Efficacy and Safety of a Citrate-Based Protocol for Sustained Low-Efficiency Dialysis in AKI Using Standard Dialysis Equipment

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Summary

Background and objectives A simple anticoagulation protocol was developed for sustained low-efficiency dialysis (SLED) in patients with AKI, based on the use of anticoagulant citrate dextrose solution formulation A (ACD-A) and standard dialysis equipment. Patients' blood recalcification was obtained from calcium back-transport from dialysis fluid.

Design, setting, participants, & measurements All patients treated with SLED (8- to 12-hour sessions) for AKI in four intensive care units of a university hospital were studied over a 30-month period, from May 1, 2008 to September 30, 2010. SLED interruptions and their causes, hemorrhagic complications, as well as coagulation parameters, ionized calcium, and blood citrate levels were recorded.

Results This study examined 807 SLED sessions in 116 patients (mean age of 69.7 years [SD 12.1]; mean Acute Physiology and Chronic Health Evaluation II score of 23.8 [4.6]). Major bleeding was observed in six patients (5.2% or 0.4 episodes/100 person-days follow-up while patients were on SLED treatment). Citrate accumulation never occurred, even in patients with liver dysfunction. Intravenous calcium for ionized hypocalcemia (< 3.6 mg/dl or < 0.9 mmol/L) was needed in 28 sessions (3.4%); in 8 of these 28 sessions (28.6%), low ionized calcium was already present before SLED start. In 92.6% of treatments, SLED was completed within the scheduled time (median 8 hours). Interruptions of SLED by impending/irreversible clotting were recorded in 19 sessions (2.4%). Blood return was complete in 98% of the cases. In-hospital mortality was 45 of 116 patients (38.8%).

Conclusions This study protocol affords efficacious and safe anticoagulation of the SLED circuit, avoiding citrate accumulation and, in most patients, systematic calcium supplementation; it can be implemented with commercial citrate solutions, standard dialysis equipment, on-line produced dialysis fluid, and minimal laboratory monitoring.

Introduction

Prolonged intermittent renal replacement therapies (RRTs), commonly denominated as sustained low-efficiency dialysis (SLED), are increasingly used in critically ill patients with AKI (1–6).

SLED, usually lasting 8–12 hours, shares most advantages of both the conventional intermittent (4 hours) and the continuous forms of RRT (4,7–11).

Finding the best compromise between the risks of circuit coagulation (12) and bleeding (13) still represents a major challenge of AKI treatment. In the last 20 years, citrate has emerged as a safe and efficacious alternative to heparin for extracorporeal circuit anticoagulation (12,14). Citrate chelates ionized calcium (Ca++, the most important cofactor of the coagulation cascade, causing ionized hypocalcemia and impaired thrombin generation (12). The low molecular weight citrate anion is removed by diffusion/convection, with the patient's citrate load eventually resulting from the balance between citrate administration and its removal by RRT (12). Longer circuit survival with lower bleeding rates (15,16) and improved biocompatibility (17–20) are recognized advantages of the citrate-based continuous RRT modalities.

Although regional citrate anticoagulation has also been recommended by the recent Kidney Disease Improving Global Outcomes guidelines (21), several physicians are still reluctant to adopt this technique because of the following: (1) the heterogeneity and complexity of most of the available protocols, based on dedicated machines and circuits; (2) the need for customized and expensive citrate solutions and replacement fluids; (3) the fear of metabolic complications (particularly hypocalcemia and metabolic alkalosis); and (4) difficulties in predicting and preventing citrate accumulation, especially when liver function is impaired (12).
The reported incidence of clotting within the extracorporeal circulation during SLED is 26%–46% when no anticoagulation is administered, but it decreases to 10%–26% with the use of prostacyclin or unfractionated heparin (9–11,22–24). The incidence of hemorrhagic complications in patients with AKI on RRT ranges from 4% to 30%–50% (25–30).

Currently, few data are available about citrate use for SLED in critically ill patients with AKI.

In this study, prospectively studied indicators of safety and efficacy of our simplified citrate protocol are reported for 807 SLED sessions in 116 consecutive patients with AKI admitted to the four adult intensive care units (ICUs) of our university hospital. Citrate levels were also measured in a subgroup of the same patients, in order to gain insights about the risk of citrate accumulation.

Materials and Methods

Patients

SLED with citrate is the standard-of-care RRT modality for critically ill patients with AKI at our institution since May 2008. The indications are as follows: hemodynamic intolerance to previous intermittent 4-hour hemodialysis, fluid overload (>10% of usual or ideal body weight at the time of RRT initiation), severe catabolism, concomitant neurologic problems, or neurotrauma. Patients with a platelet count <20,000/mm³ usually receive SLED without any antithrombotic agent.

