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Continuous hemodialysis with citrate anticoagulation and standard dialysate for managing acute kidney injury in patients with moderate to severe hyponatremia—A retrospective study

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Background: The safety of continuous veno-venous hemodialysis (CVVHD) with citrate-calcium anticoagulation for acute kidney injury (AKI) with coincident hyponatremia remains unclear. We aimed to explore the feasibility of CVVHD with standard dialysate and citrate-calcium anticoagulation in hyponatremic critically ill AKI patients.

Methods: Thirty-seven of the 493 critically ill AKI patients requiring CVVHD and admitted to our intensive care unit during a 10-year period had hyponatremia (<130 mmol/L) and were included in this retrospective study. All patients received CVVHD with citrate-calcium anticoagulation and standard commercial dialysate and plasma sodium concentrations were frequently controlled until death or CVVHD discontinuation. Clinical data, mortalities and cases of central pontine myelinolysis within one-year follow-up were recorded.

Results: Median plasma sodium concentration was 127 (IQR 124-129) mmol/L at CVVHD initiation. CVVHD duration was median 3 (IQR 1.5-5.5) days and the mean daily sodium load of the trisodium citrate solution during the first 3 days of CVVHD was 1754 (SD 730) mmol. The plasma sodium concentration increased a median 8 (IQR 5-10) mmol/L during the first 24 hours of CVVHD and excessively high plasma sodium correction (>8 mmol/L/24 h) was observed in 18 (48.6%) patients. However, increased mortality in association to rapid plasma sodium correction was not observed in this study.

Conclusions: CVVHD using standard citrate-calcium anticoagulation effectively increased plasma sodium concentration in this study. However, excessively high plasma sodium correction was observed in half of the patients and the sodium load provided by the standard citrate anticoagulation solutions was substantial.

1 | INTRODUCTION

Hyponatremia is a common condition in critically ill patients with an incidence of 13%-17% and is associated with increased mortality in intensive care unit (ICU) patients.[1,2] Furthermore, excessively high correction rate of plasma sodium concentration is associated with increased mortality and central pontine myelinolysis and the current guidelines, thus, recommend the correction rate of 4-8 mmol/L/24 h in the management of hyponatremia.[3-5]

Continuous veno-venous hemodialysis (CVVHD) is commonly used to manage acute kidney injury (AKI) in the ICU setting. CVVHD promptly corrects electrolyte imbalances and volume overload, thus creating a therapeutic challenge in critically ill patients with hyponatremia. The feasibility of CVVHD and continuous veno-venous hemodiafiltration (CVVHDF), with adjusted dialysate and/or replacement fluid sodium concentrations to control the correction speed of plasma sodium concentration, in the management of hyponatremia has been recently explored in a number of small studies with heparin analogues for anticoagulation.[6,7] To the best of our knowledge only a single previous small case series is available on the use of citrate-calcium anticoagulation and CVVHDF to treat AKI in hyponatremic patients. The study by Redant et al (2020) included only five patients and the dialysate and replacement fluids were diluted to avoid excessive sodium correction[8] and the mean increase in sodium concentration during the first 24 hours was 7.8 mmol/L. The increased risk for rapid sodium correction during citrate-anticoagulation is due to the high sodium concentration of the trisodium citrate solution.

By now, however, no data exist on the treatment of AKI and coincident hyponatremia with CVVHD using standard commercial dialysate and citrate solutions. For this reason, we sought to investigate the management of AKI and hyponatremia with CVVHD using standard dialysate and citrate-calcium anticoagulation in critically ill patients.

