Severe Hyponatremia and Continuous Renal Replacement Therapy: Safety and Effectiveness of Low-Sodium Dialysate

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Rationale & Objective: In patients with severe hyponatremia in the setting of acute kidney injury or end-stage kidney disease, continuous renal replacement therapy (CRRT) using standard-sodium (140 mEq/L) fluids may lead to excessively rapid correction of plasma sodium concentration. Use of dialysate and replacement fluids with reduced sodium concentrations can provide a controlled rate of correction of plasma sodium concentration.

Study Design: We performed a single-center retrospective analysis of the safety and effectiveness of this approach in patients with plasma sodium concentrations ≤ 126 mEq/L who underwent CRRT for 24 or more hours using low-sodium (119 or 126 mEq/L) dialysate and replacement fluids. Change in plasma sodium level was assessed at 24 and 48 hours after initiation of low-sodium CRRT and at the end of treatment.

Setting & Participants: Between January 2016 and June 2018, a total of 23 hyponatremic patients underwent continuous venovenous hemodiafiltration using low-sodium dialysate and replacement fluids; 4 patients were excluded from analysis because of CRRT duration less than <24 hours.

Results: The 19 patients included in the study had a mean age of 56 years, 11 (58%) were men, and 15 (79%) were white. The initial mean plasma sodium level was 121 mEq/L and the initial CRRT effluent dose was 27 mL/kg/h. Only 2 (11%) patients had an increase in plasma sodium concentration > 6 mEq/L at 24 hours. Mean changes in plasma sodium levels at 24 and 48 hours and at the time of CRRT discontinuation were 3, 3, and 6 mEq/L, respectively. None of the patients developed osmotic demyelination syndrome.

Limitations: Key limitations were small sample size and lack of a control group.

Conclusions: Use of low-sodium dialysate and replacement fluids is a safe strategy for the prevention of overly rapid correction of plasma sodium levels in hyponatremic patients undergoing CRRT.

Continuous renal replacement therapy (CRRT) is often required in critically ill patients with acute kidney injury (AKI) or end-stage kidney disease (ESKD). Hyponatremia is a common complicating problem in critically ill patients requiring CRRT and, when severe, poses a special management challenge due to the risk for osmotic demyelination syndrome associated with rapid correction of plasma sodium concentration.

Although CRRT has been proposed as a means to address both AKI and hyponatremia in these patients, the rate of increase in plasma sodium level needs to be carefully controlled and closely monitored. Commercially available solutions for use as dialysate and replacement solutions have a sodium concentration of 140 mEq/L. Using these solutions in conjunction with standard CRRT prescription parameters (including blood and effluent flow rates) is associated with a risk for overly rapid correction (>6 mEq/L over 24 hours) in patients with severe hyponatremia. Methods proposed to overcome this issue include using lower effluent flow rates to limit solute clearance, the use of electrolyte-free water infusions (given as 5% dextrose in water) through the CRRT circuit, and the use of dialysate and replacement fluids with a reduced sodium concentration. Although the theoretical issues involved in these methods have been discussed in detail, reports describing clinical experience using low-sodium CRRT fluids (dialysate and/or replacement fluid) are limited.

We report our experience with using CRRT solutions with reduced sodium concentrations (119 and 126 mEq/L) in a series of patients who received continuous venovenous hemodiafiltration in the setting of concomitant moderate to severe hyponatremia. The purpose of selecting these 2 values of reduced-sodium CRRT solutions was 2-fold: (1) appropriate for most commonly encountered levels of hyponatremia in the clinical setting, and (2) ease of compounding and lower risk for compounding errors with a predefined volume of standard sodium fluid substitution with sterile water.

METHODS

Study Population

We conducted a retrospective review of all adult patients admitted to the Presbyterian Hospital campus of the University of Pittsburgh Medical Center between January 2016 and June 2018 who received CRRT using low-sodium CRRT solutions and had moderate to severe hyponatremia. Patients who had plasma sodium levels ≤ 126 mEq/L were included in the study. Patients...
who were receiving CRRT for less than 24 hours were excluded due to inadequate exposure time to assess response to therapy. The study was approved by the University of Pittsburgh Institutional Review Board (PRO18070355) with a waiver for informed consent given the deidentified data collection and minimal risk to study participants.