For this study, we considered eligible all patients undergoing SLED because of AKI at the four adult ICUs (general/trauma, surgical, heart surgery, renal) at our university hospital starting from May 1, 2008 to September 30, 2010.

SLED Procedure and Antithrombotic Technique

SLED was performed using the AK200S Ultra type 1 machine (Gambro, Medolla, Italy) and polysulfone filters (F8HPS, 1.8 m², Kuf 18 ml/mmHg per hour; Fresenius Italia, Palazzo Pignano, Italy), with a blood flow of 200 ml/min, on-line generated ultrapure dialysate (cocurrent flow, 300 ml/min), and dialysate Ca²⁺ 1.25 mmol/L (5 mg/dl). We used ACD-A (3% citrate, 0.8% citric acid, 2.2% trisodium citrate, 112.9 mmol/L total citrate anion in 2.5% dextrose; Fresenius Italia) as an anticoagulant, infused before the filter, initially at 400 ml/h, then at 300 ml/h (200 ml/h at discretion of the attending nephrologists in the case of possible liver dysfunction). Because blood flow rate was invariably set at 200 ml/min, citrate levels in the whole treated blood can be predicted to be approximately 4 mmol/L with an ACD-A infusion rate of 400 ml/h, 3 mmol/L with 300 ml/h, and 2 mmol/L with 200 ml/h on the basis of the following formula:

\[ \text{Whole Blood Citrate (mmol/L)} = \frac{(C_{\text{ACD-A}} \times Q_{\text{ACD-A}})}{Q_{\text{blood}}} \]

where \( C_{\text{ACD-A}} \) is the citrate concentration in the ACD-A solution (mmol/L), \( Q_{\text{ACD-A}} \) is the infusion rate of ACD-A solution (L/h), and \( Q_{\text{blood}} \) is the blood flow into the circuit (L/h).

Initially, treatment monitoring involved serial Ca²⁺ (ABL800 Flex Hemogasanalyzer; Radiometer, Copenhagen, Denmark) and activated coagulation time (ACT) (Hemochron Signature Elite; ITC, Edison, NJ) measurements at SLED start, every 2 hours, and at SLED end. Circuit sampling points were set as follows: patient’s blood before the filter (i.e., before blood mixing with ACD-A, “systemic ACT”), circuit blood before the filter (after blood mixing with ACD-A), and circuit blood after the filter (i.e., blood returning to the patient). In 91 sessions, serum citrate levels in the patient’s blood were measured by commercially available ultraviolet test kits for enzymatic spectrophotometric analysis (Enzyplus EZA785⁺; Biocontrol Systems, Rome, Italy) at the same circuit sampling points.

In the day-by-day routine, sampling for monitoring was limited to the patient’s blood before the filter at SLED start (systemic ACT), at 2 hours from SLED, and at the end of SLED. Calcium gluconate 10% infusion (calcium 0.24 mmol/ml) was started by the nephrology nurses at 5 ml/h whenever Ca²⁺ fell below 0.9 mmol/L in the blood coming from the patient and/or below 0.60 mmol/L in the blood returning to the patient; Ca²⁺ was rechecked in 30-60 min calcium gluconate infusion was in case increased to 10 ml/h (see the Supplemental Material for the detailed ACD-A protocol).

Data Collection

Data regarding SLED monitoring and treatment complications were extracted from sheets routinely filled in by nurses and nephrologists, as previously described (10).

Demographic and clinical data were taken from the clinical and administrative database of the ward, including the Acute Physiology and Chronic Health Evaluation (APACHE) score in version II (31) at RRT start (32), and the Model for End-Stage Liver Disease (MELD) score (33). MELD is a prospectively developed and validated liver disease severity scoring system that uses a patient’s laboratory values for serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time.

The study was conducted in accordance with the Helsinki Declaration and was approved by the Review Board of Parma University. Informed consent to RRT was obtained from either the patient or a close relative.

Safety Measures

Safety was evaluated as follows. The incidences of major bleeding episodes during RRT comprised all bleeding episodes actually occurring during the day of SLED session, or in the ensuing 48 hours, were considered hemorrhagic complications of treatment. Because SLED...
was performed with a daily or alternate-day schedule, the incidence of major bleeding was obtained by computing person-days as the time period (days) between the first and the last SLED treatment. Major bleeding was defined as overt bleeding leading to either hypotension or transfusion of at least two packed red cell units (10). Additional parameters included ACT levels in the patient’s blood during RRT; Ca++ concentration in the patient’s blood, in which we calculated the number of treatments with Ca++ decrease below 0.90 mmol/L after SLED start, whatever the time point of the Ca++ measurement was; and serum citrate levels in the patient’s blood during RRT.