2 | MATERIALS AND METHODS

This retrospective cohort study consecutively included all patients admitted to the ICU of the Turku University Hospital requiring CVVHD (493 participants) between 1 January 2010 and 31 December 2019. As this pre-specified report examined the management of AKI patients with hyponatremia using CVVHD with citrate-calcium anticoagulation, all patients with plasma sodium concentration >130 mmol/L (453 participants) at dialysis initiation and those with hyponatremia (<130 mmol/L) receiving CVVHD without citrate anticoagulation (three patients with acute liver failure considered at risk for citrate accumulation by clinicians) were excluded. The final study cohort included 37 patients. No power calculations were performed due to the retrospective nature of the study.

All patient demographics, clinical disease history and medications at baseline were manually collected from the electronic patient records of the research hospital. Extensive baseline and follow-up biochemical data (every 6 hour for the first 24 hours and daily afterwards for the first four days of CVVHD) as well as daily total parenteral nutrition and intravenous fluid solution volumes were extracted from the clinical information software of the research ICU. Overall daily fluid balance for the first 3 days of CVVHD was calculated as: total input volume—total output volume.

Hyponatremia was defined as plasma sodium concentration <130 mmol/L. The increase in plasma sodium concentration exceeding 8 mmol/L/24 h was defined as an excessively high plasma sodium correction.

Editorial Comment

Electrolyte imbalance and need for continuous renal replacement therapy can present a clinical management challenge. This analysis from one large center showed that continuous renal replacement therapy in patients with hyponatremia can lead to too rapid correction of sodium levels in many patients. Future larger studies should assess whether this may influence the outcome of patients.

All patients were followed-up from the electronic patient archives to collect data on mortalities and cases of central pontine myelinolysis up to 1 year. Data gathered on pontine myelinolysis included MRI scans and diagnoses made by a consultant neurologist or, in the case of deceased patients, pathological autopsy findings.

2.1 | CVVHD modality

CVVHD for all patients was performed according to a standard protocol employed in our center using Fresenius Multifiltrate continuous renal replacement therapy (CRRT) monitors and 1.80 m^2 polysulfone hemofilter Ultraflux AV1000 or Ultraflux EMiC2 membranes with the CiCa® dialysate K2 and 4% trisodium citrate to achieve regional citrate anticoagulation (Fresenius Medical Care). Continuous hemodiafiltration was not performed and therefore replacement fluids were not administered to any of the patients. The CiCa® K2 dialysate electrolyte concentrations are: sodium 133 mmol/L, potassium 2 mmol/L, calcium 0 mmol/L, magnesium 0.75 mmol/L, chloride 116.5 mmol/L in addition to bicarbonate 20 mmol/L and glucose 1 g/L. Post-filter ionized calcium levels were used for anticoagulation monitoring. The starting citrate dose used was 4 mmol per liter of treated blood; a standard dose recommended for CiCa-CVVHD by the manufacturer. This corresponds to a citrate fluid flow rate of 176 mL/h at a blood flow rate of 100 mL/min. A standard 4% (136 mmol/L) trisodium citrate solution containing 408 mmol/L sodium and pH of 7.1-7.5 (Fresenius Medical Care) was used. The citrate dose was then titrated during the treatment to achieve a target Ca++ level and thereby sufficient regional anticoagulation without systemic effects. Blood and dialysate flow rates were prescribed according to the weight of the patient and by the caring ICU physician to target a dialysis dose of 30 mL/kg/h.

2.2 | Ethics

The study protocol was approved by the Turku University Clinical Research Center scientific review board and the Hospital district of Southwest Finland (Reference number: T143/2019). The data from the hospital software were combined and the patient identity numbers removed before the statistical analyses. For this retrospective,

register-based, non-interventional study the regulatory review board waived the need for informed consent in terms of data collection and analysis and publication of results.

2.3 | Statistics

Results were presented as mean ± standard deviation (SD) for normally distributed covariates and as median inter-quartile range (IQR) for skewed covariates. Categorical covariates were reported with absolute and relative (percentage) frequencies. Normality in continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Student's *t* test or Mann-Whitney test was used to compare continuous normally distributed or skewed covariates, respectively, and Pearson x2 or Fisher's exact test was used to compare categorical covariates.

