urea nitrogen, and creatinine were monitored at least daily. Activated clotting times (ACTs) were not monitored routinely. We did not measure solute clearance rates during this study. However, prior to this study, we determined the urea and creatinine clearances provided by our CVVH technique. Clearances were calculated by dividing the ultrafiltrate concentration by the serum concentration and multiplying by the ultrafiltration rate. Urea clearance was between 25 and 28 ml/min, and creatinine clearance was between 19 and 23 ml/min (data not shown).

Statistics

Data are reported as a mean and standard deviation (SD).

RESULTS

Clinical features

The clinical characteristics of the 17 patients are shown in Table 2. There were 7 male and 10 female patients. The mean age was 58.2 ± 19.5 ($\pm$ SD) years. Twelve of the 17 patients were postoperative. Eleven had cardiac or major vascular surgery, and one underwent a Whipple's procedure. All 17 patients had circulatory failure with vasopressor dependency. All of the patients also required mechanical ventilation. The mean APACHE II score at the time of ICU admission was 25.6 ± 7.5 ($N = 16$). Fourteen patients had acute renal failure, and all were severely oliguric or anuric. One of these 14 patients had acute renal failure in a functioning renal allograft with a baseline serum creatinine of 1.3 mg/dl. Three

Table 2. Clinical features of the 17 patients treated with citrate-CVVH

Patient	Age/sex	Diagnosis	APACHE II score	Contraindication to heparin	Duration of citrate-CVVH	Outcome
1	57/M	Hepatic failure, hepatorenal syndrome	42	Intraperitoneal hemorrhage	<1 day	D
2	84/F	AVR, CABG	23	Mediastinal hemorrhage	3 days	S
3	62/F	Endocarditis and septic shock	24	Acute GI hemorrhage (on heparin)	26 days	D
4	73/F	Thoracoabdominal aortic aneurysm resection, sepsis	30	Postoperative	4 days	D
5	38/F	Ebstein's anomaly, cardiac transplantation	12	Recurrent mediastinal hemorrhage	9 days	S
6	74/F	MVR, CABG	18	Mediastinal hemorrhage, thrombocytopenia	4 days	S
7	69/F	Splenorenal bypass with subsequent thrombectomy and redo anastomosis, sepsis	28	Thrombocytopenia	4 days	S
8	21/M	Disseminated meningococcemia, DIC	20	Bleeding from surgical wounds (on heparin), thrombocytopenia, coagulopathy	6 days	S
9	79/M	Lower extremity bypass graft	31	GI hemorrhage	3 days	D
10	38/F	Aortic root replacement for abscess, CRF	18	Thrombocytopenia	4 days	S
11	70/M	AVR, sepsis, CRF	27	Thrombocytopenia	5 days	S
12	66/M	Whipple procedure, candida sepsis, CRF	28	Postoperative	24 days	D
13	45/F	ASD repair, CABG, hepatic failure	29	Mediastinal hemorrhage	5 days	D
14	71/F	Ascending aortic aneurysm resection	21	Mediastinal hemorrhage	6 days	S
15	34/F	Endocarditis, septic pulmonary emboli, hepatic failure, DIC	37	Thrombocytopenia, coagulopathy	Data missing	D
16	77/M	MVR, CABG	21	Mediastinal hemorrhage, thrombocytopenia, coagulopathy	10 days	D
17	32/M	Hemorrhagic pancreatitis	Data missing	Hemorrhagic pancreatitis	13 days	S

APACHE II scores are at the time of admission to ICU (many were higher at the time of initiation of CVVH). Patients 10, 11, and 12 were on chronic dialysis. All other patients had acute renal failure. Most patients also received additional forms of RRT at other times during their ICU course. Abbreviations are: M, male; F, female; AVR, aortic valve replacement; MVR, mitral valve replacement; ASD, atrial septal defect; CABG, coronary artery bypass grafting; DIC, disseminated intravascular coagulation; CRF, chronic renal failure; GI, gastrointestinal; D, died; S, survived.

