Regional Anticoagulation with Citrate is Superior to Systemic Anticoagulation with Heparin in Critically Ill Patients Undergoing Continuous Venovenous Hemodiafiltration

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Background/Aims: Short hemofilter survival and anticoagulation-related life-threatening complications are major problems in systemic anticoagulation with heparin (SAH) for continuous renal replacement therapy (CRRT). The present study examined if regional anticoagulation with citrate (RAC) using commercially available solutions can overcome the associated problems of SAH to produce economical benefits.

Methods: Forty-six patients were assigned to receive SAH or RAC. We assessed the coagulation state, clinical outcomes, and adverse events. A Kaplan-Meier analysis was used to estimate hemofilter life span. The economical benefit related to the prolonged hemofilter survival was examined on the basis of the average daily cost.

Results: The mean age of patients was 66.5 ± 13.8 years and the majority were male (60.9%). While elective discontinuation was most common cause of early CRRT interruption in the RAC group (34.3%, \( p < 0.01 \)), hemofilter clotting was most prevalent in the SAH group (82.2%, \( p < 0.01 \)). The patient metabolic and electrolyte control and survival rate were not different between the two groups. When compared with the RAC group, the anticoagulation-associated bleeding was a major complication in the SAH group (15.0% vs. 61.5%, \( p < 0.01 \)). Regional anticoagulated hemofilters displayed a significantly longer survival time than systemic anticoagulated hemofilters (59.5 ± 3.8 hr vs. 15.6 ± 1.3 hr, \( p < 0.01 \)). Accordingly, the mean daily continuous venovenous hemodiafiltration costs in the RAC and SAH groups were $575 ± 268 and $1,209 ± 517, respectively (\( p < 0.01 \)).

Conclusions: RAC prolonged hemofilter survival, displaying an economical benefit without severe adverse effects. The present study therefore demonstrates that RAC, using commercially available solutions, may be advantageous over SAH as a cost-effective treatment in CRRT. (Korean J Intern Med 2011;26:68-75)

Keywords: Anticoagulation; Citric acid; Renal replacement therapy; Heparin

INTRODUCTION

In Korea, continuous renal replacement therapy (CRRT) is widely applied to patients in treating hemodynamically unstable acute renal failure (ARF). While systemic anticoagulation with heparin (SAH) is most frequently used, its complications are poorly tolerated in critically ill patients. Citrate displays anticoagulation properties through chelating ionized calcium and inducing deep hypocalcemia in the hemofilter, without systemic bleeding complications. Regional anticoagulation with citrate (RAC) has been increasingly employed for the anticoagulation modality in CRRT [1]. Despite the merits of RAC; its widespread implementation has been hindered by a lack of convenient methods and complexity of patient monitoring [2].

CRRT is a very expensive procedure; an expensive
hemoﬁlter and circuit in addition to a large volume of ﬂuid are required and the National Health Insurance Cooperation (NHIC) does not insure additional hemoﬁlter-related costs. In addition, over-coagulation may lead to severe complications including cerebral or gastrointestinal hemorrhage while under-coagulation can lead to an early interruption of the CRRT session. All of these conditions have a direct impact on medical costs as patients with ARF have an increased utilization of health care resources.

The methodological and economical problems in current CRRT highlight the requirement of efﬁcient anticoagulation procedures to prevent the clotting of the extracorporeal circuit, reducing CRRT-related medical costs without severe complications. When compared with conventional pharmacy-produced compounds, anticoagulation protocols that utilize the regional anticoagulation properties of citrate would be expected to improve the current anticoagulation modality, minimizing medical costs in the process. However, little data exist regarding the suitability of RAC protocols in CRRT and its superiority to SAH in terms of safety and medical costs. To address this issue, we designed a RAC protocol using an Anticoagulant Citrate Dextrose Formula A (ACD-A®, Baxter, Deerﬁeld, IL, USA) solution and calcium gluconate (CG; ChoongWae Pharma Co., Seoul, Korea).