As the correction of plasma sodium concentration during CVVHD was the focus of the study, the univariate correlations between studied covariates and excessively high (>8 mmol/L/24 h) plasma sodium correction using Pearson's and Spearman's coefficients were explored. Furthermore, the association between excessively high plasma sodium correction and mortality was analyzed by entering the plasma sodium correction as a continuous variable in the Cox proportional hazard model. Moreover differences between the groups (rapid sodium correction rate >8mmol/L/24 h vs moderate sodium correction rate) in terms of delivered dialysis dose, blood flow rate, dialysate flow rate, trisodium citrate infusion rate, received total intravenous fluid volume, median sodium concentration per liter of daily total intravenous fluid input and fluid balance were examined using repeated measures analysis of covariance.

All analyses were two-sided and $P < .05$ was considered statistically significant. IBM SPSS Statistics software version 26.0 was used to perform all analyses.

3 | RESULTS

Altogether 37 (7.5%) of the 493 critically ill patients receiving CVVHD with standard citrate-calcium anticoagulation during the study period at our center had hyponatremia (<130 mol/L) at dialysis initiation. Mean age was 58 (SD 15) years and 9 (24.3%) were female. 6 (16.2%) and 18 (48.6%) of the study patients had heart failure or diabetes, respectively, and 10 (27.0%) patients were on diuretics. The baseline characteristics are depicted in Table 1.

CVVHD was initiated after median 0 (IQR 0-1) days of ICU treatment and had a median duration of 3 (IQR 1.5-5.5) days. Median plasma sodium concentration was 127 (IQR 124-129) mmol/L. Eight patients (21.6%) had pH <7.2, seven (18.9%) were hyperkalemic (>4.8 mmol/L) and 26 (70.3%) had a urine output of <0.3 mL/kg/h at the time of CVVHD initiation. (Table 1).

The correction of plasma sodium concentration during CVVHD in the study patients is shown in Figure 1. Alterations in other plasma solutes as well as cumulative sodium load of the trisodium citrate solution and parenteral fluids and the 24-hour fluid balances are summarized in Table 2. Mean sodium loads of the trisodium citrate solution and parenteral fluids during the first three days of CVVHD were 1754 (SD 730) mmol and 297 (SD 193) mmol per day, respectively. Overall, median plasma sodium correction during the first 24 hours of CVVHD was 8 (IQR 5-10) mmol/L and excessively high plasma sodium correction (>8 mmol/L/24 h) was observed in 18 (48.6%) patients. Concordantly, plasma sodium correction of (8-10 mmol/L/24 h), (10-12 mmol/L/24 h) and (>12 mmol/L/24 h) was observed in 8 (21.6%), 4 (10.8%) and 6 (16.2%) study patients, respectively. One patient, in whom no excessive sodium correction was observed, died during the first 24 hours of ICU care. Furthermore, excessively high plasma sodium (Table 2) correction was observed in 2 (6.7%) of the 30 study patients on CVVHD within the time from 24 to 48 hours after initiation. There were no differences in terms of delivered dialysis dose ($P = .49$), blood flow rate ($P = .89$), dialysate flow rate ($P = .58$), trisodium citrate infusion rate ($P = .75$), received total intravenous fluid volume ($P = .93$), sodium concentration per liter of daily total intravenous fluid input ($P = .43$) or fluid balance ($P = .94$) between patients with excessively rapid plasma sodium correction and those with a correction rate below 8 mmol/L/24 h.

No significant associations between the studied clinical or biochemical covariates and excessively high plasma sodium correction were observed in the univariate correlation models. Moreover we did not observe increased one-year mortality (HR 2.54, CI 95% 0.76-8.45, $P = .13$) associated with an undesirably high increase in plasma sodium exceeding 8 mmol/L/24 h in the univariate Cox proportional hazards model. None of the study patients were observed with central pontine myelinolysis during the one-year follow-up. Furthermore, autopsy data was available for 6 (46.2%) of the 13 patients who died within one-year follow-up and no cases central pontine myelinolysis were observed.

