Safety and Efficacy of Regional Citrate Anticoagulation During 8-Hour Sustained Low-Efficiency Dialysis

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Background and objectives: Patients who may benefit from sustained low-efficiency dialysis therapy are often at risk for bleeding. A safe and simple “regional” anticoagulation strategy would be beneficial. The modification of existing regional citrate anticoagulation protocols to typically performed 8-h sustained low-efficiency dialysis is necessary.

Design, setting, participants, & measurements: Sustained low-efficiency dialysis was performed at blood and dialysate rates of 250 and 300 ml/min, respectively. The circuit was anticoagulated with 4% sodium citrate (citrate 136, sodium 408 mmol/L) and reversed with CaCl₂. Every 2 h, electrolytes, ionized circuit, and patient calcium were monitored during the first two versions. The second version differed by an increased infusion of CaCl₂ and lower infusion of citrate, both by 10%. The third version measured only laboratory values before and after sustained low-efficiency dialysis.

Results: There were 41 treatments in the first iteration, 42 in the second, and 34 in the final iteration. All versions were titrated to maintain patient ionized calcium of 4.0 to 4.8 mg/dl (1.0 to 1.2 mmol/L) and the circuit ionized calcium between 0.8 and 1.6 mg/dl (0.2 and 0.4 mmol/L). The final protocol infusion was 31 mmol/h citrate and 41 mmol/h elemental calcium, which kept circuit and patient ionized calcium at targets. No unexpected metabolic complications occurred.

Conclusions: Compared with continuous renal replacement therapy, one must increase the calcium infusion because of the more efficient removal of the calcium citrate complex. Safe and effective regional citrate anticoagulation can be performed in 8-h sustained low-efficiency dialysis without metabolic complications with laboratory surveillance only before and after sustained low-efficiency dialysis treatment; however, certain safeguards are mandatory.


Since regional citrate anticoagulation (RCA) for hemodi-
alysis (HD) was first introduced in 1961, it has been modified throughout the world to apply to many dial-
ysis modalities (1–4). It is an ideal alternative to heparin in patients who are at increased risk for bleeding (5,6). The tech-
nical application and concentration of citrate does vary (7,8). The pharmacokinetics of citrate anticoagulation are well under-
stood as citrate chelates free calcium in the blood, essentially removing Ca²⁺ from its role as a co-factor in the coagulation cascade. To date, the main application of citrate has been to continuous renal replacement therapy (CRRT), including continuous sustained low-efficiency dialysis (SLED), but it has not been shown to have a role or application in intermittent hybrid therapies such as 8-h SLED, as performed in the United States.

The major metabolic complications of RCA are due to excess retained sodium and citrate ions (hypernatremia and metabolic alkalosis) (9,10). Trisodium citrate (TSC) is metabolized to bicarbonate in skeletal muscle and liver and, when metabolism is complete, results in the generation of three molecules of bicar-
bonate from one citrate molecule. Because TSC contains on a molar basis three times as many sodium ions as citrate ions, the sodium load can increase the serum sodium concentration. Thus, hypernatremia has been observed in our experience, as well as others using RCA during continuous venovenous HD. The correction often requires the addition of hemodiafiltration with 0.45% NaCl replacement fluid to remove excess sodium and bicarbonate (HCO₃⁻) (11). Other metabolic complications and adverse effects of RCA have been due to the difficulty of correcting the decalcification and impaired citrate metabolism that accompany liver failure (12–14). Thus, RCA is not without potential problems. Developing a protocol that is safe and effective is in itself time-consuming and will not be undertaken unless there is a significant demand for SLED for patients who are at high risk for bleeding. Thus, we believe that describing the protocol that we developed for this population will have broad utility. Furthermore, the development of the protocol itself is instructive.

Finkel and Foringer (15) described the use of RCA during continuous SLED (C-SLED), demonstrating that in >2200 h of therapy, none of the 20 patients had significant derangements in serum sodium concentration or acid base status to require cessation of RCA during this therapy. Their explanation for the lack of hypernatremia and metabolic alkalosis was that the higher dialysis dosage delivered by C-SLED likely corrected the problems as they developed and the problems never became clinically evident. Finkel and Foringer used different blood flow (Qb) and dialysate flow (Qd) than are used in our 8-h SLED, so the RCA regimen was only theoretically applicable. Marshall et al. (16) simulated RCA during SLED using a crys-
ossal solution instead of blood. Again, this is only of theoretical benefit as applied to 8-h SLED. RCA was also applied to a hybrid therapy similar to 8-h SLED using the Genius system (17); however, the Genius system is not available worldwide, and 8-h SLED with the operating conditions that we apply is available almost everywhere.

