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Regional citrate anticoagulation for continuous arteriovenous hemodialysis in critically ill patients

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Continuous arteriovenous hemodialysis (CAVHD) is being used increasingly as renal replacement therapy for critically ill patients with acute renal failure (ARF) [1–4]. Generally, the procedure has required systemic anticoagulation utilizing heparin or, in a few cases, prostacyclin to maintain filter patency [5]. Although heparin is removed by CAVHD membranes, systemic anticoagulation is usually unavoidable and has been associated with an increased incidence of bleeding [6]. In order to circumvent this problem, regional heparin anticoagulation has been tried [7], but this has not gained widespread acceptance due to the difficulty in accurately adjusting protamine doses. Similarly, CAVHD has been attempted with frequent saline flushes through the filter, but it has been difficult to keep the filter patent for longer than 24 hours [8].

We describe here a technique employing sodium citrate as a regional anticoagulant for CAVHD (citrate CAVHD). Citrate is an anticoagulant by virtue of its ability to chelate calcium. The anticoagulant effect is overwhelmed and neutralized when citrated blood from the extracorporeal circuit returns to and mixes with central venous blood. Citrate has been used for conventional hemodialysis [9–12], but not previously for CAVHD. In citrate CAVHD, trisodium citrate is infused at the origin of the extracorporeal circuit, but the low dialysate flow rate limits its removal across the membrane. To compensate for the metabolic consequences of the sodium citrate load, we have developed a special dialysate containing no alkali, subnormal sodium concentration and no calcium. Calcium homeostasis is restored by a separate calcium infusion.

In 2,000 hours of citrate CAVHD in eleven critically patients, this system has proved smooth, practical and effective, and has minimized the risks of hemorrhage and thrombocytopenia encountered with heparin use.

Methods

Patients

From December 1988 through July 1989, 18 patients with acute renal failure in the intensive care units at the University of California, San Diego (UCSD) Medical Center were treated with CAVHD; eight of them also received intermittent hemodialysis (IHD) (Table 1). Eleven patients received citrate CAVHD, eight underwent heparin CAVHD, and three had CAVHD using saline flushes for maintaining filter patency. We retrospectively reviewed their clinical course with respect to the method of anticoagulation used to maintain patency of the CAVHD filter.

Vascular access

Arterial access was through an 8 F, single lumen 6 or 8 inch silastic catheter (Medcomp catheter, Medcomp Corp., Harleyville, Pennsylvania; Vygon catheter, Renal systems, Minneapolis, Minnesota, USA) inserted into the femoral artery utilizing a Seldinger technique. Venous access utilized a double-lumen 14 or 16 F catheter (Vascath, Quinton Instruments, Seattle, Washington) inserted into the femoral or subclavian vein.

Filter

All patients were treated with a polyacrylonitrile membrane hemofilter in a parallel plate configuration with a surface area of 0.5 square meters (Hospal AN69S, Hospal-Gambro-Engstrom Inc., Lincolnshire, Illinois, USA).

Extracorporeal Circuit

Heparin CAVHD. A schematic of the circuit used is shown in Figure 1A. The filter was primed with two liters of heparinized saline containing 2500 U of heparin. Following an initial bolus of 5 to 10 U/kg, heparin was infused pre-filter at a rate of 3 to 12 U/kg/hr to maintain activated clotting times (ACT), (Hemochron 400, Kentec Inc., Irvine, California, USA), between 200 and 250 seconds post-filter. These determinations were made hourly with adjustment of the heparin infusion rate as frequently as needed to adhere to this range. Activated partial thromboplastin times (PTT) were checked peripherally one to two times per day.