patients (10, 11, and 12) had chronic renal failure and were on maintenance dialysis. Fluid overload was the most common indication for initiating RRT. In all cases, CVVH was chosen as the RRT modality because of hemodynamic instability. Heparin anticoagulation was judged to be contraindicated because of ongoing or recent hemorrhage in 11 patients, severe thrombocytopenia and/or coagulopathy in 4 patients, and recent major surgery in 2 patients. Four patients had developed severe complications during RRT with heparin anticoagulation and were switched from heparin to citrate anticoagulation. Three of these patients had suffered life-threatening bleeding episodes, and one had developed heparin-induced thrombocytopenia. Five patients briefly received CVVH with saline flushes without anticoagulant therapy but were converted to citrate anticoagulation because of frequent clotting.

Efficacy

Data on filter life were available for 85 filters from 15 patients. Two patients were excluded from this part of the analysis because of inadequate information in their medical records. The total duration of citrate CVVH therapy was 2374 hours, and the mean duration was 143.1 ± 136.3 hours. Sixty-four filters (75.3%) were lost because of clotting at a mean filter life of 29.5 ± 17.9 hours. The rate of citrate replacement fluid infusion varied hourly, depending on the volume of other parenteral solutions administered, the net fluid removed, and the achieved rate of ultrafiltration. The average infusion rate of citrate replacement fluid was 1.4 liters per hour, which is equivalent to 18.6 mmol/hr of citrate. This provides 2.0 mmol of citrate per liter of blood in the extracorporeal circuit. We did not find an increase in clotting associated with hours of relatively low rates of citrate infusion due to high rates of infusions of other solutions. If the low rate of citrate infusion was due to a low rate of achieved ultrafiltration, then clotting was usually imminent. The use of 21 filters was discontinued for other reasons than clotting (catheter problems, performance of diagnostic tests or surgical procedures, discontinuation of RRT, or patient's death).

Control of fluid and electrolyte balance and azotemia was excellent in all 17 patients (Table 3). The mean serum creatinine after 48 to 72 hours of treatment was 2.4 mg/dl ± 1.2 ($N = 16$) despite severe oliguria or anuria in all patients. Acid-base balance was well controlled except for two episodes of worsening metabolic acidosis

Table 3. Control of azotemia in 16 of the 17 patients

Variable	N	Onset	48–72 hr
BUN	16	67.5 ± 38.4	36.3 ± 18.0
Creatinine	16	4.7 ± 2.7	2.4 ± 1.2

in patients with septic shock and severe hepatic failure, respectively (discussed later here).

Complications

No patient suffered bleeding during CVVH with citrate anticoagulation, despite the high-risk population studied. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were measured routinely, and in no case were these prolonged by the treatment. Two patients developed citrate toxicity manifested by low serum-ionized calcium levels (with an elevated serum total calcium level in one), together with exacerbation of metabolic acidosis with a high serum anion gap. Patient 8 had septic shock caused by meningococcemia, and patient 13 had fulminant hepatic failure and candida sepsis. Serum-ionized calcium levels fell to 0.7 and 0.8 mmol/liter, respectively, and did not correct despite intravenous infusion of large doses of calcium (18 and 81 mEq over 12 hr, respectively) in addition to the calcium infusion determined by the sliding scale. Neither patient had a significant change in clinical status attributable to the hypocalcemia. In both cases, the replacement fluid was changed to a fluid containing bicarbonate instead of citrate, and CVVH was carried out in the absence of anticoagulant. Both patients had improvement of the ionized calcium level and the high anion gap metabolic acidosis after discontinuation of the citrate anticoagulation. All other patients had stable serum calcium levels. No other significant complications occurred during the treatment. No patient developed metabolic alkalosis or hypernatremia.