Thus, because of the unique properties of 8-h SLED therapy and its widespread use, we proposed an RCA protocol to fit this expanding modality. We used standard commercially available solutions and implemented a step-wise evolution of titration and safety monitoring of RCA adverse effects. We now are convinced that RCA can be applied to our 8-h SLED therapies in a safe and efficacious manner without the measurement of intradialytic ionized calcium, sodium, or bicarbonate concentrations.

Material and Methods

Study Protocols and Design

We used Fresenius 2008H (retrofitted to allow a Qd rate as low as 100 ml/min) or K machine for 8-h SLED treatments in our intensive care units or the dialysis unit at Vanderbilt University Hospital. We preferred the K machine for its touchscreen interface and the added feature of the Diasafe, which filters dialysate water just before the dialysate enters the hemo dialyzer. The flow rates were rigidly set at Qb of 250 ml/min and Qd of 300 ml/min, which differ considerably from that of Finkel and Foringer when they performed C-SLED (15). The Qb of 250 ml/min was selected because of the theoretical antithrombotic benefit of higher Qb causing less stasis within the blood pathway. The “low efficiency” term is descriptive because both Qb and Qd are much lower than in standard intermittent HD. When the mandated Qb or Qd were not achieved, the RCA protocol was not applied. This is because the dosages of citrate and calcium depend on Qb and dialytic clearance.

During the treatment, switching among heparin, saline flushes, and RCA was not allowed. The standard dialysate [Na+] was 140 mEq/L and did not vary. Dialysis machine set-up, hemodynamic and technical monitoring, and laboratory surveillance were exclusively performed by dialysis staff.

TSC (4% TSC solution manufactured by Baxter [Deerfield, IL], citrate 136 mmol/L, and sodium 408 mmol/L) was infused by a volumetric pump into a three-way stopcock at the blood pick-up site, and CaCl2 (pharmacy formulated to make the 39-g/L CaCl2 final solution [1 mmol elemental Ca2+ /ml] from a standard stock 10% calcium chloride concentrate) was infused in the same manner into a three-way stopcock at the blood return site. The dialysis machines generate dialysate from concentrate, and there is flexibility in the concentration of many constituents. The calcium-free dialysate contained 33 mEq/L bicarbonate. Net ultrafiltration rates were determined by individual patient needs.

Table 1. Standard titration protocols for RCA with CRRT

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>if patient iCa2+ &gt;5.8 mg/dl (&gt;1.45 mmol/L), then increase CaCl2 rate by 10 ml/h.</td>
<td></td>
</tr>
<tr>
<td>if patient iCa2+ &gt;4.8 mg/dl (1.2 to 1.45 mmol/L), then decrease CaCl2 by 5 ml/h.</td>
<td></td>
</tr>
<tr>
<td>if patient iCa2+ &gt;4.0 mg/dl (1.0 to 1.2 mmol/L), then do not change CaCl2 rate.</td>
<td></td>
</tr>
<tr>
<td>if patient iCa2+ &gt;3.6 mg/dl (0.8 to 1.0 mmol/L), then increase CaCl2 by 5 ml/h.</td>
<td></td>
</tr>
<tr>
<td>if patient iCa2+ &lt;3.6 mg/dl (&lt;0.8 mmol/L), then bolus CaCl2 0.091 mmol/kg CaCl2, which is 0.25 mmol/kg elemental Ca2+, then additionally increase CaCl2 rate by 10 ml/h.</td>
<td></td>
</tr>
</tbody>
</table>

Notify nephrology if patient’s serum HCO3− rises >10 mEq/L.

Notify nephrology if patient’s serum Na rises >10 mEq/L or if >155 mEq/L.

Serum HCO3 and serum Na should be measured before initiation protocol.

Sodium citrate and calcium must always run or be stopped at the same time.

If stopped >5 min, then dialysis nurse must change fluid to a calcium solution.

If total Ca2+/iCa2+ ratio ≥2.5, stop citrate anticoagulation.