**CRRT Management and Formulation of Low-Sodium CRRT Solution**

CRRT was provided to all patients as continuous venovenous hemodiafiltration using a Prismaflex CRRT machine (Baxter Inc, Deerfield, IL). Regional anticoagulation was not used for any of the patients. The primary CRRT solution used as dialysate or replacement fluid (for both pre- and postfilter infusion) for normonatremic patients at our institution is PrismaSATE BGK 4/2.5 (Baxter Inc; sodium concentration, 140 mEq/L; potassium concentration, 4.0 mEq/L; calcium concentration, 2.5 mEq/L). For patients with severe hyponatremia, the hospital pharmacy compounded low-sodium CRRT solution with sodium concentrations of either 126 or 119 mEq/L by removing either 500 (for solution with sodium of 126 mEq/L) or 750 mL (for solution with sodium of 119 mEq/L) from the 5-L PrismaSATE bag and replacing it with an equal volume of sterile water. Although it is possible to prepare CRRT solutions with many different sodium concentrations, the reconstituted solutions were restricted to 2 reduced-sodium values of 119 and 126 mEq/L for the following reasons: (1) to simplify the implementation process given the limited clinical experience with using low-sodium dialysate solutions, (2) reduce delay in obtaining dialysate for CRRT initiation, and (3) minimize risk for compounding errors.
The approach to the preparation of different low-sodium solutions (112, 119, 126, and 133 mEq/L) is shown in Table 1 (see Table S1 for all other electrolyte changes for solutions with sodium concentrations of 119 and 126 mEq/L). Electrolyte compositions were confirmed through laboratory measurement during initial implementation but were not confirmed routinely during patient care. The choice of sodium concentration in dialysate and replacement fluids was dependent on the severity of hyponatremia in the patient. The usual protocol followed was to use the solution with the next higher sodium concentration that was available. For example, if plasma sodium concentration was 113 mEq/L before CRRT initiation, the fluid with a sodium concentration of 119 mEq/L was selected initially and after plasma sodium concentration approached 119 mEq/L, it was converted to 126 mEq/L. Similarly, when it approached 126 mEq/L, the solution was changed to 140 mEq/L.

Regional anticoagulation is not used at our institution. Heparin was the mainstay of anticoagulation for CRRT, if needed.

Data Collection
Clinical data were abstracted through review of electronic medical records in EPIC (Epic Systems Corp) for outpatient data and Citrix Cerner (Citrix Systems, Inc) for inpatient data. A list of patients who were treated with low-sodium CRRT solutions was obtained from the hospital pharmacy department. Data collected from patient charting in the electronic medical records included demographic information, patient weight, urine output, CRRT treatment data and duration, and biochemical data at baseline, just before CRRT initiation, and during CRRT therapy.

Additional information collected included indications for CRRT initiation, comorbid conditions, cause of hyponatremia, presence of AKI and its cause or ESKD, and death during hospitalization or 6 months from the index hospitalization. Home therapy for hyponatremia on discharge was obtained from the nephrology daily progress notes and discharge summary. The CRRT prescription at the time of initiation, including blood flow rate, dialysate and replacement fluid sodium concentrations, dialysate flow rate, pre- and postfilter replacement fluid rates, and ultrafiltration rate were recorded. Effluent dose was calculated based on weight at the initiation of CRRT. Serial plasma sodium levels at the time of initiation and during and at the time of discontinuation of low-sodium CRRT were recorded. Whether hyponatremia persisted in subsequent laboratory results following the index hospitalization (outpatient or subsequent hospitalizations) was also recorded when available.

Outcomes
The primary outcome was the proportion of patients who had an increase in plasma sodium level > 6 mEq/L in 24 hours. Secondary outcomes were mean changes in plasma sodium levels in the first 24 and 48 hours after starting low-sodium CRRT and at the time of stopping CRRT.

Statistical Analysis
Data are presented using descriptive statistics. Baseline characteristics are presented as mean with standard deviation or median with range for continuous variables and as proportion for categorical variables. Changes in plasma sodium levels at 24 and 48 hours are presented as mean with standard deviation. Analyses were performed with the use of STATA software (version 15.1; StataCorp, College Station, TX).

RESULTS
Study Cohort
Between January 2016 and June 2018, a total of 23 patients were treated with CRRT using low-sodium fluids. Four patients were excluded from the study because they received less than 24 hours of CRRT, leaving a study population of 19 patients. A summary of all 23 patients is provided in Table 2.