Outcome

The outcome for each patient is shown in Table 2. Nine of the 17 patients (53%) survived to be discharged from the hospital. Among the survivors, six out of seven patients with acute renal failure recovered their renal function, but one patient continued to require dialysis. Most of the patients who died had supportive measures withdrawn because of persistent multiorgan failure. The mean APACHE II score at the time of ICU admission was 20.9 ± 5.2 for survivors ($N = 8$) and 30.2 ± 6.7 for those who died ($N = 8$).

DISCUSSION

The results show that our design of regional citrate anticoagulation for use with CVVH is effective and can be employed safely in patients at high risk of bleeding. Compared with the previously described technique by Mehta et al, our approach carries significantly less complexity, does not require the use of dialysate, and is associated with a lower complication rate [10, 11].

Our technique of citrate anticoagulation resulted in a mean filter life of 29.5 hours, which is comparable to what has been reported for heparin anticoagulation [25]. Our hemofilter patency rates are similar to those reported by Falkenhain et al, who employed low-dose citrate with CAVHD (abstract; Falkenhain et al, *J Am Soc Nephrol* 4:344, 1993). Mehta et al have reported a mean filter life of 44 hours with their technique of regional citrate anticoagulation in CVVHDF (abstract; Mehta et al, *J Am Soc Nephrol* 4:368, 1993). Although previous studies have shown a correlation between ACT and filter survival [26], we elected not to monitor ACT in order to keep the complexity as low as possible. Like several other investigators [3, 11], we had poor experience with frequent saline flushes, without anticoagulation.

An adequate concentration of citrate in the extracorporeal circuit is necessary to chelate calcium in sufficient amounts to prevent clotting. We administered citrate-based replacement fluid containing 13.3 mmol/liter of trisodium citrate at an average rate of 1.4 liter/hr. The net rate of citrate administration was, therefore, 18.6 mmol/hr. A blood flow rate of 180 ml/min measured after the infusion of the replacement fluid produces a citrate concentration in the extracorporeal circuit of 2.0 mmol/liter of blood. Mehta et al used 4% trisodium citrate (140 mmol/liter), which was infused at an initial rate of 170 ml/hr (range 110 to 210 ml/hr), resulting in 24 mmol/hr (range 18.0 to 28.2 mmol/hr) of citrate administered. The blood flow rate is not specified in their reports, but citrate was administered at 3 to 8% of blood flow, giving a predicted range of citrate concentration of approximately 4.2 to 11.2 mmol/liter of extracorporeal blood. Thus, when compared with our system, Mehta's technique involves a greater amount of citrate administered per liter of blood, which results in longer durations of hemofilter patency. However, similar levels of blood citrate concentration can be achieved with our system by reducing the blood flow to rates similar to those used by Mehta et al or by increasing the rates of ultrafiltration and replacement fluid administration. We have recently been using a blood flow rate of 120 ml/min (measured after replacement fluid infusion), which should provide further prolongation of filter life without appreciable effect on the solute clearance rates.

We have used a fixed rate of ultrafiltration and varied the rate of replacement fluid administration to maintain fluid balance. This approach leads to variation in the ratio of citrate to blood on an hourly basis. Although we did not observe an increase in clotting during hours

of relatively low rates of citrate replacement fluid infusion, it is possible that these hours contributed to partial clotting, which, in turn, may have led to a shorter filter life. An alternative approach would be to set a fixed rate of citrate replacement fluid infusion that would provide more consistent regional anticoagulation. Fluid balance could then be maintained by adjusting the ultrafiltration rate as desired. Currently, we are unable to use this design because of limitations of our ability to control the ultrafiltration rate by the equipment we are currently employing.

In the system described by Mehta et al, the infusion of concentrated sodium citrate must be counterbalanced by using an appropriate amount of hypotonic, bicarbonate free dialysate. Alkali and sodium balances are dependent on dialysis efficiency, which may be inconsistent. They have reported a high rate of metabolic alkalosis (25 to 38%) requiring treatment with hydrochloric acid [10, 11]. In contrast, we infuse an isotonic solution with a citrate concentration set to be similar to the concentration of alkali in standard dialysis solutions (40 mEq/ liter). There is no apparent risk of metabolic alkalosis or hypernatremia associated with our system, and we did not observe these complications in any of our patients. However, our system requires a high infusion rate of replacement fluid in order to administer sufficient citrate for anticoagulation. This demands a high rate of ultrafiltration for maintenance of fluid balance. Therefore, a filter with a high ultrafiltration coefficient must be used. This high rate of ultrafiltration also results in the high clearances we achieve.