Efficacy Measures

As previously reported (10), we measured efficacy as the proportion of nonprematurely interrupted treatments, and the proportion of blood return at the end of each SLED session. Reasons for session interruption were usually represented by unexpected clotting of the filter and/or the lines, or by an increase in transmembrane pressure exceeding the maximum value recommended by the filter manufacturer. In some cases, interruptions were due to urgent procedures or diagnostic tests, or to impending death of the patient. Blood return after each circuit discontinuation was also recorded. The volume of blood returned to the patient was defined on the basis of visual inspection of the extracorporeal circuit by the nurses; complete return was defined by a complete rinsing from blood of the lines and the filter at the end of SLED; no blood return was defined by complete occlusion of the air traps by visible clots rendering blood flow not possible; and intermediate conditions were defined as partial return. The urea reduction ratio was calculated according to standard methods (34).

Statistical Analyses

Nonrepeated continuous and categorical unpaired data were compared by Mann–Whitney and Fisher’s exact tests, respectively. The 95% confidence interval (95% CI), as well as the P value for estimates of premature interruption of the SLED circuit and of the difference between prescribed and obtained weight loss, were computed using logistic and linear regression analysis with a sandwich estimator of the variance whenever appropriate. For the computation of the MELD score, creatinine was set to 4 mg/dl for all patients. A P value <0.05 was regarded as statistically significant. All analyses were performed using GenStat (release 15.0; VSN International, Hemel Hempstead, UK) and the Stata Statistical Software package (release 12.0; StataCorp, College Station, TX).

Results

Patients Characteristics and Follow-Up

The average APACHE II score was 23.8 (Table 1). AKI was oliguric in 90 of 116 patients (77.6%). Two thirds of the patients were mechanically ventilated by invasive

| Table 1. Demographic and clinical characteristics of patients at SLED start (first session) |
|---------------------------------|------------------|
| Characteristic                  | Value            |
| Age, yr                         | 70 (12.1)        |
| Male                            | 61 (52.6%)       |
| Body weight, kg                 | 79.4 (14.2)      |
| APACHE II score                 | 23.8 (4.6)       |
| Serum creatinine, mg/dl         | 4.8 (2-11)       |
| BUN, mg/dl                      | 67 (17-184)      |
| Oliguria                        | 90 (77.6%)       |
| Conventional intermittent dialysis before SLED | 40 (34.5%) |
| Sodium, mEq/L                   | 138 (4.4)        |
| Potassium, mEq/L                | 4.7 (0.8)        |
| Bicarbonate, mEq/L              | 21.3 (3.6)       |
| Total calcium, mg/dl            | 8 (0.8)          |
| Phosphorus, mg/dl               | 4.6 (1.94)       |
| Magnesium, mg/dl                | 1.9 (0.5)        |
| Lactate, mg/dl                  | 18 (17)          |
| Total bilirubin, mg/dl          | 2 (2.9)          |
| Serum albumin, g/dl             | 2.2 (0.6)        |
| Mechanical ventilation          | 111 (95.7%)      |
| Noninvasive                     | 33 (29.7%)       |
| Postoperative status            | 63 (54.3)        |
| Urgent surgery                  | 42 (36.2%)       |
| Heart surgery                   | 29 (25%)         |
| Hypotension/hemodynamic instability | 92 (79.3%)     |
| Use of vasopressors             | 65 (56.0%)       |
| Sepsis, comorbidity             | 38 (32.8%)       |
| MELD score                      | 23.3 (16-41)     |
| Recent major bleeding           | 11 (9.5%)        |
| Platelet count <100,000/mm³     | 57 (49.1%)       |
| Platelet count <50,000/mm³      | 18 (15.5%)       |
| Prophylaxis with low molecular weight heparin | 75 (64.7%)   |
| Therapy with heparin            | 7 (6.0%)         |
| Artificial nutrition            | 106/116 (91.4%)  |
| Enteral                         | 18 (15.5%)       |
| Parenteral                      | 26 (22.4%)       |
| Enteral + parenteral            | 62 (53.4%)       |
| Chronic comorbidities           |                  |
| Ischemic heart disease          | 41 (35.3%)       |
| Heart failure                   | 39 (33.6%)       |
| CKD                             | 66 (56.9%)       |
| Diabetes mellitus               | 34 (29.3%)       |
| Severe malnutrition             | 38 (32.2%)       |
| (SGA class C)                   |                  |
| ICU mortality                   | 41/116 (35.3%)   |
| In-hospital mortality           | 45 (38.8%)       |

Categorical variables are presented as n (%), and continuous variable as mean (SD) or median (range). SLED, sustained low-efficiency dialysis; APACHE II, Acute Physiology and Chronic Health Evaluation II; MELD, Model for End-Stage Liver Disease; SGA, subjective global assessment of nutritional status; ICU, intensive care unit.
mechanical ventilation. Many patients showed hypoten-
sion and/or hemodynamic instability. Previous RRT in
the form of conventional intermittent hemodialysis had
been attempted in 40 of 116 patients (34.5%). Eleven pa-
tients (9.5%) had a history of recent major bleeding (48
hours before SLED start). Seventy-five patients (64.7%) re-
ceived dalteparin as thromboprophylaxis (median daily
dose 2500 IU; interquartile range, 1250–5000). Seventy-
one patients survived to be discharged from the hospital;
thus, the overall in-hospital mortality was 38.8%.