Dialysate was Dianeal 1.5% (Baxter Corp., Deerfield, Illinois, USA) and dialysate flow rate was one liter/hr. The ultrafiltrate and effluent dialysate were collected in a urine bag, the height of which was adjusted to maintain an ultrafiltration rate of 400 to 600 ml/hr. Hourly measurements of ultrafiltrate were made and the desired net balance was achieved by replacing the excess removed with two replacement solutions given alternately. Solution A was one liter of 0.9% saline with 10 cc of 10% calcium gluconate, while Solution B was one liter of 0.45% saline with 50 cc of 7.5% sodium bicarbonate. Both replacement solutions were given pre-filter. Measurements of

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Table 1. Patient characteristics

Pt. no.	Age	Sex	Condition	Anti-coag.	Days Rx	Outcome
1	33	M	IVDA, sepsis	H	3.5	Died
2	49	M	S/P MVR, CHF	H	2.5	Died
3	29	M	Fascitis, sepsis	H	5	Lived
4	75	M	Necrotic bowel, sepsis	S	1	Died
5	36	M	Liver failure, sepsis	H	1	Died
6	57	M	Pulm thromboendarterectomy	H, S, C	13.8	Lived
7	61	M	Liver failure, sepsis	S, H	2.7	Died
8	32	M	Liver failure, hemoperitoneum	C	4.2	Died
9	39	M	Pulm thromboendarterectomy	C	2	Died
10	35	M	GI bleed, liver failure, sepsis	C	7.3	Died
11	41	M	Perirectal abcess, sepsis	C	5.1	Died
12	63	F	S/P Whipple, sepsis	C	1.7	Died
13	43	F	Pancreatitis, ARDS	C	10.7	Died
14	62	M	Nephrectomy, sepsis, ARDS	H, C	38.6	Lived
15	29	F	Trauma (MVA), sepsis	C	1.4	Died
16	29	F	IVDA, liver failure, sepsis	C	1.4	Died
17	81	F	Trauma (MVA)	C	5.3	Lived
18	49	F	Liver failure	H	3.9	Died

Abbreviations are: ARDS, adult respiratory distress syndrome; CHF, congestive heart failure; IVDA, intravenous drug abuse; MVA, motor vehicle accident; MVR, mitral valve replacement; S/P, status post; C, citrate; H, heparin; S, saline flush.