Safety and surveillance protocol used by dialysis nurse and staff. Units are expressed in mEq or mmol. Derived from that of Swartz et al. CRRT, continuous renal replacement therapy; iCa2+, ionized calcium; RCA, regional citrate anticoagulation.

Sample sizes were not predetermined because this was a clinical protocol development strategy. Thus, after acceptable safety parameters were met during the first version of the protocol, the second version protocol was initiated using the mean infusion rates for TSC and CaCl2, as that seen for the mean of the eighth-hour infusion rate from protocol version 1. After consistent safety parameters were met in the second protocol version without significant change in infusions, the final protocol was started using the same approach as the first set of changes. The final protocol was designed to have no change in infusion rate during the course of the SLED treatment unless initial laboratory values were very unusual and further stipulated that the only laboratory surveillance was pre- and post-SLED treatment.
Surveillance and Safety Monitoring
Surveillance of circuit and patient laboratory values was managed by the dialysis nurse and the physician. Standard titration protocols from RCA with CRRT were applied to the SLED monitoring (Table 1).

Patients
All patients presented with one or more indications to avoid systemic anticoagulation, such as recent surgical procedure, thrombocytopenia, or coagulopathy. We implemented a modified standard RCA protocol from our CRRT protocols (derived from that of Swartz et al. [18] from the University of Michigan Medical Center) into our SLED practice, because the operational characteristics for SLED were more similar to CRRT than they were for intermittent HD, which had a different RCA protocol. We calculated the mmol/h citrate infused during CRRT with a Qb rate of 180 ml/min. Our SLED operational Qb rate was 250 ml/min, so we increased the citrate infusion accordingly. The CRRT protocol uses anticoagulant citrate dextrose-formulation A (ACD-A) as the citrate source. We had to convert the source to 4% TSC because the operational characteristics for SLED were more similar to the University of Michigan Medical Center) into our SLED practice, anticoagulation, such as recent surgical procedure, thrombocytopenia, or coagulopathy. We implemented a modified standard RCA protocol from our CRRT protocols (derived from that of Swartz et al. [18] from the University of Michigan Medical Center) into our SLED practice, because the operational characteristics for SLED were more similar to CRRT than they were for intermittent HD, which had a different RCA protocol. We calculated the mmol/h citrate infused during CRRT with a Qb rate of 180 ml/min. Our SLED operational Qb rate was 250 ml/min, so we increased the citrate infusion accordingly. The CRRT protocol uses anticoagulant citrate dextrose-formulation A (ACD-A) as the citrate source. We had to convert the source to 4% TSC because the amount of ACD-A bags was labor-intensive because it is less citrate concentrated. We used the same math reasoning for CaCl₂ and eventually had to make a more concentrated solution there as well. Typically, the patients who required SLED therapy were in the intensive care unit, but an occasional treatment was performed in the dialysis unit. Only some patients were on mechanical ventilation, and management of the ventilators was often performed without obtaining arterial blood gases. The choice of 8-h SLED over intermittent HD or CRRT was determined by clinical, technical, or staffing criteria. Baseline characteristics of admitting diagnosis, age, race, and gender are shown in Table 1. Informed consent for the dialysis included a discussion of the anticoagulation regimen, which included the reasons to avoid systemic anticoagulation.

Statistical Analyses
Unpaired t test was used to assess the changes between time points within a protocol version and against other versions. A significant difference was defined as P < 0.05. All results are expressed as the means ± SD. Group sizes were not chosen/selected in advance for any statistical purposes because this was not a prospective study. When we felt comfortable that we understood the results of the protocols, we moved to the next protocol, each protocol with less laboratory surveillance.

Results
Baseline Patient Characteristics
The number of patients and 8-h SLED treatments that compose the date for each protocol version are shown in Table 2. The first protocol version had a mean of 6.78 ± 1.85 h of 100% open dialysis circuit time from 41 treatments. The second protocol version had a mean of 6.71 ± 1.94 h of 100% dialysis circuit time from 42 treatments. The final version protocol had a mean of 7.32 ± 1.34 h of 100% open dialysis circuit time from 34 treatments. There were no statistical differences in open circuit time among the three versions of the RCA protocol.