Safety
Six of 116 patients (5.2%; 95 CI, 2.4 to 10.8) had major
bleeding (upper gastrointestinal tract, 2 patients; lower
gastrointestinal tract, 2 patients; lung, 1 patient; central
nervous system, 1 patient); the incidence rate was 0.4
episodes per 100 person-days follow-up while patients
were on SLED treatment (95% CI, 0.2 to 0.9). No patient
with a history of recent hemorrhage had new bleeding
episodes or required urgent surgery for bleeding control.
ACT levels during the course of SLED are reported in Fig-
ure 1; they were similar in patients with MELD above and
below the median value of 25 (Figure 1). Serum ionized
calcium was slightly reduced during SLED (Table 2), and
systemic intravenous calcium administration was needed
in 8 of the 28 sessions (28.6%); ionized hypocalcemia was

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Table 2. Intradialytic variables related to regional anticoagulation with citrate

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before SLED</th>
<th>SLED 2 h</th>
<th>End SLED</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citrate, mmol/L</td>
<td>0.14 (0.05)</td>
<td>0.26 (0.11)</td>
<td>0.33 (0.14)</td>
<td>&lt;0.001&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Citrate postfilter, mmol/L</td>
<td>1.07 (0.37)</td>
<td>1.22 (0.55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citrate reduction ratio, %</td>
<td>68 (3.3)</td>
<td>65 (12.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ionized calcium, mmol/L</td>
<td>1.06 (0.11)</td>
<td>0.99 (0.09)</td>
<td>0.98 (0.07)</td>
<td>&lt;0.001&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ionized calcium, &lt;0.90 mmol/L</td>
<td>5.7</td>
<td>9.5</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>136 (4.3)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Bicarbonate, mEq/L</td>
<td>24.0 (3.3)</td>
<td>25.2 (2.9)</td>
<td>26.8 (2.7)</td>
<td>&lt;0.001&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) or the percentage of patients. Values are intended as measured on patients’ blood if not otherwise indicated. P values refer to test for trend across all of the available sample times (which were unbalanced between patients). The analysis for time trend was performed using 383, 2907, and 2592 measurements of citrate, ionized calcium, and bicarbonate, respectively. SLED, sustained low-efficiency dialysis; NA, data not available.

<sup>a</sup>Significant (P<0.05) pairwise comparison of before SLED versus SLED 2 hours.
<sup>b</sup>Significant (P<0.05) pairwise comparison of SLED 2 hours versus end SLED.
<sup>c</sup>Significant (P<0.05) pairwise comparison of before SLED versus end SLED.
already present at SLED start. As expected, citrate levels in
the blood before the filter approximated 4 mmol/L with
ACD-A infusion rates of 200 ml/h, 300 ml/h, and 400
ml/h. There were no citrate levels available in the patients with MELD score above the median receiving an intermediate infusion rate of
ACD-A (300 ml/h). The total number of citrate measurements used for the plot is 290. SLED, sustained low-efficiency dialysis; MELD, Model for
End-Stage Liver Disease; ACD-A, anticoagulant citrate dextrose-formulation A. The dots represent outside values, defined as values that are
larger than the upper quartile plus 1.5 times the interquartile range, or values that are smaller than the lower quartile minus 1.5 times the interquartile range.

Figure 2. | Citrate levels in the blood before the filter at 2, 4, 6, and 8 hours of SLED with ACD-A infusion rates of 200 ml/h, 300 ml/h, and 400
ml/h. The total number of citrate measurements used for the plot is 166. SLED, sustained low-efficiency dialysis; ACD-A, anticoagulant citrate
dextrose-formulation A. The dots represent outside values, defined as values that are larger than the upper quartile plus 1.5 times the interquartile range, or values that are smaller than the lower quartile minus 1.5 times the interquartile range.

Figure 3. | Systemic citrate levels stratified by MELD score. Systemic citrate levels at 0, 2, 4, 6, and 8 hours of SLED in patients with a MELD score below (left panel) and equal to or above (right panel) the median value of 25, receiving ACD-A infusion rates of 200 ml/h, 300 ml/h, and 400 ml/h. The total number of citrate measurements used for the plot is 290. SLED, sustained low-efficiency dialysis; MELD, Model for
End-Stage Liver Disease; ACD-A, anticoagulant citrate dextrose-formulation A. The dots represent outside values, defined as values that are
larger than the upper quartile plus 1.5 times the interquartile range, or values that are smaller than the lower quartile minus 1.5 times the interquartile range.
the median value) receiving ACD-A infusion rates of 400 ml/h, there was a nonstatistically significant trend toward a greater increase of citrate levels compared with the other patients (P=0.15; Figure 3). However, even these values were well below the levels known to produce anticoagulation (Figure 3). Citrate concentration drop in the blood returning to the patients was about two thirds of the prefilter levels (Table 2). Metabolic alkalosis was observed in eight patients (1%), yet no patient had venous serum bicarbonate levels >34 mmol/L. Clinically relevant hypotension was documented in 191 of 807 treatments (23.7%).