Baseline Characteristics
Baseline characteristics of the study population are shown in Tables 2 and 3. Mean age was 56 years, 11 (58%) were men, 15 (79%) were white, and mean weight was 94 kg. Seven (37%) patients had heart failure and 5 (26%) had diabetes mellitus. No patient was receiving oral sodium chloride or urea for hyponatremia management. None of the patients were treated with hypertonic saline solution. Baseline plasma sodium level before CRRT initiation was 121 mEq/L. Two patients were receiving hemodialysis before the initiation of CRRT, and in the remaining patients, baseline premorbid mean plasma creatinine level was 1.2 mg/dL. Mean plasma creatinine level just before CRRT initiation (excluding those who were receiving hemodialysis pre-CRRT) was 5.1 mg/dL. In the 24 hours before initiating CRRT, urine output was >500 mL in only 1 patient (1,025 mL for patient 5) and was not recorded in the chart for 1 patient. In the remaining patients, urine output ranged from 0 to 400 mL/d (Table 4).

CRRT Parameters
Patients were receiving CRRT with low-sodium solutions for an average of 4 days (range, 2-11 days, excluding 4 patients with <24 hours of CRRT). Blood flow rate for all patients was 250 mL/min except in 2 patients, for whom it was 200 and 300 mL/min, respectively. Prefilter replacement fluid was used in only 1 patient at the rate of 500 mL/h. Postfilter replacement fluids were used in all patients and ranged from 250 to 750 mL/h. Ultrafiltration rates were between 0 and 500 mL/h. Mean effluent dose was 27 (range, 13-35) mL/kg/h.

The most commonly used reduced-sodium CRRT fluid was 126 mEq/L. Among the 19 patients who were receiving reduced-sodium CRRT for more than 24 hours, 15 patients...
| Patient | Age, y | Sex | Race | Indication for CRRT Initiation (other than hyponatremia) | Cause of Hyponatremia | History of Diabetes Mellitus | Use of Diuretics | Use of Salt Tablets | Other Medications That Could Influence Plasma Sodium | Follow-up/Home Therapy |
|---------|--------|-----|------|--------------------------------------------------------|-----------------------|-----------------------------|-----------------|-------------------|-----------------------------------------------|----------------------------|
| 1       | 70s    | F   | O    | ESKD patient with shock                                | Excess free-water intake in ESKD patient | No                          | No              | No                | None                                         | Death 53 d after index hospitalization, no follow-up lab tests |
| 2       | 40s    | M   | O    | Persistent AKI from refractory HRS vs ATN, hyperkalemia| Appropriate ADH release from liver cirrhosis, impaired free-water excretion from AKI | No                          | Yes (furosemide) | No                | Desmopressin (1 dose)                         | Death 14 d after hospitalization |
| 3       | 40s    | M   | O    | Anuric AKI from HRS vs ATN, volume overload            | Appropriate ADH release from liver cirrhosis vs beer potomania | No                          | No              | No                | None                                         | Death 5 d after hospitalization |
| 4       | 50s    | M   | W    | ESKD patient with volume overload, acidosis           | Excess free-water intake in ESKD patient | No                          | No              | No                | Duloxetine (unlikely cause of hyponatremia in ESKD patient) | Death 103 d after index hospitalization, no follow up lab tests |
| 5       | 30s    | M   | W    | Persistent AKI from ATN, uremia with altered mentation, acidosis | Impaired free-water excretion in AKI | No                          | No              | No                | None                                         | Discharged to hospice, all medications discontinued |
| 6       | 30s    | M   | W    | Persistent anuric AKI from refractory HRS vs ATN, hyperkalemia, acidosis, volume overload | Appropriate ADH release from liver cirrhosis, impaired free-water excretion from AKI | No                          | No              | No                | None                                         | Death following discharge (unknown time), no follow-up lab tests available; no specific hyponatremia treatment on discharge |
| 7       | 50s    | F   | W    | Persistent AKI from ATN, hyperkalemia, acidosis       | Appropriate ADH release from liver cirrhosis, impaired free-water excretion from AKI | No                          | No              | No                | Vasopressin drip                               | Death 4 d after hospitalization |
| 8       | 40s    | F   | W    | Persistent oliguric AKI from HRS vs ATN, hyperkalemia, acidosis | Appropriate ADH release from liver cirrhosis, impaired free-water excretion from AKI | No                          | No              | No                | None                                         | Discharged with comfort measures only, all medications discontinued |