Metabolic Complications and Safety
There was an approximately 10% failure to obtain the appropriate laboratory values in all protocol versions. The reasons for omitted laboratory values included nursing error, inadequate sample, laboratory error, or absent order entry. The surveillance laboratory results for all three protocol versions are summarized in Table 3 where the initial value at 0 h is contrasted to the value at the end of therapy (eighth hour). Serum sodium and total calcium concentrations, as intended, did not change during the course of the SLED, whereas the bicarbonate concentration and venous pH did change and in the direction toward normalization, again as intended. Although there were no statistical differences from pre- to post-SLED, the final protocol version started out with a statistically lower initial total calcium concentration than the previous protocol versions (P = 0.002).

Table 2. Baseline demographics*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>First Protocol</th>
<th>Second Protocol</th>
<th>Third Protocol</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>9</td>
<td>11</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Treatments</td>
<td>41</td>
<td>42</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>53.6 ± 4.8</td>
<td>53.5 ± 5.0</td>
<td>50 ± 5.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Male gender</td>
<td>6</td>
<td>7</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Race</td>
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<td>white</td>
<td>6</td>
<td>8</td>
<td>8</td>
<td>NS</td>
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<td>black</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Renal failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acute</td>
<td>5</td>
<td>6</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>chronic</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline laboratory values</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>138.8 ± 0.8</td>
<td>138.8 ± 0.9</td>
<td>139 ± 0.7</td>
<td>0.54</td>
</tr>
<tr>
<td>HCO₃⁻ (mmol/L)</td>
<td>25.5 ± 0.6</td>
<td>25.9 ± 0.6</td>
<td>26.2 ± 0.9</td>
<td>0.48</td>
</tr>
<tr>
<td>Venous pH</td>
<td>7.33 ± 0.01</td>
<td>7.33 ± 0.01</td>
<td>7.33 ± 0.01</td>
<td>0.95</td>
</tr>
<tr>
<td>Ionized calcium (mg/dl)</td>
<td>4.6 ± 0.09</td>
<td>4.65 ± 0.09</td>
<td>4.33 ± 0.07</td>
<td>0.012</td>
</tr>
<tr>
<td>Total calcium (mg/dl)</td>
<td>9.1 ± 0.2</td>
<td>9.1 ± 0.2</td>
<td>8.0 ± 0.2</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*P values were compared from first protocol to final version. P < 0.05 is significant.
versions of the RCA protocol, as shown in Table 5.

concentrations did drop during the SLED treatment in all three

Table 4.

Ionized circuit calcium

infusion rate was initially 31 ml/h (31 mmol/h elemental Ca$_{2+}$)

surveillance. Subsequent treatments were started at lower in-

approximately 241 ml/h (32.8 mmol/h citrate) with routine

was 261 ml/h (35.5 mmol/h citrate), it was rapidly decreased to

Table 6. Although the first protocol initial TSC infusion rate

infusion was requiring a large amount of volume, so a

temporarily a 20-mg/ml solution during the first few infusions. This

infusion was requiring a large amount of volume, so a

39-mg/ml solution was made by the pharmacy, which reduced the

volume needed to achieve the same calcium levels. CaCl$_2$

infusion rate was initially 31 ml/h (31 mmol/h elemental Ca$_{2+}$)

but was also quickly titrated up during routine surveillance. The

mean initial CaCl$_2$ infusion rate was 37.5 mmol/h elemental

calcium but was statistically elevated at 8 h to 43.3 mmol/h

elemental Ca$_{2+}$. We explain this dosing in both ml/h and

mmol/h elemental Ca$_{2+}$ so that the reader can prepare the

concentration of CaCl$_2$ to address the local facility’s desires.

The second protocol version had very similar decrease in TSC

infusion rate with subsequent increase in CaCl$_2$ infusion rate.

The initial TSC infusion rate was 241 ml/h (32.8 mmol/h

citrate), which statistically decreased to 231 ml/h (31 mmol/h

citrate) by 8 h ($P = 0.02$). Mean CaCl$_2$ infusion rates also

expectedly increased as well from 38.5 mmol/h elemental Ca$_{2+}$
to 43.4 mmol/h elemental Ca$_{2+}$ ($P = 0.006$) at 8 h. The final

protocol version infusion rates were set for TSC at 231 ml/h (31

mmol/h citrate) and for CaCl$_2$ (41 mmol/h elemental Ca$_{2+}$).

There were no significant changes in requirements of infusion

of TSC or CaCl$_2$.