Efficacy

Overall, 807 SLED sessions were carried out. The median number of SLED sessions per patient was 4 (range, 1–33; interquartile range, 2–10). Planned duration was 8, 10, and 12 hours, respectively, in 789 (98.9%), 12 (1.5%), and 6 (0.7%) of the sessions. Of the 807 sessions performed, 60 (7.4%; 95% CI, 5.8 to 9.6) were prematurely interrupted (Table 3). Impending or irreversible clotting occurred in 19 sessions (2.4%). No difference was observed in the rate of premature interruptions according to the use of low molecular weight heparin (P=0.78). Blood return was accomplished in the vast majority of the patients on SLED; in fact, it was complete in 791 sessions (98.1%) and partial in 10 sessions (1.2%); total loss of circuit blood complicated 6 sessions (0.6%).

Average percent urea reduction at the end of treatment was 67% (SD 6.4). Patient weight was available in 610 of 807 sessions (75.6%); 40 of 807 sessions (5.0%) were performed without weight loss. In the remaining sessions, the median weight change was −2.5 kg (range, −6.5 to +1; interquartile range, −3 to −1.5), without any difference between the prescribed and obtained weight loss (P=0.88).

Discussion

Our regional anticoagulation protocol for SLED based on ACD-A, standard dialysis equipment, and dialysis fluid with calcium was simple, safe, and efficacious. Compared with previous reports in AKI patients on RRT, the incidence of major bleeding was similar or even lower (15,16,25–30). Systemic coagulation remained unchanged, with rare occurrence of ionized hypocalcemia during SLED requiring calcium supplementation; metabolic and fluid control was easily achieved.

We acknowledge two major limitations of our study. First, even though the lack of a control group precluded a direct comparison between our ACD-A–based protocol and the others, clotting rate compared very favorably either with our own SLED retrospective series without antithrombotic agents (10), and with previous reports based on heparin or prostacyclin (9,10,22–24).

Second, this is a single-institution study. Because our results were obtained in a wide cohort of unselected patients consecutively admitted to four different clinical settings of adult ICUs, they might be cautiously generalized to adult critically ill patients. Furthermore, we used standard dialysis equipment, being that SLED practice at our institution is not substantially different from that of other centers caring for AKI patients in the ICU (1,7,9,11,22–24).

On the other hand, our study highlights several important issues about safety and efficacy of citrate in SLED. Safety of citrate versus unfractionated heparin has been recently demonstrated for continuous RRT (15,16), and confirmed in high hemorrhagic risk AKI patient categories, such as those liver dysfunction (38–41), burns with septic shock (42), and heart surgery (43). Two major issues of our approach deserve discussion: the hemorrhagic risk and the complications associated with citrate accumulation.

The reported incidence of hemorrhage in patients with AKI on RRT ranges from 4% to 30%–50% (15,16,25–30). Data on SLED are scanty: no bleeding was reported in 56 sessions with heparin on 24 patients in one series (23), whereas 2 of 37 patients (5.4%) had bleeding during SLED in another series (11). The use of prostacyclin for SLED was associated with a slightly higher hemorrhagic risk (5.7% of patients, corresponding to 1.1 episode per 100 person-days) (10). Thus, data on hemorrhagic complications in our patient series seem to compare favorably with those reported in the literature.

As to the citrate toxicity, we did not document any clinically relevant citrate accumulation. This was not unexpected, owing to the operational characteristics of our RRT modality. In fact, in the case of SLED, most of the citrate is removed by diffusion, with an average citrate reduction ratio that was numerically close to the urea reduction ratio, including patients with liver dysfunction. The lack of citrate accumulation was mirrored by the very low incidence of both ionized hypocalcemia and metabolic alkalosis. In this regard, albeit rapid onset metabolic alkalosis can be potentially associated with dangerous ionized hypocalcemia, in our study the average initial change in serum bicarbonate levels was only mild, averaging +1.2 mmol/L after the first 2 hours of SLED (from 24.0 to 25.2 mmol/L).