(Continued)
| Patient | Age, y | Sex | Race | Indication for CRRT Initiation (other than hyponatremia) | Cause of Hyponatremia | History of Diabetes Mellitus | Use of Diuretics | Use of Salt Tablets | Other Medications That Could Influence Plasma Sodium | Follow-up/Home Therapy |
|---------|-------|-----|------|----------------------------------------------------------|-----------------------|-----------------------------|----------------|-------------------|---------------------------------|----------------------|
| 9       | 60s   | F   | O    | Persistent anuric AKI from HRS vs ATN, acidosis, hyponatremia | Appropriate ADH release from liver cirrhosis, impaired free-water excretion from AKI, SIADH from venlafaxine | Yes | Yes (furosemide) | No | Venlafaxine, stopped before CRRT initiation | Death after 14 d of hospitalization |
| 10      | 60s   | F   | W    | Persistent anuric AKI from ATN, acidosis | Appropriate ADH release from liver cirrhosis, impaired free-water excretion from AKI | No | Yes (furosemide) | Yes | Olanzapine, used as needed for ICU delirium | No specific hyponatremia treatment at discharge, plasma sodium 138 mEq/L on repeat lab tests after 3 mo |
| 11      | 90s   | F   | W    | Persistent AKI from ATN, acidosis | Appropriate ADH release from decompensated heart failure, impaired free-water excretion | No | Yes (furosemide, metolazone) | No | None | No specific hyponatremia treatment at discharge, plasma sodium 135 mEq/L after 9 mo |
| 12      | 50s   | M   | W    | Persistent AKI on CKD from treatment-refractory cardiorenal syndrome, volume overload | Appropriate ADH release from decompensated heart failure, impaired free-water excretion | Yes | Yes (chlorothiazide, furosemide, metolazone) | No | Vasopressin drip, stress dose hydrocortisone | Death after 11 d of hospitalization |
| 13      | 40s   | M   | W    | Persistent AKI, volume overload | Appropriate ADH release from liver cirrhosis versus beer potomania | No | No | No | None | Death after 9 d of hospitalization |
| 14      | 40s   | M   | W    | Persistent AKI secondary to ATN after orthotopic heart transplant, acidosis | Appropriate ADH release from decompensated heart failure, impaired free-water excretion | No | Yes (furosemide, metolazone) | No | None | Hemodialysis dependent after discharge |
| 15      | 60s   | M   | W    | Persistent AKI secondary to treatment-refractory cardiorenal syndrome vs ATN, volume overload | Appropriate ADH release from decompensated heart failure, impaired free-water excretion | Yes | Yes (furosemide) | No | None | Death after 14 d of hospitalization |
| Patient | Age, y | Sex | Race | Indication for CRRT Initiation (other than hyponatremia) | Cause of Hyponatremia | History of Diabetes Mellitus | Use of Diuretics | Use of Salt Tablets | Other Medications That Could Influence Plasma Sodium | Follow-up/Home Therapy |
|---------|--------|-----|------|-------------------------------------------------------|------------------------|-----------------------------|----------------|----------------|-----------------------------------------------|-------------------------|
| 16      | 50s    | M   | W    | Persistent AKI secondary to ATN in the setting of LVAD placement | Appropriate ADH release from decompensated heart failure, impaired free-water excretion | Yes             | No             | No             | None                                | Hemodialysis dependent after discharge; death 71 d after index hospitalization |
| 17      | 50s    | F   | W    | Persistent AKI from contrast induced-nephropathy, acidosis | SIADH, unidentified cause | No              | No             | No             | Stress dose hydrocortisone, sodium bicarbonate tablets | Death after 39 d of hospitalization |
| 18      | 70s    | F   | W    | Persistent AKI from ATN, acidosis | Appropriate ADH release from decompensated heart failure, impaired free-water excretion | Yes             | Yes            | No             | Vasopressin drip                          | Death after 12 d of hospitalization |
| 19      | 50s    | M   | W    | Persistent AKI secondary to treatment-refractory cardiorenal syndrome vs ATN, volume overload | Appropriate ADH release from decompensated heart failure, impaired free-water excretion | No              | Yes            | No             | Tolvaptan                                | Death after 45 d of hospitalization |
| 20      | 60s    | F   | W    | Persistent AKI secondary to BK nephropathy and ATN in patient with simultaneous liver-kidney transplantation | Impaired free-water excretion | No              | No             | No             | No                                    | Death after 7 d of hospitalization |
| 21      | 60s    | M   | O    | Persistent AKI secondary to treatment-refractory cardiorenal syndrome vs ATN, volume overload, hyperkalemia | Appropriate ADH release from decompensated heart failure, impaired free-water excretion | No              | Yes            | No             | No                                    | Advised fluid restriction on discharge, plasma sodium 136 mEq/L on follow-up |
were receiving CRRT fluid with a sodium concentration of 126 mEq/L in both the dialysate and postfilter replacement fluids, with no prefilter replacement fluid used. In 2 patients (pre-CRRT plasma sodium of 113 and 116 mEq/L, respectively), CRRT was initiated with the 119-mEq/L of sodium fluid as both dialysate and postfilter replacement fluid and then switched to 126 mEq/L after 30 and 24 hours, respectively. In the remaining 2 patients, dialysate was the standard CRRT solution with a 140-mEq/L sodium concentration and postfilter replacement fluid was sodium concentration of 126 mEq/L, with 1 patient also receiving prefilter replacement fluid of 126 mEq/L of sodium.