We did not monitor solute clearance rates routinely. Rather, we monitored the ultrafiltration rate hourly, and clotting was suspected when the ultrafiltration rate was persistently low. It is well known that ultrafiltration rates fall with a longer duration of membrane use, possibly because of fiber clotting or because of an intrinsic property of the membrane [27, 28]. However, studies have shown that sieving coefficients are preserved up to a mean of 43 hours during hemofiltration (abstract; Golper et al, *J Am Soc Nephrol* 3:367, 1992). Thus, as long as ultrafiltration is maintained, clearance rates are also maintained.

No hemorrhagic episodes occurred during citrate anticoagulation in this high-risk population, which confirms previous reports on the safety of regional citrate anticoagulation in CRRT (abstract; Mehta et al, *J Am Soc Nephrol* 4:368, 1993) [11]. No effect on coagulation parameters was observed. In contrast, three of our patients had developed severe bleeding complications during anticoagulation with heparin. Furthermore, one patient had developed heparin-induced thrombocytopenia.

Evidence of citrate toxicity occurred in two of our patients. Both patients had severe lactic acidosis, one from meningococcal sepsis and the other because of liver failure and sepsis. Inadequate metabolism of citrate to bicarbonate presumably led to accumulation of citrate and resulted in systemic chelation of calcium, manifested by low levels of serum-ionized calcium in both patients with a high serum total calcium level in one. There was an exacerbation of the high anion gap metabolic acidosis in these patients, probably because bicarbonate production from citrate metabolism did not keep up with the loss of bicarbonate through the filter [21]. These findings were recognized early in both patients, and they were switched to a replacement solution containing bicarbonate before there was any alteration in their clinical status. Although citrate toxicity is rare, patients must be monitored closely for this potential complication. We currently check ionized calcium levels every four hours at the beginning of therapy. Subsequently, the frequency of monitoring ionized calcium can be individualized based on the status of the patient.

The 53% survival rate in our group of patients is at least comparable to what generally has been achieved in critically ill patients with acute renal failure [29, 30]. This is intriguing in view of the fact that all the patients were severely ill, as is illustrated by the high ICU admission APACHE II scores. Furthermore, many of the patients deteriorated appreciably from the time of ICU admission to the time of initiation of CVVH. However, the survival of our patients is not directly comparable to previous studies of acute renal failure in critically ill patients, as our study includes patients with chronic renal failure. Finally, our study lacks a control group, which makes it unsuitable for determining the impact of citrate anticoagulation on survival in comparison with other methods of anticoagulation.

In most respects, the performance of our system is similar to that described by Mehta et al. However, our system is considerably less complex. First, only a single replacement solution is employed without the use of dialysate. In contrast, the technique used by Mehta et al requires separate citrate and saline infusions as well as a hypotonic, bicarbonate free dialysate. Second, their technique requires close monitoring for metabolic alkalosis and hypernatremia and treatment of these complications when they occur. These complications are not associated with our system.

Currently, the main drawback of citrate-CRRT is the cost of customized production of the citrate solution. With advances in CRRT equipment and standardization of protocols, we believe that the demand for citrate solutions will grow and will soon be enough to attract manufacturers.

We conclude that our simplified technique of regional citrate anticoagulation with CVVH is practical and effective and can be used safely in critically ill patients with a high risk of bleeding.

ACKNOWLEDGMENTS

Reprint requests to John L. Niles, M.D., Bigelow 1052, Dialysis Unit, Massachusetts General Hospital, 55 Fruit Street, Boston, Massachusetts 02114, USA.
E-mail: JLNiles@Partners.org

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