As to the treatment efficacy, thanks to the adequate anticoagulation of the extracorporeal circulation, in our study nearly all SLED sessions were completed as planned, and the effective dose of RRT reflected that prescribed in most treatments.

| Table 3. Causes of SLED interruption |
| Cause | Value |
| Prescribed time elapsed | 747 (92.6) |
| Circuit clotting |  |
| Irreversible | 4 (0.5) |
| Impending | 15 (1.9) |
| Technical problems |  |
| Central venous catheter malfunctioning | 15 (1.9) |
| Dialysis machine | 2 (0.2) |
| Clinical reasons |  |
| Urgent diagnostic procedure or surgery | 6 (0.7) |
| Arrhythmias/refractory hypotension | 15 (1.9) |
| Impending death | 3 (0.4) |

Data are presented as n (%) of the 807 sessions.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study</th>
<th>Sessions and Patients (n)</th>
<th>Targeted and Achieved SLED Duration</th>
<th>Citrate Protocol and Dialysis Machine</th>
<th>Routine Ca Infusion</th>
<th>Extracorporeal Circuit Clotting Rates</th>
<th>Hemorrhagic Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morgera et al. (44)</td>
<td>Crossover with standard heparin</td>
<td>42 sessions in 21 patients with AKI in the ICU</td>
<td>Targeted duration 4–6 h; mean achieved duration 5.4 h with citrate versus 4.6 h with heparin</td>
<td>4% sodium citrate in the arterial line, average rate 199 ml/h; blood flow 200 ml/min; dialysis fluid calcium 1 mmol/L, Genius machine</td>
<td>No</td>
<td>Not reported in detail: “no differences in filter longevity between citrate and heparin”</td>
<td>Not reported</td>
</tr>
<tr>
<td>Madison et al. (unpublished data, 2005)</td>
<td>Observational</td>
<td>59 sessions in 14 patients with AKI in the ICU</td>
<td>Targeted duration 6–8 h; achieved duration not reported</td>
<td>Dialysis fluid (Citrasate) with citrate 0.8 mmol/L and calcium 1.3 mmol/L</td>
<td>Not reported</td>
<td>9/59 (15%)</td>
<td>No adverse events reported</td>
</tr>
<tr>
<td>Clark et al. (45)</td>
<td>Observational</td>
<td>117 sessions in 30 patients (19 with AKI)</td>
<td>Targeted duration 8 h with three different protocols of citrate administration; achieved duration: 6.78 ± 1.85 first protocol, 6.71 ± 1.94 second protocol, 7.32 ± 1.34 third protocol</td>
<td>4% sodium citrate in the arterial line at 231–261 ml/h; blood flow 250 ml/min; dialysis fluid at 300 ml/min; zero calcium dialysis fluid, Fresenius 2008H machine</td>
<td>Yes</td>
<td>0/117 (0%)</td>
<td>No hemorrhage</td>
</tr>
<tr>
<td>Mariano et al. (42)</td>
<td>Observational</td>
<td>AKI with severe burns, 54 sessions with citrate in 8 patients, 460 sessions with standard heparin in 32 patients</td>
<td>Median achieved duration 8 h with citrate, 8 h with heparin</td>
<td>ACD-A in the predilution replacement fluid; average citrate load 21 mmol/h multifiltrate Fresenius machine, zero calcium dialysis fluid</td>
<td>Yes</td>
<td>Not reported</td>
<td>Not reported separately for citrate and heparin treatments</td>
</tr>
<tr>
<td>Kron et al. (8)</td>
<td>Observational</td>
<td>289 sessions in 21 patients with AKI in the ICU (268 sessions with standard heparin, 31 with citrate)</td>
<td>Targeted duration 6–23 h; achieved median duration 10.15 h</td>
<td>Citrate protocol not reported; hemodiafiltration, Gambro AK 200 Ultra S machine in the predilution mode</td>
<td>Yes</td>
<td>15/289 (5.1%); no separate data for citrate and heparin</td>
<td>Not reported</td>
</tr>
<tr>
<td>Fiaccadori et al. (this study)</td>
<td>Observational</td>
<td>807 sessions in 116 patients with AKI in the ICU, including patients with liver dysfunction and/or high hemorrhagic risk</td>
<td>Targeted duration: 8 h in 98.9%, 10 h in 1.5%, 12 h in 0.7%, median achieved duration 8 h</td>
<td>ACD-A at 300 ml/min in the arterial line; blood flow 200 ml/min; dialysis fluid at 300 ml/min; cocurrent flow, calcium 1.25 mmol/L, Gambro AK 200 Ultra S machine</td>
<td>No</td>
<td>Median duration 8 h; early interruption due to circuit clotting 19/807 (2.4%)</td>
<td>6/116 (5.2%)</td>
</tr>
</tbody>
</table>