METHODS

Study population

From a total of 1,790 patients admitted to the intensive care unit at the Hanyang University Hospital from January 2006 to December 2007, 97 required CRRT as a renal replacement therapy. We excluded patients with advanced liver disease and cirrhosis or severe coagulation disorders from the study. During this study, the SAH was performed as a ﬁrst choice treatment, and the RAC was chosen as anticoagulation for patients unable to use heparin. Fifty-one patients used neither the SAH nor the RAC and received complete anticoagulation-free CRRT using saline ﬂushing. Thus, our observational study was based on 46 patients; 26 patients were assigned to receive the SAH for a total of 1,435 hours and 20 patients were assigned to receive the RAC for 1,333 hours.

Continuous Venovenous Hemodiaﬁltration (CVVHDF) protocol

CVVHDF was performed using the PRISMA quadruple pump system (Gambro Renal Products, Mirandola, Italy) with an AN69 hollow ﬁber biocompatible membrane in a predilution setting for all patients. Venovenous access was obtained by inserting an 11 F 15-cm double-lumen GamCath catheter (Gambro Katheterotechnik, Hechingen, Germany) into a femoral vein.

The replacement solution, composed of 4,750 mL of Hemosol® Bo solution (Hospal, Lyon, France) combined with 250 mL of Hemosol® Bo 5.88% HCO₃Na solution (Hospal), was delivered initially at a rate of 1,200 mL/hr. The solution composition was adapted to the acid-base status of the patient in the dialysate bag. In cases of hypernatremia (Na⁺ > 145 mmol/L) or metabolic alkalosis (pH > 7.5 or HCO₃⁻ > 40 mmol/L), Hemosol® Bo 5.88% HCO₃Na solution was not added to the Hemosol® Bo solution. Otherwise, the dialysate was made from 4,750 mL of Hemosol® Bo solution and 250 mL of Hemosol® Bo 5.88% HCO₃Na solution. The dialysate was delivered initially at a rate of 1,200 mL/hr. Net ultraﬁltration was adjusted according to the patient's condition by changing the rate of total ﬂuid input.

Anticoagulation protocols

In cases of SAH, the patients received an initial bolus of 2,000 U followed by an infusion of 500 U/hr. Subsequent adjustments to the rate of heparin infusion were guided by the activated partial thromboplastin time (aPTT) drawn every 6 hours, based on a predefined nomogram that aimed to maintain an aPTT of 40-45 seconds (Table 1). Contraindications to the use of heparin included a prior history of heparin-induced thrombocytopenia, heparin allergy, intracranial hemorrhage within 3 months, gastrointestinal hemorrhage requiring a transfusion within 3 months, active bleeding or signiﬁcant trauma within 3 days, and a platelet count < 40,000/µL. Regional anticoagulation was achieved using an ACD-A® solution, containing dextrose 2.45 g/dL, sodium citrate 2.2 g/dL, and citric acid 730 mg/dL, which was infused proximal to the hemoﬁlter targeted to maintain a post-ﬁlter ionized calci-
Contraindication to the use of the ACD-A® solution included a serum ionized calcium level of < 0.70 mmol/L, a serum pH of > 7.6, and a serum sodium concentration of > 160 mmol/L [3]. CG was selected as a calcium replacement solution. CG (97.6 mmol/L) in 1 L of isotonic saline was initially infused at a rate of 10 mL/hr (0.976 mmol/hr). The rate adjustments of anticoagulation and calcium replacement solutions were made at 6 hours and every 12 hours following (Tables 2 and 3).

### Table 2. Continuous venovenous hemodiafiltration nomogram to adjust the citrate infusion rate

| Post-filter iCa²⁺, mmol/L | Rate change                      |
|---------------------------|----------------------------------|
| < 0.25                    | Decrease rate by 10 mL/hr         |
| 0.25 - 0.35               | No change in rate                 |
| 0.35 - 0.45               | Increase rate by 10 mL/hr         |
| > 0.45                    | Increase rate by 20 mL/hr         |

iCa²⁺, ionized calcium.