Complications

We encountered several technical and staffing issues during

the evolution of the protocol. There was some initial confusion

regarding which citrate solution to use (4% TSC versus ACD-A)

because ACD-A is commonly used as the anticoagulant during

apheresis and CRRT. We also initially struggled with supplying

a large enough volume of TSC to avoid having to change the

initial set-up of solutions during treatment. Using 500-ml bags

of TSC is preferred. The CaCl$_2$ concentration had to be in-

increased from its original 20-mg/dl solution because it required

such large volumes, which complicated the net ultrafiltration

goals. Nursing staff had to remember to increase the hourly

fluid removal to meet this extra intravenous fluid intake. An-

other serious problem was in order entry and set-up of the

calcium-free dialysate baths. Three SLED treatments during the

final protocol were initiated with a 2.5-mEq/L calcium bath

instead of a calcium-free dialysate bath. This caused hypercal-

Table 3. Safety

<table>
<thead>
<tr>
<th>Parameter</th>
<th>First Protocol</th>
<th>Second Protocol</th>
<th>Final Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 H</td>
<td>8 H</td>
<td>Range</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>138.80</td>
<td>139.80</td>
<td>132.00 to 151.00</td>
</tr>
<tr>
<td>HCO$_3$ (mEq/L)</td>
<td>25.50</td>
<td>29.40</td>
<td>20.00 to 38.00</td>
</tr>
<tr>
<td>Venous pH</td>
<td>7.33</td>
<td>7.40</td>
<td>7.17 to 7.52</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.12</td>
<td>8.62</td>
<td>6.80 to 11.90</td>
</tr>
</tbody>
</table>

$^a$P values were compared from 0 to 8 h.

Efficacy of Citrate Anticoagulation

No dialyzers clotted, and no treatments were terminated as a

result of dialyzer clotting. Also of significance, no bleeding was

recognized. During the titration of each version of the RCA

protocol, the circuit ionized calcium levels were maintained in

an acceptable range (Table 4). The first and second protocol

mean ionized calcium concentration was unchanged from the

second to the eighth hour. The final protocol ionized calcium

concentration was 0.99 mg/dl at 8 h, and, by protocol, no

sample was obtained at 2 h. There was no statistical difference

in circuit ionized calcium concentration from the first version to

the final version ($P = 0.23$). The patient’s ionized calcium

calculations did drop during the SLED treatment in all three

versions of the RCA protocol, as shown in Table 5.

Dosage of Citrate Anticoagulation

The infusion dosages of 4% TSC (Figure 1) and CaCl$_2$ (Figure

2) were able to maintain therapeutic circuit and patient’s ion-

ized calcium concentrations.

Evolution from First Protocol Version to Final Protocol Version

The first protocol version evolved to the final version over 6

mo. The summaries of each protocol infusion are shown in

Table 6. Although the first protocol initial TSC infusion rate

was 261 ml/h (35.5 mmol/h citrate), it was rapidly decreased to

approximately 241 ml/h (32.8 mmol/h citrate) with routine

surveillance. Subsequent treatments were started at lower in-

fusions by the end of the first protocol version. The CaCl$_2$

temporarily a 20-mg/ml solution during the first few infusions.

This infusion was requiring a large amount of volume, so a

39-mg/ml solution was made by the pharmacy, which reduced the

volume needed to achieve the same calcium levels. CaCl$_2$

infusion rate was initially 31 ml/h (31 mmol/h elemental Ca$_{2+}$)

but was also quickly titrated up during routine surveillance.

The initial TSC infusion rate was 241 ml/h (32.8 mmol/h

citrate), which statistically decreased to 231 ml/h (31 mmol/h

citrate) by 8 h ($P = 0.02$). Mean CaCl$_2$ infusion rates also

expectedly increased as well from 38.5 mmol/h elemental Ca$_{2+}$
to 43.4 mmol/h elemental Ca$_{2+}$ ($P = 0.006$) at 8 h. The final

protocol version infusion rates were set for TSC at 231 ml/h (31

mmol/h citrate) and for CaCl$_2$ (41 mmol/h elemental Ca$_{2+}$).