SLED, sustained low-efficiency dialysis; ICU, intensive care unit; ACD-A, anticoagulant citrate dextrose.
Although no extracorporeal circuit clotting has been reported with unfractionated heparin in SLED (9), other series reported clotting in 17%–26% of treatments (11,22–24); clotting rates are 29%–46% without any anticoagulation (11,22–24). Few data are currently available in the literature on extended RRT modalities with citrate (Table 4) (8,42,44,45). With the use of citrate-based dialysis concentrate (Citrasate), a clotting rate of 15% has been reported for 6- to 8-hour SLED in critically ill patients (Madison et al., unpublished data, 2005). In extended high-volume hemo-dialfiltration (6–23 hours) in 21 ICU patients (258 sessions with unfractionated heparin and 31 with citrate) with septic multiple organ failure and AKI (8), the reported clotting rate of 15 of 289 sessions (0.51%) was close to the frequency of interruptions due to irreversible clotting in our study (0.5%), but separate data for heparin and citrate were not available in that article. In the most important series of diffusive prolonged intermittent modalities available thus far (45), (117 SLED in 30 patients) circuit clotting never occurred. However, only 19 patients had AKI, only a few were critically ill patients, and the average treatment duration was 6.7–7.3 hours. Moreover, the protocol required zero calcium dialysis fluid and calcium supplementation (45). Thus, our protocol seems to be at least as simple, safe, and efficacious as those in the literature.

Although citrate as an anticoagulant for SLED in critically ill patients with AKI has been demonstrated to be safe, two important aspects are stressed in the case the present protocol is implemented in other institutions. First, the same length of SLED treatment and operational characteristics (blood and dialysis fluid flow rates, filter characteristics, ACD-A dose, etc.) are to be applied. Second, Ca++ measurements are to be used for monitoring. Ca++ should be measured more frequently in the implementation phase (i.e., for the first 20–30 sessions) then, at least before SLED start, after 1 hour of SLED and at the end of the treatment.

In conclusion, although the ideal anticoagulant for SLED remains to be found, the use of ACD-A in the context of a mainly diffusive prolonged intermittent modality could represent an easy method to maintain extracorporeal circuit. In this regard, it is likely that SLED with near-automated regional citrate anticoagulation protocols optimized for very low blood flows and low citrate loads (46), as well as the availability of routine citrate measurements (47), could represent important developments, in order to improve the safety and efficacy of the citrate-based “hybrid” extracorporeal modalities.

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Disclosures

None.

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Protocol: Regional Anticoagulation with Citrate (RCA) for Sustained Low-Efficiency Dialysis (SLED)

Version May 26, 2013

Background and aims

The present protocol is aimed at describing the operational procedures for Regional Anticoagulation with Citrate during SLED, i.e. at explaining how to anticoagulate only the extracorporeal circulation of dialysis with citrate, leaving unchanged patient’ hemostasis.

The protocol is based on the use of citrate. Citrate is an anticoagulant agent because it chelates ionized (i.e. free) calcium in the blood (Ca$^{2+}$), thus reducing the availability of the most important co-factor activating the coagulation cascade.

Citrate is infused in the circuit as ACD-A solution (Anticoagulant Citrate Dextrose, citrate concentration 112.9 mmol/L) before the filter, in the predilution port of the circuit, in order to decoagulate the blood entering the circuit.

When Ca$^{2+}$ levels (normal values 0.9-1.2 mmol/L) are reduced < 0.4 mmol/L the blood in the circuit is fully anticoagulated. Average citrate levels of 2-4 mmol/L in the circuit are needed in order to decrease Ca$^{2+}$ to 0.4 mmol/l or below, thus providing sufficient anticoagulation of the extracorporeal circuit.

The present protocol is aimed at obtaining an average citrate level of 3 mmol/L in the circuit segment before the blood pump and in the filter; this can be obtained with an ACD-A infusion rate of 300 ml/hour and a blood flow rate of 200 ml/min. Thus a fixed ratio of ACD-A to blood of 1.5:1 between absolute values of flows is to be employed (taking into account that citrate and blood flow rates are expressed respectively in ml/hour and ml/min).

For different combinations of ACD-A administration rates and blood flow, citrate levels in the whole treated blood can be approximately estimated by the following formula:

$$ \text{Whole Blood Citrate (mmol/L)} = \left( C_{ACD-A} \times Q_{ACD-A} \right) \div Q_{blood} $$

where $C_{ACD-A}$ is the citrate concentration in the ACD-A solution (mmol/L), $Q_{ACD-A}$ in the infusion rate of ACD-A solution (L/hr), and $Q_{blood}$ is the blood flow into the circuit (L/hr).