4 | DISCUSSION

In this retrospective cohort study, we assessed for the first time, using real world clinical data, the feasibility of managing critically ill AKI patients with coincident hyponatremia using CVVHD with citrate-calcium anticoagulation and standard commercial dialysate. Plasma sodium concentrations increased effectively during treatment, and half of the patients experienced an excessively rapid correction of plasma sodium. However, no association between mortality and excessively fast sodium correction was detected and no cases of central pontine myelinolysis were observed in this study.

The prevalence of hyponatremia (7.5%) in our study was in line with previous studies on critically ill patients under intensive care.[1,2] Hyponatremia frequently burdens highly comorbid patients and has been associated with adverse outcomes in the general population as well as in intensive care patients.[1,2,4] Furthermore, critically ill patients commonly develop AKI, with associated volume overload, decreased urine output and electrolyte abnormalities, which

TABLE 1 Baseline characteristics of the study patients

	Study patients (N = 37)
Age mean (median) years	58 (58)
Female	9 (24.3)
Body mass index mean (SD) kg/m^2	28.4 (4.7)
Hypertension	23 (62.2)
Diabetes	18 (48.6)
Coronary artery disease	7 (18.9)
History of heart failure	6 (16.2)
Atrial fibrillation	6 (16.2)
Prior stroke	5 (13.5)
Peripheral artery disease	4 (10.8)
Chronic lung disease	5 (13.5)
Cirrhosis	3 (8.1)
Active malignancy	2 (5.4)
Cause of ICU admission	
Sepsis	19 (51.4)
Acute kidney injury	10 (27.0)
Rhabdomyolysis	3 (8.1)
Surgery[a]	3 (8.1)
Other[b]	2 (5.4)
ICU management	
Maintenance dialysis	1 (2.7)
SOFA-score mean (SD)	10 (4)
SAPS II-score mean (SD)	54 (14)
APACHE II-score mean (SD)	27 (7)
Mechanical ventilation	20 (54.1)
Vasopressor support	33 (89.2)
Laboratory tests	
Blood hemoglobin median (IQR) g/L	105 (93-125)
Plasma CRP mean (SD) mg/L	145 (126.6)
Plasma creatinine median (IQR) µmol/L	339 (248-566)
Plasma urea mean (SD) mmol/L	22 (10.5)
Blood pH mean (SD)	7.25 (0.1)
Blood bicarbonate mean (SD) mmol/L	16.0 (3.7)
Blood base excess mean (SD) mmol/L	-10.9 (5.4)
Blood chloride mean (SD) mmol/L	98 (5.6)
Blood glucose median (IQR) mmol/L	7.9 (6.3-10.6)
Plasma sodium median (IQR) mmol/L	127 (124-129)
Plasma potassium mean (SD) mmol/L	4.3 (0.7)
Blood lactate median (IQR) mmol/L	2.2 (1.1-4.7)

Note: Values in parentheses are % unless stated otherwise. Continuous variables are expressed as mean (SD) or median (IQR) for normally distributed and skewed covariates, respectively. The baseline laboratory values were measured at the initiation of continuous veno-venous hemodialysis.

Abbreviations: APACHE II-score, Acute Physiology And Chronic Health Evaluation II score; CRP, C-reactive protein; ICU, intensive care unit; IQR, inter-quartile range; SAPS II-score, Simplified Acute Physiology II score; SD, standard deviation; SOFA-score, Sequential Organ Failure Assessment score.

[a]One case of elective back surgery, one case of non-elective heart surgery and one case of non-elective gastric surgery.

[b]One case of severe pancreatitis and one case of severe congestive heart failure.