### Table 3. Continuous venovenous hemodiafiltration nomogram to adjust the calcium gluconate solution infusion rate

| Systemic iCa²⁺, mmol/L | Rate change                                                                 |
|------------------------|-----------------------------------------------------------------------------|
| < 0.75                 | Decrease rate by 4 mL/hr and Ca²⁺ 10 mmol bolus over 1 hr                   |
| 0.75 - 1.13            | No change in rate                                                           |
| 1.13 - 1.32            | Increase rate by 2 mL/hr                                                    |
| > 1.32                 | Increase rate by 4 mL/hr                                                    |

iCa²⁺, ionized calcium.

### Follow-up and outcome measurements

Data collected at the initiation of CVVHDF included demographics, clinical parameters, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and the Liaño ARF severity of illness score. We additionally assessed the hemofilter survival time, hemorrhagic episodes, aPTT, and post-filter iCa²⁺ levels. Serum electrolytes, blood urea nitrogen and creatinine, arterial blood gases, and platelet counts were measured at baseline, 1 and 6 hours, and every 12 hours following. Early termination was defined as any reason the full prescribed dose was not administered in the first 24 hours. Successful anticoagulation was achieved when heparin and citrate were administered to achieve their target level at 24 hours or later. Definitive bleeding was defined as an acute bleeding episode and/or the need for transfusion of more than 2 units of packed red blood cells (PRC) within 48 hours. Any incidence of hypotension (systolic blood pressure < 90 mmHg), and metabolic alkalosis (pH > 7.45 and base excess > 3 mmol/L) or acidosis (pH < 7.35 and base excess < -3 mmol/L) were recorded. We detected citrate toxicity through monitoring the changes in serum pH, sodium, bicarbonate, and iCa²⁺ levels.

### Cost analyses

The average daily costs of the CVVHDF were determined as the cost to the hospital. Routine laboratory and care costs, physician fees, and the capital cost of the treatment were not included in this analysis as these payments are identical irrespective of the anticoagulation method. The costs of all dialysates and replacement solutions, hemofilters, double-lumen catheters, concentrates, infusions, transfusions, and disposables that were related to dialysis were included. In the cases of early termination when the hemofilter cost was not charged to insurance, we assigned additional hemofilter costs to the prior costs.

### Statistical analyses

The baseline characteristics are presented as the mean ± SD or as the proportion of patients in each group. The comparisons between numeric variables were performed using the Mann-Whitney U test. The chi-square test with Fisher’s exact test was used to evaluate the association between nominal variables. Repeated measurements of the analysis of variance within the subject factor (time) and between the subjects factor (group) was used. If the assumed sphericity was not achieved, the Greenhouse-Geisser adjusted p values were reported. The relationships between one or more independent variables of interest were analyzed by logistic regression. The time to hemofilter failure was measured from the time of initiation to the time of elective discontinuation (surgery) or spontaneous failure (such as clotting). The elective discontinuations were treated as censored data and spontaneous failures as uncensored data. The Kaplan-Meier survival analyses were used to present the results and generate the estimated mean times to hemofilter failure. The log-rank test was used to compare the time to the hemofilter failure between the groups. All p values were analyzed by a two-sided test, and p values less than 0.05 were considered statistically significant. All analyses were performed using the SAS version 9.1 (SAS Inc., Cary, NC, USA).
Table 4. Clinical and demographic features of patients at the initiation of CVVHDF