### Outcomes

Two (11%) patients had overcorrection of plasma sodium concentration, defined as an increase > 6 mEq/L in 24 hours. Mean changes in plasma sodium concentrations at 24 hours, 48 hours, and the time of CRRT discontinuation were 3 (range, –4 to 12), 3 (range, –4 to 8), and 6 (range, –4 to 21) mEq/L, respectively (Tables 5 and S2; Fig 1). Changes in other electrolyte levels are also listed in Table 6.

### Adverse Events

There were no adverse events pertaining to the preparation or administration of low-sodium fluids for CRRT. None of
| Patient | 24-h Urine Output Before CRRT Initiation, mL | Weight, kg | Dialysate Rate, mL/kg/h (sodium concentration, mEq/L) | Prefilter Replacement Fluid Rate, mL/h (sodium concentration, mEq/L) | Postfilter Replacement Fluid Rate mL/h (sodium concentration, mEq/L) | Ultrafiltration Rate, mL/h | Effluent Dose, mL/kg/h | Blood Flow Rate, mL/min | Duration of Low-Sodium Dialysate CRRT, d |
|---------|---------------------------------------------|------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|---------------------------|----------------------|----------------------|--------------------------|
| 1       | Not recorded                                | 101.6      | 2,000 (126)                                     | 0                                               | 250 (126)                                      | 0                         | 22                   | 250                  | 2                        |
| 2       | 160                                          | 103        | 2,500 (126)                                     | 0                                               | 250 (126)                                      | 0                         | 27                   | 250                  | 4                        |
| 3       | 0                                            | 92         | 1,800 (126)                                     | 0                                               | 250 (126)                                      | 500                       | 28                   | 250                  | 2                        |
| 4       | 400                                          | 81         | 1,900 (126)                                     | 0                                               | 250 (126)                                      | 0                         | 27                   | 250                  | 9                        |
| 5       | 1,025                                        | 140.9      | 3,000 (126)                                     | 0                                               | 250 (126)                                      | 0                         | 23                   | 250                  | 11                       |
| 6       | 40                                           | 128.5      | 3,500 (140)                                     | 500 (126)                                       | 500 (126)                                      | 0                         | 35                   | 3003                       |
| 7       | 25                                           | 73         | 1,700 (140)                                     | 0                                               | 750 (126)                                      | 0                         | 34                   | 250                  | 4                        |
| 8       | 70                                           | 100        | 1,000 (126)                                     | 0                                               | 250 (126)                                      | 0                         | 13                   | 250                  | 2                        |
| 9       | 210                                          | 85.5       | 2,500 (126)                                     | 0                                               | 250 (126)                                      | 0                         | 32                   | 200                  | 2                        |
| 10      | 67                                           | 90         | 2,500 (126)                                     | 0                                               | 250 (126)                                      | 0                         | 33                   | 250                  | 2                        |
| 11      | 150                                          | 91.2       | 2,000 (126)                                     | 0                                               | 500 (126)                                      | 50                        | 28                   | 250                  | 4                        |
| 12      | 150                                          | 102.4      | 2,000 (126)                                     | 0                                               | 250 (126)                                      | 50                        | 22                   | 250                  | 2                        |
| 13      | 30                                           | 109        | 2,000 (126)                                     | 0                                               | 250 (126)                                      | 0                         | 21                   | 250                  | 3                        |
| 14      | 28                                           | 87.2       | 2,300 (126)                                     | 0                                               | 250 (126)                                      | 50                        | 30                   | 250                  | 4                        |
| 15      | 350                                          | 92.4       | 2,000 (126)                                     | 0                                               | 250 (126)                                      | 0                         | 24                   | 250                  | 3                        |
| 16      | 225                                          | 93.8       | 2,500 (119, 126)                                | 0                                               | 250 (119, 126)                                 | 150                       | 31                   | 250                  | 5                        |
| 17      | 60                                           | 66.7       | 2,000 (126)                                     | 0                                               | 500 (126)                                      | 0                         | 37                   | 250                  | 5                        |
| 18      | 300                                          | 73.2       | 1,600 (119, 126)                                | 0                                               | 250 (119, 126)                                 | 30                        | 26                   | 250                  | 4                        |
| 19      | 130                                          | 82.8       | 2,000 (126)                                     | 0                                               | 250 (126)                                      | 100                       | 28                   | 250                  | 3                        |
| 20      | 10                                           | 62.2       | 1,500 (126)                                     | 0                                               | 250 (126)                                      | 0                         | 28                   | 250                  | <1                       |
| 21      | 320                                          | 144        | 2,250 (126)                                     | 0                                               | 750 (126)                                      | 50                        | 21                   | 250                  | <1                       |
| 22      | 250                                          | 41.8       | 1,200 (126)                                     | 0                                               | 250 (126)                                      | 200                       | 39                   | 250                  | <1                       |
| 23      | 350                                          | 65.1       | 1,600 (126)                                     | 0                                               | 250 (126)                                      | 0                         | 28                   | 250                  | <1                       |