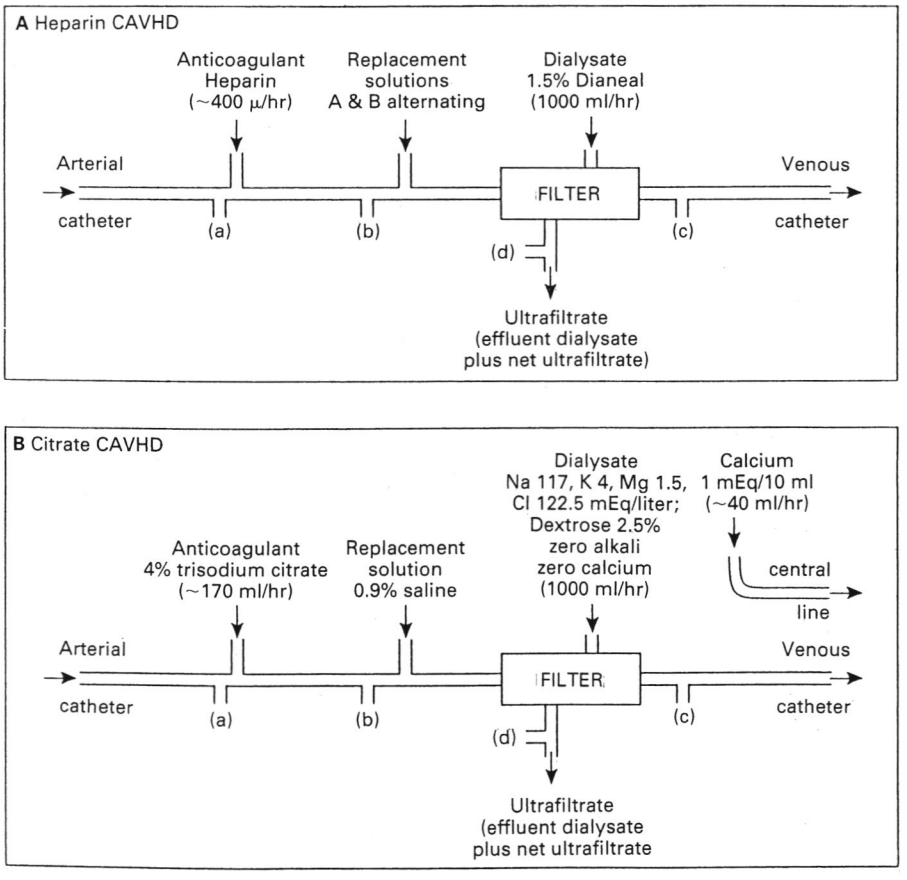

Fig. 1. *Comparison of circuit diagrams for heparin CAVHD (A) and citrate CAVHD (B).* Sampling ports are marked (a) peripheral, (b) pre-filter, (c) post-filter, and (d) ultrafiltrate. See text for details.

blood levels of electrolytes, including calcium, magnesium and phosphorus were made every 6 to 12 hours and any deficiencies were corrected.

Citrate CAVHD. The circuit is depicted in Figure 1B. The method used has now been standardized as follows: A 3-way stopcock is placed between the arterial catheter and the tubing connecting the filter, and 4% trisodium citrate (140 mmol citrate and 420 mmol sodium/liter, Baxter Corp.) is infused at this site at an initial rate of 170 ml/hr with a range of 100 to 210 ml/hr, depending upon the blood flow rate. The citrate flow rate is

adjusted to maintain the post-filter ACT at 200 to 250 seconds in the same manner as is done for CAVHD using heparin. Generally, citrate flow rates range from 3 to 8% of the blood flow rate. A total of 0.9% saline is utilized as replacement fluid and is administered pre-filter distal to the citrate infusion. The volume of replacement fluid is determined by the fluid balance required every hour. The dialysate solution is prepared from 0.45% saline, to each liter of which is added 50 ml of 50% dextrose, 4.0 mEq of potassium chloride, 1.5 mEq of magnesium sulfate and 10 mls of 23.4% sodium chloride (4 mEq per ml). The resulting dialysate contains sodium 117 mEq per liter, chloride 122.5, potassium 4.0, magnesium 1.5 and dextrose 2.5%. It contains no calcium and no alkali (alkali here means bicarbonate, acetate, lactate or other base). This dialysate is infused at a rate of 1 liter per hour through the filter. Ultrafiltrate is collected in a bag, the height of which is adjusted to achieve a net ultrafiltration rate of approximately 400 to 600 ml/hr. Calcium is replaced via a separate central venous access using a solution comprised of 20 ml of 10% calcium chloride added to 250 ml of 0.9% saline (1 mEq of calcium per 10 ml). This is infused at an initial rate of 40 ml/hr, (4 mEq/hr), with a range of 3 to 5 mEq/hr depending upon the level of ionized calcium and the citrate infusion rate.

Routine blood sampling and monitoring

Routine sites for sampling are shown in Figure 1 and include: (a) Peripheral, drawn from an arterial line or the side port of the CAVHD catheter (Medcomp), or if neither of these exist, from an additional 3-way stopcock inserted proximal to the citrate infusion site. (b) Pre-filter, drawn from the stopcock distal to the citrate infusion site. The citrate infusion is continued during sampling from the pre-filter site and at all other times. (c) Post-filter, which is distal to the filter. (d) Ultrafiltrate, from a sample port and not from the bag. Blood flows are derived from hematocrit readings in pre- and post-filter samples and ultrafiltrate flow rates [13], and are done at initiation and every 12 hours. Infusion of the replacement solution is temporarily stopped while samples for blood flow and clearance studies are being drawn. Clearance studies on the filter are done at least twice a day. In calculating our dialyzer clearances, we adapted the method described by Sigler and Teehan as shown below [14]:

$$KD = \frac{Qf\ (CDo) + QD\ (CDo)}{(CBi)\ (CBi)}$$

Clearances are determined by first measuring the ratio of BUN in ultrafiltrate/dialysate to plasma BUN to derive the sieving coefficient, (CDo/CBi). The sieving coefficient is then multiplied by the dialysate infusion rate and the net ultrafiltration rate at the time of sampling to derive separate convective and diffusive clearances, which are then added for the total dialyzer clearance. We did not correct for the intraerythrocytic pool of BUN to achieve a corrected whole blood BUN. If this had been done, we estimate that our dialyzer clearances would be increased by approximately 10%. Both blood and dialyzer clearances are calculated. The sieving coefficient for urea was monitored every 12 hours, and if the ratio fell below 0.6 the filter was changed. Peripheral blood electrolytes, BUN, creatinine, total and ionized calcium, phosphate and magnesium are monitored every 6 to 12 hours, or more frequently as necessary. Arterial blood gases are monitored similarly.

Citrate measurement

Monitoring of plasma citrate levels is not necessary for routine operation of citrate CAVHD. Citrate levels for our studies were determined using an enzymatic assay [15].

Citrate-CAVHD modifications

Variation of the formulation of all infusates and dialysates is possible to accommodate special metabolic requirements. We have chosen the following methods, although others are possible, to deal with special situations as indicated: (a) In the event of systemic acidosis we give an extra infusion of bicarbonate. Alternatively, appropriate amounts of bicarbonate could be added to the replacement solution. (b) In the event of systemic alkalosis we give a central infusion of 0.2 molar hydrochloric acid (HCl) usually at 100 ml/hr for 5 to 10 hours. (c) In the event of hypernatremia we reduce dialysate sodium from 117 to 97 mEq per liter. The alternative of lowering sodium in the replacement fluid is less efficacious in our experience. (d) Potassium or magnesium can be supplemented extraneously or altered in the dialysate formulation. (e) We routinely give the calcium solution via a separate central line. We do not favor infusing calcium in the post-filter circuit because this tends to promote clotting of the venous access, particularly if the blood flow rate is very low. The alternative of administering calcium by adding it to the dialysate solution has proved troublesome in our experience.

Statistical analysis

Performance parameters for citrate CAVHD were expressed as means and standard errors. These were compared to results obtained in our heparin CAVHD experience using Student's unpaired *t*-test for all factors except filter longevity. Filter longevity was assessed by comparing the median values for each patient in each group using the Wilcoxon rank sum test. A pseudo-filter lifetime survival analysis of median filter longevity times for each patient was performed by Gehan's Wilcoxon test [16].

Results

Clinical features

The clinical characteristics of the 18 patients with ARF are shown in Table 1. Six of the patients received CAVHD after failing to tolerate IHD. Anticoagulation modalities were selected based on clinical criteria, with patients adjudged to be at highest risk of bleeding receiving citrate or saline flushes. Heparin was used as an anticoagulant for CAVHD in eight patients, two of whom were changed to citrate CAVHD because of critical heparin-induced thrombocytopenia (case #6), and life threatening bleeding (case #14). Three patients were treated with saline flushes through the filter. Two of these patients also received heparin CAVHD; one with hepatic failure (case #7) clotted his filter on saline flushes and was converted to heparin. Citrate anticoagulation was the sole method in nine patients, and replaced heparin CAVHD in another two.

Four patients initially survived, two with return of renal function and two requiring IHD. However, the two patients