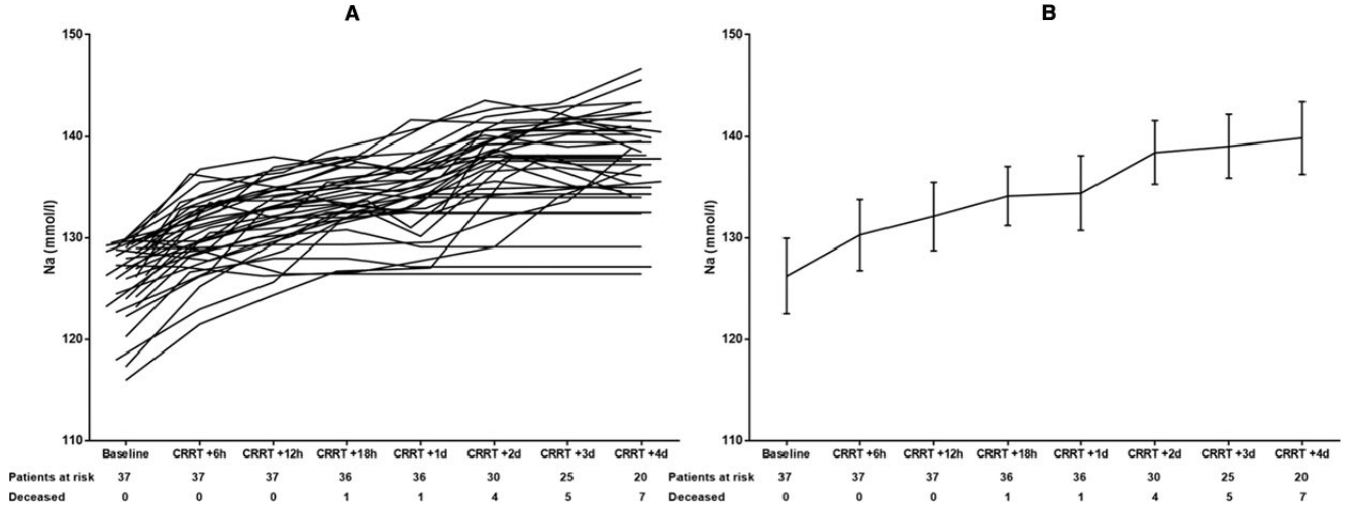

FIGURE 1 The correction of plasma sodium concentration depicted as a spaghetti plot (panel A) for the study patients, separately, and a single line plot (panel B) for the mean (±SD) of the study cohort, respectively, during the first four days of continuous veno-venous hemodialysis. SD, standard deviation

complicates the treatment of hyponatremia—especially so if renal replacement therapy is required.[9] Moreover excessively prompt correction of plasma sodium concentration has been associated with iatrogenic myelinolysis of the pons[3] and this risk is further highlighted during renal replacement therapy as volume overload can be rapidly corrected and standard dialysate and replacement fluids contain substantial amounts of sodium.[10] For this reason, CVVHD, especially in critically ill patients, offers advantages over intermittent hemodialysis in terms of hyponatremia management as fluid balance can be restored over a longer period of time and the dialysate flow rate is lower compared to intermittent hemodialysis.[6] The sodium concentration of dialysate and replacement fluids can be modified, although not easily as in intermittent hemodialysis. Previous studies have reported favorable results in the management of hyponatremia with CRRT techniques.[6-8]