Abbreviations: CRRT, continuous renal replacement therapy; CVVHDF, continuous venovenous hemodialfiltration.

3M10 filter was used for patient 6, who had concomitant hyperammonemia and a higher effluent dose was administered. All other patients used the conventional M100 filter.

3Patients 16 and 18 were switched from CRRT solutions with 119 mEq/L to 126 mEq/L of sodium after 30 and 24 hours, respectively, of initiating CRRT.
**DISCUSSION**

Hyponatremia is a common electrolyte disorder occurring concomitantly in patients with acute and chronic kidney disease. The prevalence of hyponatremia is around 15% to 30% in hospitalized patients and up to 30% in intensive care unit (ICU) patients. AKI occurs in 5% to 20% of patients admitted to the ICU and RRT is required in approximately 5% to 10% of ICU admissions, often in the form of CRRT. Conventional CRRT using standard-sodium dialysate of 140 mEq/L may result in overly rapid correction of hyponatremia. In this case series, we found the use of low-sodium fluids for CRRT to be a safe and effective strategy that allowed for a slow controlled increase in plasma sodium levels in hyponatremic patients.

Overly rapid correction of chronic hyponatremia, defined as a change in plasma sodium level > 6 mEq/L within 1 day in someone who has been hyponatremic for more than 48 hours can lead to osmotic demyelination syndrome and even death. Both European and American guidelines recommend a daily limit of a 10-mEq/L increase in the first day and 8-mEq/L increase thereafter in plasma sodium levels in moderate to profound hyponatremia (strong recommendation, very low evidence [1D]). However, in patients with high risk for osmotic demyelination syndrome, a lower limit of 8 mEq/L and goal of 4 to 6 mEq/L in the first 24 hours is desirable. In ICU patients who require RRT for AKI or ESKD but have concomitant hyponatremia, CRRT can provide controlled osmocorrection and gradual correction of hyponatremia.

There are 2 approaches described in the literature to avoid overcorrection of plasma sodium levels in the setting of hyponatremia in patients with CRRT-dependent AKI or ESKD while providing adequate clearance of urea and other solutes: (1) customizing the CRRT circuit, or (2) customizing the dialysis solution. They reported a gradual increase in plasma sodium levels over 6 days with CRRT fluid sodium concentration. This will reduce the need for frequent monitoring and adjustments to the CRRT prescription. Customization of the CRRT circuit with infusion of electrolyte-free water as 5% dextrose in water postfilter requires constant vigilance with frequent monitoring of plasma sodium levels and modifications of the electrolyte-free water infusion according to changes in plasma sodium levels so as not to exceed the recommended safe limit for correction.

In contrast, use of low-sodium CRRT fluids provides a safe and effective alternative, with low risk for rapid correction of plasma sodium levels because plasma sodium level should generally not increase above the CRRT fluid sodium concentration. This will reduce the need for frequent monitoring and adjustments to the CRRT prescription. Dangoisse et al discussed a similar protocol that they used to modify the CRRT circuit for hyponatremic patients in their institution. Instead of replacing a fixed volume of dialysate fluid with sterile water, their protocol entailed adding a fixed volume of sterile water to the 5-L bag of premixed dialysate solution with resulting minor variations in electrolyte concentrations as compared to our protocol. They reported a gradual increase in plasma sodium levels over 6 days with CRRT using low-sodium solutions in their hyponatremic patient after it initially overcorrected with intravenous fluids. In our opinion, either of these techniques of modifying the dialysate solution is acceptable, provided the practice is internally standardized and protocolized for the institution to avoid confusion with preparation of the modified sodium solution.