|                      | SAH (n = 26)       | RAC (n = 20)       | p value |
|----------------------|--------------------|--------------------|---------|
| Age, yr              | 66.8 ± 11.2        | 64.9 ± 16.7        | NS      |
| Male                 | 16 (61.5)          | 12 (60.0)          | NS      |
| APACHE II            | 23.3 ± 4.8         | 30.6 ± 5.2         | 0.0031  |
| Liaño ARF severity of illness score | 63.5 ± 16.4   | 72.4 ± 21.7        | NS      |
| Septic acute tubular necrosis | 10 (38.5)     | 8 (40.0)           | NS      |
| Surgical acute tubular necrosis | 0             | 2 (10.0)           | NS      |
| Medical acute tubular necrosis | 16 (61.5)    | 10 (50.0)          | NS      |
| Hematocrit           | 29.8 ± 5.6         | 30.0 ± 6.0         | NS      |
| Platelet, /mm³       | 167.5 ± 101.7      | 129.7 ± 69.3       | NS      |
| Sodium, mmol/L       | 135.8 ± 5.1        | 136.9 ± 6.9        | NS      |
| Bicarbonate, mmol/L  | 17.3 ± 6.1         | 16.5 ± 5.8         | NS      |
| Arterial blood pH    | 7.33 ± 0.10        | 7.29 ± 0.15        | NS      |
| Plasma BUN, mg/dL    | 52.9 ± 30.7        | 56.8 ± 34.4        | NS      |
| Prothrombin time, INR| 1.37 ± 0.05        | 1.15 ± 0.14        | NS      |
| Plasma creatinine, mg/dL | 5.5 ± 2.9    | 4.0 ± 2.0          | NS      |
| Oliguria or anuria   | 9 (34.6)           | 14 (70.0)          | 0.0173  |
| Required mechanical ventilator | 15 (57.7) | 11 (55.0)         | NS      |
| Required vasopressor | 16 (61.5)          | 9 (45.0)           | NS      |

Values are presented as mean ± SD or number (%).
CVVHDF, continuous venovenous hemodiafiltration; SAH, systemic anticoagulation with unfractionated heparin; RAC, regional anticoagulation with citrate; NS, not significant; APACHE II, Acute Physiology and Chronic Health Evaluation II; ARF, acute renal failure; BUN, blood urea nitrogen; INR, international normalized ratio.

Table 5. Reasons for hemofilter circuit discontinuation during CVVHDF

|                     | SAH (n = 101) | RAC (n = 35) | p value |
|---------------------|---------------|--------------|---------|
| Hemofilter life span ≥ 72 hr | 0             | 6 (17.1)     | 0.0002  |
| Elective discontinuation | 12 (11.9)    | 12 (34.3)    | 0.0027  |
| Hemofilter clotting | 83 (82.2)     | 11 (31.4)    | < 0.0001|
| High transmembranous pressure | 1 (1.0)      | 2 (5.7)      | NS      |
| Circuit failure      | 5 (4.9)       | 4 (11.4)     | NS      |

Values are presented as number (%).
CVVHDF, continuous venovenous hemodiafiltration; SAH, systemic anticoagulation with unfractionated heparin; RAC, regional anticoagulation with citrate; NS, not significant.

Table 6. Newly developed adverse events during CVVHDF

|                | SAH (n = 26) | RAC (n = 20) | p value |
|----------------|-------------|--------------|---------|
| Bleeding episode | 16 (61.5)  | 3 (15.0)     | 0.0023  |
| Hypotension     | 9 (34.6)   | 1 (5.0)      | 0.0278  |
| Metabolic acidosis | 2 (7.7)    | 0            | NS      |
| Metabolic alkalosis | 3 (11.5)  | 7 (35.0)     | NS      |

Values are presented as number (%).
CVVHDF, continuous venovenous hemodiafiltration; SAH, systemic anticoagulation with unfractionated heparin; RAC, regional anticoagulation with citrate; NS, not significant.
RESULTS

Patient clinical characteristics
The clinical details of all 46 patients are listed in Table 4. They consisted of 28 men and 18 women, with a mean age of 66.5 ± 13.8 years. When compared with the SAH group, those patients receiving RAC displayed greater organ failure (APACHE II scores, 23.3 ± 4.8 vs. 30.6 ± 5.2; \(p < 0.01\)) and more oliguric ARF (34.6% vs. 70.0%, \(p < 0.05\)), which was not associated with the anticoagulation efficacy in this study (data not shown). No significant differences were observed in other baseline characteristics between the two groups.