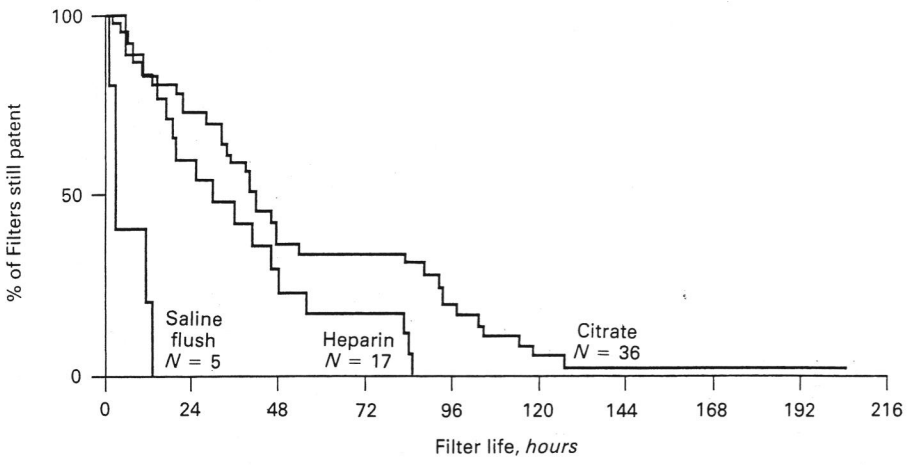

Fig. 2. *Percent of filters patent over time using saline flush heparin or citrate anticoagulation.*

who received IHD after stabilizing on CAVHD subsequently expired. Of the 16 patients who died, six had support withdrawn for a diagnosis of irreversible brain damage, and two patients succumbed to hepatic encephalopathy.

Technical adequacy

Fluid and electrolyte balance was readily achieved in all 18 patients. Mean blood flow rates ranged from 52 to 125 ml/min in all patients and were not significantly different in the heparin or citrate treated groups. Ultrafiltration rates ranged between 5.6 and 14.8 ml/min for both groups. Mean dialyzer urea clearances ranged from 13.8 to 26.8 ml/min, with an average of 22.0 ml/min. The heparin CAVHD group dialyzer clearances ranged from 13.8 to 24.3 (average 20.1 ± 1.4 ml/min), whereas the clearances for the citrate group varied from 20.3-26.8 ml/min (average 24.1 ± 0.9 ml/min; $P = 0.016$).

Anticoagulation adequacy in the extracorporeal blood circuit was similar in both groups as profiled by ACT and PT/PTT determinations. ACT values were intentionally kept within a narrower range for heparin CAVHD to minimize the impact on systemic anticoagulation as reflected in PTT values. Baseline ACT values were done in all patients prior to anticoagulation. Peripheral ACT determinations were done periodically during CAVHD and revealed minimal tendency toward progressive elevation with heparin infusion, and no elevation with citrate infusion. We found a higher incidence of filter clotting if postfilter ACT values were much below 200 seconds in both groups because of the low blood flow rates.

A total of 2,652 hours of CAVHD was done in these 18 patients, utilizing 58 filters. The median filter life was markedly reduced for the saline flush group as compared with those on heparin or citrate, but does not permit statistical comparison due to the limited number of hours. The median filter life for citrate-anticoagulated CAVHD tended to be superior to heparin CAVHD, but was not statistically significant ($P = 0.186$). Median filter duration ranged from 8.6 to 83.2 hours for heparin CAVHD and 24.6 to 127.0 hours for citrate CAVHD. Comparison of the medial filter "survival" times by lifetable analysis showed only that the citrate and heparin groups had similar results, ($P = 0.09$). When all filters placed in any patient were considered, 33.3% of citrate CAVHD filters were patent for longer than 72 hours, while only 17.6% of heparin CAVHD filters were patent for that time. Overall, 49.1% of all filters were changed due to clotting, 22.8% due to decreased efficacy, 12.3% were electively discontinued, and 5.3% were due to the patient's death. The proportion of clotted filters for citrate and heparin CAVHD were similar, (citrate 41.6%, heparin 47.1%), as was the rate of discontinuation due to decreased efficacy, (citrate 22.2%, heparin 29.4%).