Regional citrate-calcium-anticoagulation is superior compared to systemic anticoagulation with heparin analogues in terms of bleeding-risk and circuit and filter patency.[11] Despite the ever-increasing popularity of regional citrate anticoagulation for CVVHD, strikingly little data exist on the management of hyponatremic AKI patients with this method. Especially considering the high incidence of hyponatremia in critically ill patient populations.[1,2] Recently, Redant et al (2020) published a report on CVVHDF with citrate-calcium anticoagulation and modified low-sodium dialysate and replacement fluids in the management of AKI and coincident hyponatremia in a small case series of five patients.[8] A mean correction rate of 7.8 mmol/L/24 h in plasma sodium concentration was achieved at the cost of increased labor intensity and concerns over sterility of the modification of dialysate and replacement fluid bags. Furthermore, all the patients in their case series had plasma sodium exceeding 130 mmol/L at CVVHDF initiation in contrast to our current study.[8] The use of standard dialysate and citrate solutions for CVVHD in the management of hyponatremia has not been tested in a clinical study before probably because of concerns over excessive sodium correction due to the high sodium concentration of the citrate anticoagulation fluid. However, the correction rate of plasma sodium concentration was similar in our study with a standard commercial hyponatremic (Na 133 mmol/L) dialysate solution. Furthermore, central pontine myelinolysis has rarely been observed in uremic patients and it has been suggested that the risk for iatrogenic myelinolysis is lower in uremic patients with hyponatremia undergoing dialysis due to decreasing urea concentration acting as counterbalancing agent and causing a fluid shift to the opposite direction in the brain compared to the one caused by the increasing sodium concentration.[12,13] Furthermore, the blood and, thus, the citrate flow rate can still be adjusted and hypotonic parenteral fluids may be used to offset the effect of the sodium load of the citrate-calcium anticoagulation fluid. Moreover, use of standard dialysate and citrate solutions would eliminate the extra work and contamination risk associated with the sodium concentration adjustment of the dialysis fluids.

In the current study, the sodium concentration increased in half of the study patients at a higher rate (>8 mmol/L/24 h) than recommended by the current guidelines.[4,5] However, the hyponatremia management guidelines were updated (in 2013) during the course of the study and the sodium correction rate was within the limits of the prior guidelines (<12 mmol/L/24 h) in most (31/37, 83.8%) of the study patients.[4] Nevertheless, there are multiple explanations for the overly rapid correction rate of plasma sodium concentration in our study. First, the baseline sodium concentration was not very low (Table 1) or the leading cause for ICU admission in the study patients and this may have caused attending physicians to be "less attentive" to the developing sodium concentration during ICU care. Second, the study patients received mostly isotonic fluids, perhaps due to the relatively mild level of hyponatremia in most patients: 26

TABLE 2 Correction of electrolytes, cumulative sodium load, fluid management and dialysis data at the time of initiation and during the first three days of continuous veno-venous hemodialysis, separately

	Baseline (N = 37)	1 d (N = 36)	2 d (N = 30)	3 d (N = 25)
Plasma sodium median (IQR) mmol/L	127 (124-129)	135 (132-137)	139 (137-140)	140 (136-142)
Plasma potassium mean (SD) mmol/L	4.3 (0.7)	3.8 (0.5)	3.7 (0.3)	3.8 (0.3)
Blood pH mean (SD)	7.25 (0.1)	7.36 (0.1)	7.41 (0.1)	7.41 (0.1)
Blood bicarbonate mean (SD) mmol/L	16.0 (3.7)	22.0 (3.9)	24.9 (3.5)	25.9 (1.7)
Blood chloride mean (SD) mmol/L	98 (5.6)	104 (3.8)	107 (3.1)	108 (2.9)
Blood lactate median (IQR) mmol/L	2.2 (1.1-4.7)	1.5 (1.1-2.8)	1.1 (0.8-1.7)	1.1 (0.8-1.4)
Sodium load				
Trisodium citrate solution mean (SD) mmol	-	2237 (520)	2030 (676)	1880 (689)
Parenteral solutions mean (SD) mmol	-	416 (245)	341 (207)	293 (135)
Sodium concentration median (IQR) mmol/L[a]	-	132 (95-143)	125 (88-138)	114 (83-135)
Fluid management				
Total intravenous fluid volume mean (SD) mL	-	3358 (1820)	2782 (1424)	2650 (936)
Fluid balance median (IQR) mL	1920 (133-348)	1449 (−338-4228)	453 (−361-1603)	50 (−679-827)
Dialysis data				
Delivered dialysis dose median (IQR) mL/kg/h	-	34 (27-36)	33 (28-36)	32 (24-35)
Blood flow rate mean (SD) mL/min	-	137 (24)	134 (23)	128 (23)
Dialysate flow rate mean (SD) mL/h	-	2644 (881)	2600 (779)	2600 (1000)
Trisodium citrate infusion rate median (IQR) mL/h	-	241 (43)	235 (44)	226 (42)