Outcomes
In total, 136 hemofilters were included in the analysis: 101 receiving SAH and 35 receiving RAC. The reasons for hemofilter termination in the RAC group were significantly different from those in SAH group (Table 5); while elective discontinuation was the most common cause of early CVVHDF interruption in the RAC group (34.3%, \(p < 0.01\)), hemofilter clotting was most common cause in the SAH group (82.2%, \(p < 0.01\)). In addition, the hemofilter survival rate up to 72 hours was higher in the RAC group (0% vs. 17.1%, \(p < 0.01\)) when compared with the SAH group.

The majority of hemofilters in the SAH group were terminated before 24 hours, making a comparison of the groups in terms of hemofilter-related outcomes difficult. While RAC provided a good anticoagulation status for more than 80.0% of the extracorporeal circuits throughout the CVVHDF session, a wide inter- and intra-patient variability of the aPTT values was evident in the SAH group and the maintenance of target levels was difficult. Furthermore, the aPTT data showed no association between aPTT and hemofilter survival times following subgroup analysis (\(r = -0.3546, p = 0.39\)). We observed no differences between the two groups in terms of solute removal (data not shown).

No difference was observed in the patients’ survival at day 30 following the termination of CVVHDF. The survival rate of the SAH group patients was 54.2% at 30 days following cessation, compared to 50.0% in the RAC group. Such findings can be explained as either a result of the limitations of a single-center, case-controlled study, or greater organ failure in the RAC group.

Adverse effects
We observed significant differences between newly developed adverse events during the CVVHDF session (Table 6). Gastrointestinal (GI) bleeding was the most common adverse event. In the SAH group, seven of the patients with GI bleeding displayed definitive anticoagulation-associated bleeding and four of those patients required a PRC transfusion for life-saving. Three patients required a PRC transfusion of more than 2 units; one case

![Figure 1. Metabolic and electrolyte control in CVVHDF for patients receiving SAH and RAC. Repeated measurement analysis of variance shows no difference between the two groups in the light of hypernatremia or metabolic acid-base balance. CVVHDF, continuous venovenous hemodiafiltration; SAH, systemic anticoagulation with unfractionated heparin; RAC, regional anticoagulation with citrate.](image-url)
of intracranial hemorrhage and hematochezia, one case of pulmonary hemorrhage, and four cases of large hematoma at the needle puncture site were observed in the SAH group. These patients were inevitably converted to the no-anticoagulation method. In the RAC group, two patients with congestive heart failure required a PRC transfusion for anemia control and one patient displayed obscure GI bleeding.

Newly developed hypotensive episodes were more frequently observed in the SAH group compared to the RAC group (34.6% vs. 5.0%, \(p < 0.05\)). A Fisher’s exact test revealed that a hypotensive event displayed a significant association with bleeding complications \((p < 0.05)\). In the SAH group, eight patients displayed a hypotensive episode accompanied by bleeding complications. Four cases with GI bleeding occurred within 24 hours following the hypotensive episodes; one case of large hematoma at the needle puncture site occurred 11 hours prior to the hypotensive episode and three patients displayed both GI bleeding and oozing of the needle puncture site during SAH. However, such events did not display an association with the severity of the bleeding complication, namely the levels of PRC transfusion \((p > 0.05)\).

The metabolic and electrolyte controls were relatively stable during CVVHDF (Fig. 1). No episodes of citrate toxicity or hepatic dysfunction were observed in the RAC group (data not shown).

### Hemofilter survival and medical cost

A Kaplan-Meier analysis revealed that the hemofilter survival time was longer in those patients treated with RAC (SAH, 15.6 ± 1.3 hr; RAC, 59.5 ± 3.8 hr; log-rank, \(p < 0.01\)) (Table 7, Fig. 2). A life-table analysis showed that 74.0% of the hemofilter-receiving patients treated with RAC were functional at 48 hours compared to only 3.8% of those patients treated with SAH.

During the observation period, RAC significantly reduced the frequency of early CVVHDF termination when compared to SAH (2 vs. 64, \(p < 0.01\)). Because the

![Figure 2](image_url)
DISCUSSION

In this study, we compared SAH with RAC using commercially available solutions as an anticoagulation method for the treatment of critically ill patients. We found that the application of ACD-A® solution and CG to the RAC protocol prolonged the hemofilter life span and decreased the frequency and severity of several complications when compared to SAH. The efficacy was similar to other RAC protocols using commercially available solutions [4,5]. Of note, our RAC protocol (+ACD-A® solution and CG) would enable these patients to receive a cost-effective renal replacement therapy without severe complications.