Complications of treatment

Serum total and ionized calcium levels were monitored in all patients on citrate CAVHD. Peripheral ionized calcium levels ranged between 0.61 and 1.44 mmol/liter overall and 0.84 to 1.24 mmol/liter in the majority of patients. Symptomatic hypocalcemia did not develop in any patient. There was no evidence for any electrocardigraphic changes of hypocalcemia or evidence of myocardial depression referable to citrate in any patient. Peripheral serum citrate levels ranged between 0.172 and 2.95 mmol/liter, and correlated with citrate infusion rates of 120 to 210 ml/hr. Three patients developed a metabolic alkalosis related to citrate metabolism with arterial pH values ranging from 7.50 to 7.54. These patients received infusions of HCl via a central venous line, detailed in **Methods**, to correct their alkalosis. Hypernatremia was seen only while the citrate CAVHD protocol was being developed (in case #6).

During heparin CAVHD, two patients (25%) had serious bleeding and another (case #6) developed marked thrombocytopenia, whereas none of the patients on citrate CAVHD had any episode of bleeding.

Discussion

Our results show that citrate-anticoagulated CAVHD is stable and effective using the method we have developed. Several aspects of conventional CAVHD had to be modified in order to achieve this stability. These included: 1) maximizing dialyzer efficiency so that removal of citrate would be adequate; 2) addressing the calcium depletion inherent to the usage of citrate; 3) compensating for the additional sodium load imposed by the trisodium citrate solution; and 4) altering the dialysate to accommodate the alkali load engendered by citrate metabolism.

In developing our own protocol for heparin CAVHD, we modified the technique described by Geronemus and Schneider [17] and administered replacement fluid pre-filter (Fig 1A).

Kaplan has shown an 18% increase in convective clearance by giving replacement fluid pre-filter versus post-filter in continuous arteriovenous hemofiltration (CAVH) [18]. This, along with the use of highly permeable membranes, has enhanced the clearance obtainable with our CAVHD technique. Published reports on dialyzer urea clearances have shown values ranging from 14.7 to 26.6 ml/min [14, 19] using dialysate infusion rates of up to 2 liters per hour. Our overall dialyzer clearances (both convective and diffusive) with citrate CAVHD are consistent with these values infusing dialysate at only 1 liter per hour, which we find more practical and economical. Our initial attempts at citrate CAVHD were based on the published experience of Pinnick, Wiegmann and Diederich [10] and on our own experience with regional citrate anticoagulation in IHD [20]. Use of citrate in IHD has been complicated by hypervolemia as large volumes of citrate have to be infused over a short period of time to effectively anticoagulate the extracorporeal circuit; however, the volume required for infusion of citrate is easily removed with the ultrafiltration capacity inherent to our CAVHD protocol.

Since regional anticoagulation with citrate requires replacement of the chelated calcium to avoid hypocalcemia, we first adopted the strategy of Hocken and Hurst [21] in using a calcium-containing dialysate. This method works in IHD primarily because of the high dialysate flow rate and consequent clearance of citrate-calcium chelate [11]. In citrate CAVHD we found when calcium was present in the dialysate that an increased dosage of citrate was needed to maintain proper anticoagulation and led at times to evidence of systemic citrate accumulation. The use of a calcium-free dialysate has proven itself to be more satisfactory. Maintenance of calcium balance and avoidance of citrate accumulation can be adequately assured if the patient's blood levels of the following are measured every 6 to 12 hours: anion gap (Na minus the sum of Cl plus bicarb), ionized calcium and total blood calcium.

Citrate formulations are based on trisodium citrate. The sodium load imposed by citrate infusion is therefore considerable. Our initial efforts to overcome this employed low sodium or zero-sodium replacement solutions, but these were found to cause unacceptably wide swings in blood sodium levels, partly because of the variable infusion rate needed for volume reasons. Resolution of this problem was achieved by using full-strength physiological saline solution for the replacement solution, and by reducing the sodium content of the dialysate below the physiological level, so that net sodium diffusion would remove the sodium load. A dialysate sodium concentration of 117 mEq/liter provided stable control of sodium balance under most conditions. If hypernatremia occurs we use another even lower formulation (sodium of 97), or combinations of 117 or 97 to achieve the desired result. To ensure that the dialysate is never hypotonic we have incorporated dextrose (2.5% wt/vol) in all low sodium dialysates.