Neyra et al also demonstrated a gradual increase in plasma sodium level in 3 ICU patients with plasma sodium...
| Pt   | Baseline Plasma Creatinine, mg/dL | Plasma Chemistries Just Before CRRT Initiation | Plasma Chemistries 48 h After Low-Sodium CRRT Initiation |
|------|----------------------------------|-----------------------------------------------|----------------------------------------------------------|
|      | Na, mEq/L                        | Cr, mg/dL                                     | Mg/dL, mEq/L, mEq/L, mEq/L, mEq/L, mEq/L, mEq/L         |
| 1    | On HD before starting CRRT       | 126 4.6 (on HD before starting CRRT)           | 122 1.8 15 NA 4.3 94 26                                   |
| 2    | Unknown, no prior lab work       | 121 3.6                                       | 121 2 41 166 5.1 88 20                                   |
| 3    | Unknown, no prior lab work       | 121 8                                         | 125 3.7 28 101 3.9 89 23                                 |
| 4    | On HD before starting CRRT       | 122 5.3 (on HD before starting CRRT)           | 126 2.2 43 162 3.6 93 23                                 |
| 5    | Unknown, no prior lab work       | 126 8.4                                       | 129 5.9 55 103 3.3 94 22                                 |
| 6    | 0.6                              | 123 5.3                                       | 120 2.1 12 141 4.3 96 24                                 |
| 7    | 1.2                              | 126 4.5                                       | 127 2.0 28 97 5 93 19                                   |
| 8    | 1.1                              | 117 10.8                                      | 119 6.2 94 136 5.8 92 18                                 |
| 9    | Unknown, no prior lab work       | 125 4.3                                       | 129 1.3 14 185 3.5 92 21                                 |
| 10   | 0.8                              | 125 3.3                                       | 128 1.4 15 155 3.5 93 22                                 |
| 11   | 1.6                              | 118 5.4                                       | 123 1.9 13 119 4 91 23                                   |
| 12   | 1.9                              | 120 4.5                                       | 125 2.1 37 201 4.9 97 20                                 |
| 13   | 0.8                              | 118 12.2                                      | 123 3.3 11 121 3.3 90 21                                 |
| 14   | 1.2                              | 119 3.5                                       | 124 1.4 23 117 4.5 92 21                                 |
| 15   | 1.6                              | 120 3.4                                       | 123 1.7 29 150 4.6 91 24                                 |
| 16   | 1.5                              | 113 3.9                                       | 120 2.1 55 83 4.1 88 22                                 |
| 17   | 0.8                              | 118 2.3                                       | 126 1.0 33 116 4.2 96 22                                 |
| 18   | 1.1                              | 116 1.8                                       | 121 1.5 27 135 4.5 93 17                                 |
| 19   | 0.9                              | 123 2.0                                       | 124 1.6 31 115 4.3 92 22                                 |
| 20   | 2.3                              | 118 3.5                                       | 123 2.5 103 153 6.3 96 20                                 |
| 21   | 1.2                              | 118 3.5                                       | 123 2.5 103 153 6.3 96 20                                 |
| 22   | 2.3                              | 118 4.8                                       | 123 2.5 103 153 6.3 96 20                                 |
| 23   | 1.1                              | 123 4.3                                       | 127 168 3.7 92 19                                       |

Note: Conversion factors for units: Cr in mg/dL to μmol/L, ×88.4; SUN in mg/dL to mmol/L, ×0.357; glucose in mg/dL to mmol/L, ×0.05551.
Abbreviations: Cr, creatinine; CRRT, continuous renal replacement therapy; HD, hemodialysis; lab, laboratory; NA, not available; SUN, serum urea nitrogen; TCO₂, bicarbonate.
levels < 120 mEq/L using low-sodium dialysate CRRT in a single-center study. Their protocol entailed calculations to determine the exact volume of sterile water needed to replace or add to the standard-sodium dialysate bag. Although it is possible to modify dialysate to different sodium concentrations on an “on-demand” basis as in their protocol, our strategy was to limit the low-sodium dialysate to 2 different values: 119 and 126 mEq/L. This was primarily done for safety reasons because having a range of modified sodium dialysates might have resulted in the need for repeated calculations, compounding errors, and the possibility of inadvertent over- or undercorrection of hyponatremia. The 2 available low-sodium dialysates were believed to be sufficient to allow for a controlled increase in plasma sodium levels for clinical use. As noted in our results, it allowed clinicians to increase the dialysate sodium concentration in a stepwise manner knowing that plasma sodium level would not generally exceed the sodium concentration of the low-sodium dialysate solution. However, we noticed that after the first 24 hours, the rate of correction was lower than desired and patients stayed mildly hyponatremic for longer. Similarly, 8 of 19 (42%) patients who were on CRRT for more than 1 day had a plasma sodium change ≤ 3 mEq/L at 48 hours after CRRT initiation. This is not advisable and we acknowledge that this is a limitation of using low-sodium dialysate for a longer duration. This probably was related to concerns with switching from a sodium concentration of 126 to 140 mEq/L due to the absence of a solution with a reduced sodium concentration between 126 and 140 mEq/L. We are assessing whether having a low-sodium dialysate bath in the intermediate range of ~133 mEq/L would be of benefit to avoid this scenario. This could easily be achieved by replacing 250 mL of standard dialysate with sterile water. Similarly, if a patient presented with even more severe hyponatremia than encountered in our series, replacement of 1,000 mL of PrismaSATE with an equal volume of sterile water would result in a fluid with a sodium concentration of 112 mEq/L. Table 1 shows the method for compounding these low-sodium CRRT solutions and the resulting concentrations of sodium, potassium, and bicarbonate.