When considering the successful application of CRRT, the maintenance of the patient extracorporeal circuit is a major component. Unsuitable anticoagulation leads to recurrent hemofilter clotting and frequent circuit replacement. In addition, an increased cost and procedure workload, a prolonged “downtime”, a deterioration in azotemic control, and an increased mortality are observed [6-9]. Alternatively over-coagulation leads to coagulation-related complications, increased costs of care procedures, and increased mortality. A variety of anticoagulation methods have been prescribed including systemic heparin anticoagulation, low-molecular-weight heparin, prostacyclin, and nafamostat mesylate [10], of which SAH is the most common, inexpensive, and easily applied method [11]. However, systemic heparin anticoagulation increases the risk of life-threatening bleeding and hemorrhagic shock, whereas SAH yields only a minimal hemofilter survival time. Furthermore, we observed that heparin-induced minor bleeding episodes raised the incidence of hypotension. Such findings indicate that even small levels of bleeding may decrease the blood pressure of critically ill patients, increase the requirement of vasopressor agents, aggravate the clinical course, and make SAH unsuitable for CRRT. While we did not perform a cost analysis regarding hypotensive accidents and vasopressor agents, these events would cause an additional medical expense.

Citrate infusion has been utilized in numerous clinical trials based on its fundamental properties of regional anticoagulation that is fully reversible by calcium administration. In addition, the monitoring of hemofilter clotting is fast and cost-effective as a measurement of ionized calcium. However, citrate infusion may expose patients to metabolic complications including hypernatremia and metabolic alkalosis [12]. Previous clinical trials using pharmacy-based citrate solutions reported that the episodes of metabolic alkalosis requiring treatment with hydrochloric acid developed in up to 38% of critically ill patients requiring CRRT [13]. Conversely, the present study shows that the RAC protocol (+ACD-A® solution and CG) had a tendency to decrease heparin-associated and pharmacy-made citrate-associated adverse events. When compared to the SAH group, the frequency and severity of several heparin-related complications in the RAC group (including bleeding complications or hypotensive episodes) were significantly reduced. In light of citrate-related complications, seven instances of accidental over-infusion of ACD-A® occurred that led to metabolic alkalosis. These were corrected by citrate infusion without any influence on clinical outcomes. When compared with previous clinical trials [1,12], other pharmacy-made citrate-associated adverse events including hypernatremia, extreme biochemical or hematological abnormalities, and citrate toxicity were observed less frequently in the RAC group.

Regarding the hemofilter survival rate and reasons for hemofilter/circuit failure, our findings were consistent with previous studies demonstrating the superiority of RAC to SAH [3,6,10]. Cointault and colleagues reported that the ACD-A® solution with calcium chloride creates an additional anticoagulation-related cost and that RAC using commercially available solutions would be an expensive procedure [4]. When considering the anticoagulation-related costs for the maintenance of a single CRRT session, SAH is an inexpensive and easily administered method while RAC requires numerous expensive Hemosol® solutions and additional replacement solutions. However, we demonstrated that CRRTs for critically ill
patients are composed of multiple sessions and that SAH induces life-threatening complications and frequent hemofilter clotting. RAC using commercially available solutions decreases the requirement of pharmacy-based solutions providing a significant improvement in bedside care and the severity of complications [4,14]. RAC may thus establish true regional circuit anticoagulation and minimize the SAH associated economical burden.

In conclusion, to assess a beneficial anticoagulation method for CRRT, we conducted an observational study to evaluate the efficacy, safety, and economic aspects of RAC using commercially available solutions in Korea. Although this study was a single-center cross-sectional analysis, we postulate that the combination of ACD-A® solution and CG is an attractive method to prolong the hemofilter survival time and minimize the complications and economical burden of SAH, particularly in those patients with a high risk of bleeding.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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