Table 4. Ionized circuit calcium

<table>
<thead>
<tr>
<th>Parameter</th>
<th>First Protocol</th>
<th>Second Protocol</th>
<th>Final Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 H</td>
<td>8 H</td>
<td>$P$</td>
</tr>
<tr>
<td>Ionized calcium (mg/dl)</td>
<td>0.81</td>
<td>0.84</td>
<td>0.07</td>
</tr>
</tbody>
</table>

$^a$8 h $P1 =$ first/final, 8 h $P2 =$ first/second, 8 h $P3 -$ second/final. To convert Ca concentration in mg/dl to mmol/L, divide by 4.
cemia that was not recognized until therapy ended because the only surveillance was before and after SLED. Each of the three affected patients required an extra intermittent dialysis treatment to correct the ensuing hypercalcemia. Another technical problem was on set-up of the infusion ports on one patient during the first protocol. The TSC and CaCl₂ infusions were reversed, thus causing systemic infused citrate and lowering the patient’s ionized calcium levels. This was rapidly corrected as a result of the second-hour surveillance laboratory values.

The accuracy of the infusion pumps for TSC and calcium was not assessed. At the end of the SLED treatment, the volume of infused solutions was consistent with the volumetric infusion pump settings and duration of treatment. This became so reliable that we could account for it in our ultrafiltration strategy and orders written before the treatment.

Discussion

We have not attempted very many 8-h SLED treatments with similar operating characteristics in the absence of some anticoagulant (e.g., heparin, argatroban); therefore, we can only state that we have developed an RCA protocol to decalcify effectively the extracorporeal circuit. The use of RCA in our SLED system is therefore probably effective at providing anticoagulation of the dialysis circuit while maintaining systemic calcium levels and thus not altering systemic coagulation. We did not experience any circuit failures during the evolution of the citrate protocol. We did not observe hypernatremia, metabolic alkalosis, or excess citrate during our development of an RCA protocol for 8-h SLED treatments. Other errors were made, and the reader should learn from our experience and consciously establish safeguards to prevent this from recurring.

RCA is applied only during the actual RRT. For CRRT and even C-SLED, because they are continuous and lower in per-minute clearance than SLED, the metabolic complications of RCA can gradually accumulate. In SLED, in which the per-minute clearance is at least twice that of CRRT, the SLED treatment actually corrects the potential metabolic complications of RCA as they occur; for example, not allowing an increase in bicarbonate or sodium concentration. Most CRRT modalities use a Qd of 32 ml/min, resulting in a total effluent volume of 48 L/d. In C-SLED, that rate is 100 ml/min, with a daily effluent of 144 L. Qd is increased to 300 ml/min with an 8- to 12-h SLED therapy. The increased removal of the calcium

Table 5. Ionized patient calcium

| Parameter | First Protocol | | | Second Protocol | | | Final Protocol | | |
|-----------|----------------|---|---|-----------------|---|---|-----------------|---|
| 0 H       | 8 H            | P  | 0 H | 8 H            | P  | 0 H | 8 H            | P  |
| Ionized calcium (mg/dl) | 4.63 | 4.21 | 0.009 | 4.66 | 4.21 | 0.007 | 4.33 | 3.91 | 0.002 |

*8 h first/final P = 0.07, 8 h first/second P = 0.80, 8 h second/final P = 0.12. To convert Ca concentration in mg/dl to mmol/L, divide by 4.

Figure 1. 4% Trisodium citrate infusion rates during all three protocol versions. Data are means ± SD. (A and B) The first two versions have rates every 2 h. The difference between the 0- and 8-h infusion rates in both A and B is statistically significant (P = 0.02). (C) The final protocol version had pre- and final infusion rates that were not statistically different.

Figure 2. Ca²⁺ infusion rates during all three protocol versions. Data are means ± SD. (A and B) The first two versions have rates every 2 h. The difference between the 0- and 8-h infusion rates in both A and B is statistically significant (P = 0.001 and P = 0.006). (C) The final protocol version had pre- and final infusion rates that were not statistically different.
Table 6. Infusion protocols for each successive version