Abbreviations: d, day; IQR, inter-quartile range; SD, standard deviation.
[a]Median sodium concentration of daily total intravenous fluid input.

or 70.3% had a baseline sodium concentration of 125-130 mmol/L. Third, the mean sodium load of the citrate-calcium anticoagulation fluid was expectedly substantial (mean 1754 (SD 730) mmol per day) and significantly contributed to the correction speed of plasma sodium concentration despite the positive net fluid balance during the first days of CVVHD (Table 2). Despite the high correction rate, no association between mortality and excessive (>8 mmol/L/24 h) plasma sodium correction was observed and, importantly, no cases of central pontine myelinolysis were detected.

The use of CVVHD with standard citrate-calcium anticoagulation and dialysate in the management of critically ill AKI patients with hyponatremia appears to be feasible but our study raises some concerns over the safety of the technique. Although the use of standard solutions for CVVHD is simple and reduces the workload and contamination risk associated with the preparation of dialysate and replacement solutions with diluted sodium concentration, the risk for excessive sodium correction might be intuitively higher due to the high sodium load of the standard solutions.[8,11] This hypothesis, however, is yet to be tested in a clinical trial. Furthermore, maintaining a favorable correction rate (5-8 mmol/L/24 h) of plasma sodium concentration would require vigilant if not hourly control testing of sodium concentration and broader use of hypotonic parenteral

solutions such as 5% dextrose. Thus, it is not clear whether the use of standard or modified low-sodium solutions is better in CVVHD with citrate-calcium anticoagulation when treating patients with hyponatremia as both techniques are strenuous and not without risk. The issue is further complicated by the fact that there are data on hyponatremic patients undergoing CRRT and not developing adverse outcomes despite excessively high correction rate of plasma sodium concentration.[14] Ultimately, the best approach to critically ill patients with hyponatremia requiring CRRT is not known and requires further research.

This report has all the limitations of a retrospective study. The sample size was relatively small to draw definite conclusions. Due to sample size issues, we extended the data collection to 10 years. During this time guidelines have been altered to recommend a more conservative sodium correction rate in hyponatremia. It may be that the ICU physicians treating our patients may have had a more liberal approach to sodium correction rate during CVVHD compared to the current recommendations. However, data were extensively recorded and of a high quality. Moreover there was, essentially, no missing data. As this study was retrospective, there was no protocol screening for central pontine myelinolysis after ICU discharge. However, all available autopsy reports of the deceased patients were screened and all of the survivors retained high individual functionality after rehabilitation. The study was probably underpowered to detect statistically significant differences in mortality and especially central pontine myelinolysis considering the low incidence in ICU patients. Furthermore, some cases of central pontine myelinolysis might have been missed since autopsy data were not available for half of the deceased patients. Despite these limitations we believe that these results are relevant and may guide future research.

5 | CONCLUSIONS

CVVHD with standard citrate-calcium anticoagulation and dialysate solutions effectively increased the plasma sodium concentration in critically ill AKI patients with hyponatremia. However, excessively rapid sodium correction was observed in half of the patients and the sodium load provided by the regional citrate anticoagulation solution was high.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

TH, PU and MJ designed the study and were responsible for the data collection. TH performed the statistical analysis. TH drafted the manuscript. TH, PU and MJ revised the manuscript.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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