Citrate levels progressively decrease in the filter, and thus in the segments of the circuit after the filter, because of the diffusion occurring with dialysis. Since citrate removal by the treatment itself can be predicted to be about 70%, no more than 30% of the infused citrate (about 10 mmoles/hour out of the 34 mmol/hour infused as ACD-A proximally in the circuit) will be returned to the patient. This amount is immediately diluted in the whole blood pool and rapidly metabolized by the liver and the skeletal muscle. Moreover, since SLED is by definition intermittent (8-12 hours a day), there is a time window of at least 12-16 hours without citrate administration between two consecutive sessions. Therefore, significant citrate accumulation is unlikely.
No systematic calcium infusion is routinely requested with the present protocol, since Ca\(^{++}\) levels in the blood returning to the patient are restored by backtransport of calcium from dialysis fluid containing calcium; in this case backtransport of calcium is mainly by diffusion, on the basis of a favourable gradient between the dialysis fluid and the blood in the filter. However, Ca\(^{++}\) levels are to be monitored in the patient especially in the first hour of the session, and calcium supplementation as calcium gluconate is to be started whenever iCa\(^{++}\) is < 0.90 mmol/L.

**Warning:** start 10% calcium gluconate infusion at SLED start if the patient has already Ca\(^{++}\) values < 0.90 mmol/L before the treatment.

**Warning:** We recommend to avoid RCA in patients with platelet count < 20000 mm\(^3\). In patients with low platelet count and repeated problems in concluding SLED sessions in the prescribed time without RCA (for example, a cirrhotic patient with AKI), RCA at a reduced ACD-A dose (200 ml/hour) is suggested.

**Fluids**

Dialysis fluid (Gambro Diasol concentrate + Gambro Bicart): sodium 140 mmol/L, Potassium 3 or 4 mmol/L as per the attending nephrologist prescription, Chloride 110.5 mmol/L, Bicarbonate 34 mmol/L, Acetate 3 mmol/L, Calcium 1.25 mmol/L, Magnesium 0.5 mmol/L Dextrose 5.55%

ACD-A (500 ml bags): Trisodium citrate and Citric acid (total citrate concentration 112.9 mmol/L) in 2.5% dextrose

Calcium gluconate: 10 ml vials (0.24 mmol/ml), use undiluted

**Extracorporeal circulation**

Machine: Gambro AK 200S ultra type 1
Filter: Fresenius F8HPS, 1.8 m\(^2\), Kuf 18 ml/mmHg/hour
Blood flow rate: 200 ml/min
Dialysis fluid rate: 300 ml/min
Flow geometry: cocurrent
Citrate: ACD-A 300 ml/hour in the predilution port of the circuit
Dialysis fluid temperature: 35°

**WARNING:** Any change to the filter and/or the operational characteristics of the treatment (blood flow rate, flow geometry, dialysis flow rate etc.) could significantly change citrate levels in the blood returning to the patient. Therefore some of the recommendations detailed in the present protocol may no longer apply. The attending nephrologist must be aware of such changes beforehand, so he/she can adopt the required ACD-A dose adjustments and preventive measurements (e.g. additional measurements of Ca\(^{++}\)) to avoid possible adverse effects of the modified SLED treatment.
SLED start
- Priming: rinse the circuit with 2000 ml of normal saline in 15-20 min.
- Start dialysis with a blood flow of 50 ml/min, slowly increasing to 200 ml/min in 50 ml/min increments every 5 min, checking hemodynamic status
- Start ACD-A with a parenteral infusion pump at 300 ml/hour together with blood flow start, maintaining a ratio of 1.5:1 with respect to blood flow (ml/hour of ACD-A to ml/min of blood flow rate) when blood flow is at regimen (200 ml/min)
- When blood flow is 200 ml/min, access pressures should be less than -150 mmHg, with return pressures less than +200 mmHg
- Start ultrafiltration, is needed, after 30 min of SLED

Monitoring during SLED
Coagulation
- Check ACT (Hemochron) levels at baseline (SLED start), at one hour and at the end of SLED in the blood of the patient taken from the circuit before the mixing point of blood with the infused ACD-A.
- No major changes in ACT levels during SLED (> than 1.25 of ACT ratio between actual ACT values and basal ACT values) should be accepted; in case consult the attending nephrologist to reduce ACD-A infusion rate by 50% (i.e. to 200 ml/hour)

Ionized calcium
- Check Ca++ in the patient blood and in the blood returning to the patient (after the filter) at baseline (SLED start), at one hour and at the end of SLED as routine, and everytime is needed.
- Start 10% Calcium gluconate infusion (no dilution) at 5 ml/hour by an infusion pump in a peripheral vein or a central vein (not in the dialysis CVC) whenever Ca++ is < 0.90 mmol/L in the blood from the patient, or <0.60 mmol/L in the blood returning to the patient. If Ca++ values are already low before SLED start, immediately start calcium gluconate infusion.
- Check Ca++ again after one hour, and increase Calcium gluconate infusion rate to 10 ml/hour if Ca++ values are not > 0.90 mmol/L in the patient blood or > 0.60 mmol/L in the blood returning to the patient.
- If Ca++ values were still low at the end of SLED, Calcium gluconate administration is to continued for one hour, rechecking the values.

Warning: The ACD-A infusion pump must be stopped every time blood pump is stopped