<table>
<thead>
<tr>
<th>Version</th>
<th>Treatments</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>41</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>over 1 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4% TSC inf</td>
<td>261 ml/h</td>
</tr>
<tr>
<td></td>
<td>136 mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>citrate × 261 ml/h = 35.5 mmol/L citrate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.4 g/h = 35.5 mmol/h citrate = 106.5 mEq/h citrate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CaCl₂ inf</td>
<td>postfilter initially started at</td>
</tr>
<tr>
<td></td>
<td>approximately 31 ml/h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 mmol/ml elemental Ca²⁺ × 31 ml/h = 31 mmol/h or 62 mEq/h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>39 mg/ml CaCl₂ × 31 ml/h = 1.2 g/h or 10.9 mmol/h CaCl₂</td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>42</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>over 2 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4% TSC inf</td>
<td>241 ml/h</td>
</tr>
<tr>
<td></td>
<td>136 mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>citrate × 241 ml/h = 32.8 mmol/L citrate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.64 g/h = 32.8 mmol/h citrate = 98.3 mEq/h citrate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CaCl₂ inf</td>
<td>postfilter initially started at</td>
</tr>
<tr>
<td></td>
<td>approximately 36 ml/h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 mmol/ml elemental Ca²⁺ × 36 ml/h = 36 mmol/h or 72 mEq/h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>39 mg/ml CaCl₂ × 36 ml/h = 1.4 g/h = 12.7 mmol/h CaCl₂</td>
<td></td>
</tr>
<tr>
<td>Third</td>
<td>34</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>over 1.5 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4% TSC inf</td>
<td>231 ml/h</td>
</tr>
<tr>
<td></td>
<td>136 mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>citrate × 231 ml/h = 31 mmol/h citrate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.24 g/h = 31 mmol/h citrate = 93 mEq/h citrate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CaCl₂ inf</td>
<td>postfilter at exactly 41 ml/h</td>
</tr>
<tr>
<td></td>
<td>1 mmol/ml elemental Ca²⁺ × 41 ml/h = 41 mmol/h or 82 mEq/h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>39 mg/ml CaCl₂ × 41 ml/h = 1.6 g/h = 14.5 mmol/h CaCl₂</td>
<td></td>
</tr>
</tbody>
</table>

*Units are expressed in mEq or mmol. For trisodium citrate (TSC), there are 3 mmol of Na or each mmol of citrate. Only citrate is quantified. For Ca, the mmol and mg are expressed for CaCl₂ as well as for elemental Ca²⁺.*

The patients in the final protocol cohort had a higher incidence of predialysis hypocalcemia than either of the first two protocol cohorts. Thus, during the final protocol version, we started off with lower mean ionized and total calcium levels. This is important because our protocol results in lower ionized and total Ca levels after SLED with RCA. We believe that if the pre-SLED total Ca concentration (corrected for the serum albumin concentration) is <8 mg/dl, then surveillance during the SLED with RCA at 2 or 4 h would be prudent. If surveillance is not performed in patients with pre-SLED hypocalcemia, then the CaCl₂ infusion rate should be empirically increased. This is certainly a topic for further investigation. The ideal calcium level in the critically ill patient is not well understood (19–22).

The usual metabolic safety concerns (metabolic alkalosis and/or hypernatremia) are self-corrected with SLED at our dosage of dialysis, although the lowering of total and ionized calcium levels in some patients can become problematic. In those cases, we recommend frequent surveillance and continued adjustment of the infusions of TSC and CaCl₂. We think that a safety check-off list must be developed similar to the method used by airline pilots before take-off. Critical to this would be a second check that the TSC line is going into the blood pick-up line, the CaCl₂ line goes into the blood return line or delivered centrally, and the dialysate is calcium-free. We recently placed the citrate infusion into the arterial drip chamber bubble trap and the calcium infusion into the venous drip chamber bubble trap with general success. This has the obvious benefit of avoiding direct patient infusion of citrate, which could occur with catheter dysfunction. In addition, when the dialysis machine blood pump stops and the drip chambers fill, it will set off alarms on the RCA infusion pumps and they also will stop. If this safety redundancy is applied, then our RCA protocol can provide safe and effective extracorporeal circuit decalcification (and probably anticoagulation) with no routine intradialytic surveillance. Alternatively, surveillance laboratory values can be checked. This, of course, increases costs and uses nursing time. For inexperienced programs, this may be a prudent expense.

**Conclusions**

The area of RCA in SLED is a new and novel approach to anticoagulating the dialysis circuit. We believe that this therapy can be further modified into other SLED practices with further adjustment to meet specific dialysis needs of an individual patient.

**Acknowledgments**

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We thank our nursing staff, colleagues, and patients without whom we could not have developed the protocol described here. Judy Moss provided secretarial help.

**Disclosures**

T.A.G. has consulted for Fresenius-North America.

**References**

1. Ashton D, Mehta R, Ward D, McDonald B, Aguilar M: Recent advances in continuous renal replacement therapy:...