Some institutions have protocols for citrate-based anticoagulation, which has been described to cause hypo- and hypernatremia based on the tonicity of replacement solutions. The hypertonic citrate solutions may have a
sodium concentration as high as 408 mEq/L, and these solutions must be carefully used with hypotonic dialysate and replacement solutions with lower sodium concentrations to prevent hypernatremia in patients.\textsuperscript{22,23} Even isotonic citrate solutions with a physiologic sodium concentration of $\sim$140 mEq/L may defeat the purpose of using reduced sodium dialysate and replacement solutions when they are used in the CRRT circuit for hyponatrexic patients. Although strict adherence to protocols has led to a lower incidence of hypernatremia with citrate-based anticoagulation in different studies,\textsuperscript{24-27} these may still be less desirable in a patient with severe hyponatremia and high-risk features for osmotic demyelination syndrome due to a relative rapid increase in plasma sodium levels. For these reasons, it may be reasonable to avoid citrate-based regional anticoagulation in such high-risk patients.

Our study is the largest case series to our knowledge that has systematically studied the safety and efficacy of low-sodium-dialysate CRRT. We had serial sodium levels available without any missing data that allowed for accurate estimation of plasma sodium level changes during the low-sodium CRRT.

Our study had limitations. This was a single-center retrospective study with a small sample size and findings will have to be considered with these limitations. Nonetheless, the ability to achieve slow and sustained increases in plasma sodium levels with low-sodium CRRT fluids was demonstrated. In some patients, plasma sodium levels failed to increase, and in some, it was even a little lower than the value before CRRT initiation. The causes for these could not be identified with certainty for individual patients but it possibly is a combination of excess free-water intake, interruptions to CRRT due to required testing or procedures, and lack of an intermediate low-sodium dialysate concentration between 126 and 140 mEq/L.

Two patients had overly rapid correction of plasma sodium levels in 24 hours of 10 and 12 mEq/L, respectively, despite using low-sodium solutions. The cause of this again could not be identified with certainty but this could occur in patients with resolving AKI who have an increase in hypotonic urine or cessation of culprit medications such as thiazide diuretics or cessation of behavior leading to hyponatremia, such as consumption of excess free water. None of these obvious causes were found in these 2 patients but this further underscores the importance of using reduced-sodium CRRT solutions because the risk would be higher with higher sodium concentrations.

The study lacked a control group of patients with hyponatremia who were on CRRT with solutions containing the standard sodium concentration of 140 mEq/L. None of the patients developed osmotic demyelination syndrome, but 16 patients died during the hospitalization or within 4 months of discharge from the hospital. Lastly, we also were unable to obtain data pertaining to any delays in initiation of CRRT in situations needing low-sodium CRRT.

In the absence of commercially available low-sodium CRRT solutions, we believe that the protocol used in our study can be safely used for patients with moderate to severe hyponatremia who require CRRT, thereby reducing the risk for overcorrection of plasma sodium levels. Although supported by the pharmacy department at our institution, pharmacies at other institutions may be reluctant to modify the standard dialysate solutions due to fear of compounding error. These concerns can be addressed by limiting the number of modifications and using a strict protocol for evaluating compounding accuracy. An extra safety step would be to check the patient’s chemistry test results shortly after initiating CRRT with low-sodium fluids.

In this case series of critically ill patients with hyponatremia requiring CRRT, we found that using a CRRT solution with a low sodium concentration was safe, feasible, and effective in avoiding rapid hyponatremia correction.

**SUPPLEMENTARY MATERIAL**

**Table S1:** Reduced-sodium CRRT solution electrolyte composition

| Table S2: Plasma sodium trends for individual patients |

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