In the body citrate is metabolized to bicarbonate. The continuous infusion of citrate to a patient in renal failure therefore leads to marked alkalosis which after some hours would be limiting or life-threatening [22]. This trend was seen in our early attempts at citrate CAVHD. Reduction in the alkali content of the dialysate was therefore pursued, using the same mathematical approach employed to choose the sodium formulation. Alkalosis now occurs only occasionally and has been easily corrected with infusion of HCl (**Methods**).

Depression of myocardial function by citrate infusion has been demonstrated under experimental conditions [23]. This effect appears to be attributed solely to lowering of serum ionized calcium levels [24]. Many of the patients in our study had poor left ventricular function which was attributable to multiple factors. Although we did not see evidence of further impairment of ventricular function while on citrate CAVHD, we did not do rigorous testing of cardiac function pre- and post-citrate infusion to rule it out. Citrate toxicity under experimental circumstances has been seen with citrate levels above 2.4 mmol/liter [24] or infusion rates of 0.03 mmol/kg/min [25], at which time serum ionized calcium values are usually less than 0.5 mmol/liter. Our citrate infusion rates were all less than 0.007 mmol/kg/min and ionized calcium levels were carefully monitored. Citrate infusions have been well tolerated, even in patients with severe hepatic dysfunction, and we did not observe any other non-electrolyte side effects from citrate administration.

The clearances, blood flow rates and durations of filter patency with citrate CAVHD are comparable to results obtained using our heparin CAVHD protocol, but it must be emphasized that these groups were neither matched nor randomized. The only intent in making the comparison was to establish that there is no gross disparity in the technical capabilities of the two systems.

Citrate anticoagulation has the potential to avoid significant complications that can occur in heparin-anticoagulated extracorporeal systems [26, 27]. In published series the incidence of bleeding complications, even with low-dose or "tight" systemic heparinization may be as high as 30% [10, 28], which is comparable to our experience. Another complication of heparin therapy, the induction of heparin-associated platelet antibodies with resultant thrombocytopenia, is reported to occur in approximately 5% of patients receiving heparin therapy [29, 30]. We observed no bleeding complications referable to citrate anticoagulation in our patient population. Additionally, citrate does not induce platelet antibodies and eliminates this potential complication. Our observation regarding the potential for citrate anticoagulation to minimize these complications in CAVHD is encouraging. However, a prospective, randomized study is needed to better characterize the potential benefits of citrate CAVHD.

There is a trade-off in the use of citrate CAVHD in comparison with using heparin in the increased complexity of the procedure, and the risk of alkalosis. However, we feel that with careful monitoring these can be minimized and that the benefits of citrate anticoagulation in high risk patients may outweigh these factors.

Only two of 18 patients in our series survived their hospital admissions. This is reflective of the criteria employed to select CAVHD as renal replacement therapy in that it is usually employed only in patients who are hemodynamically unstable, and deemed unable to tolerate traditional IHD. This leads to a preselection of patients who are most likely to die. Our clinical experience has led us to believe that a wider and earlier use of CAVHD may possibly affect patient survival with ARF in critically ill patients; however, a randomized clinical trial is required to further address this issue.

Our experience demonstrates, using this protocol, that regional anticoagulation with citrate offers a practical alternative to systemic anticoagulation with heparin for CAVHD. When properly monitored, control of volume and solute balance can be effectively achieved in the ICU setting. This technique could lessen the potential for developing bleeding or thrombocytopenia. Citrate CAVHD can be successfully continued during major surgery and general anesthesia. The citrate anticoagulation protocol would be applicable also to pumped systems such as continuous venovenous hemodialysis (CVVHD), or indeed to any extracorporeal blood circuit in which low-flow hemodialysis occurs. We believe citrate regional anticoagulation may become an important advance in providing renal replacement therapies for critically ill patients.

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