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CLINICAL RESEARCH

A Multidisciplinary Approach for the Management of Severe Hyponatremia in Patients Requiring Continuous Renal Replacement Therapy

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Introduction: Hyponatremia is a common electrolyte disorder in critically ill patients. Rapid correction of chronic hyponatremia may lead to osmotic demyelination syndrome. Management of severe hyponatremia in patients with acute or chronic kidney disease who require continuous renal replacement therapy (CRRT) is limited by the lack of commercially available hypotonic dialysate or replacement fluid solutions.

Methods: This was a single-center quality improvement project that consisted of the development and implementation of a multidisciplinary protocol for gradual correction of severe hyponatremia in patients who were admitted to the intensive care unit (ICU) and required CRRT. The protocol utilized a simplified method based on single-pool urea kinetic modeling and a hybrid technique of volume exchange, and addition of sterile water for sodium dilution of commercially available dialysate and replacement fluid solutions.

Results: We report data of the first 3 ICU patients who required CRRT for acute kidney injury management, had severe hyponatremia (serum sodium <120 mEq/l), and were treated under the protocol. Targeted and gradual hyponatremia correction was achieved in all 3 patients. The observed versus the predicted serum sodium correction in each patient was concordant. No complications related to the protocol were reported. Q1 We detailed proponents of and hindrances to the development and successful implementation of our multidisciplinary protocol.

Conclusion: We demonstrated gradual and individualized rates of severe hyponatremia correction utilizing customized (sodium dilution) dialysate/replacement fluid solutions in ICU patients who required CRRT. It is not known whether the use of customized solutions to prevent hyponatremia overcorrection has a significant impact on patient outcomes. Further research is this susceptible population is needed.

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Hyponatremia is a common electrolyte disturbance encountered in critically ill patients and is associated with increased risk of mortality.[1] Many factors have been identified that contribute to the development of hyponatremia in these patients, including age, acute or chronic kidney disease, heart failure, liver cirrhosis, trauma, major surgery, and neurological diseases.[2]

Prevention and treatment of this condition are particularly difficult to achieve in critically ill patients. Treatment depends on the duration of hyponatremia and the volume status of the patient.[3] Rapid correction of chronic hyponatremia may lead to osmotic demyelination syndrome, a neurological condition with possible irreversible damage.[3,4]

Management of severe hyponatremia in patients with acute kidney injury (AKI) or advanced chronic kidney disease (CKD) can be challenging, especially in those requiring renal replacement therapy (RRT). Hemodialysis is frequently used in patients with renal failure; however, its use could result in rapid correction of hyponatremia. Importantly, critically ill patients are often hemodynamically decompensated and

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may require CRRT to optimize solute control and fluid regulation,[5] yet there are limited options for commercially available hypotonic dialysate or replacement fluid solutions to prevent hyponatremia overcorrection in patients who require CRRT.

There are reports of successful correction of severe hyponatremia in patients receiving CRRT[6–8]; however, there is no consensus on safety or the most cost-effective CRRT prescription for these patients. Yessayan *et al.*[7] proposed the use of the single-pool urea kinetic modeling equation to customize hyponatremia correction during CRRT (specifically continuous venovenous hemofiltration [CVVH]). Nonetheless, this method requires timely and frequent adjustments in the replacement fluid sodium concentration to ensure a safe rate of hyponatremia correction.

Based on available data about hyponatremia correction during CRRT, we assembled a multidisciplinary team comprising physicians, nurses, and pharmacists to evaluate the need, safety, and necessary logistic components for the development and implementation of the CRRT-Hyponatremia Protocol at our institution. In this quality improvement report, we describe our work from protocol development to implementation, and show the data from the first 3 patients who were treated under the protocol.

METHODS

The CRRT-Hyponatremia Protocol: Local Problem

The University of Kentucky Albert B. Chandler Hospital is an academic 854-bed facility with reported 37,466 admissions in 2016 (data obtained from the Center for Health Services Research). The incidence of hyponatremia in 2016 was approximately 7.1% (2,666 of 37,466), mostly in patients with decompensated liver cirrhosis and advanced heart failure (data queried using i2b2 framework supported by the Center for Clinical and Translational Science). The prevalence of liver cirrhosis in hospitalized patients is approximately 5%, and it is not uncommon to find severe hyponatremia in patients with decompensated liver cirrhosis and AKI that require CRRT (n = 34 in 2016, data obtained from the Center for Health Services Research). In this context, we decided to develop a protocol that delivers CRRT with customized sodium concentration in the dialysate and replacement fluid solutions.

The CRRT-Hyponatremia Protocol: Team Development

To develop the CRRT-Hyponatremia Protocol, we assembled a multidisciplinary team that consisted of nephrologists, intensivists, pharmacists, nurses, and pharmacy technicians. First, we evaluated the need for the protocol, the available literature in this topic, and the feasibility to develop the protocol with high standards of patient safety and cost–benefit. Once we were convinced that this protocol could help our current practice in CRRT, we proceeded to request corresponding institutional approvals and support for the protocol development and implementation phases. We obtained approval from the University of Kentucky Institutional Review Board (17-0444-P1G) to examine data from patients receiving CRRT in the ICU.

The CRRT-Hyponatremia Protocol: Tool Development and Prescription

Overall, the need for compounded low-sodium dialysate fluid and replacement fluid is relatively infrequent. Early in the protocol development phase, the need for a standardized process was determined for reviewing orders and accurately compounding these fluids when clinically indicated. A spreadsheet-based low-sodium CRRT tool (Supplementary Figure S1) was developed to determine *de novo* concentrations of all constituents of the dialysate and replacement fluids.

To provide gradual correction of hyponatremia, successive higher concentrations of hypotonic dialysate and replacement fluid bags were prepared at concentrations derived from the single-pool urea kinetic method described by Yessayan *et al.*, which was adjusted every 24 hours per our protocol.[7] Of note, the method described by Yessayan *et al.* was performed in patients receiving continuous venovenous hemofiltration (CVVH), which utilizes primarily convection and not diffusion. In our institution, we commonly use the continuous venovenous hemodiafiltration (CVVHDF) modality, which requires both dialysate fluid and replacement fluid for diffusion and convection, respectively. In these cases, the sodium concentration of both the dialysate fluid and replacement fluid were adjusted. It is important to note that diffusion can decline with partial clotting of the filter, which can affect the overall rate of serum sodium correction, making it less effective but still safe, avoiding rapid overcorrection. The sodium concentration of each dialysate and replacement fluid bag was calculated from the equation:

$$\text{dialysate or replacement fluid } [Na^+] = \text{patient's serum } [Na^+] + \text{desired } \Delta \text{ serum } [Na^+] + 2 \text{ or } 4 \text{ mEq/L}$$

The required dialysate or replacement fluid sodium concentration was the sum of: (i) the patient's serum sodium concentration (nadir value within the prior 12 hours of CRRT initiation for the initial CRRT day, or the most updated value for all subsequent days); (ii) the desired change of the serum sodium for a

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24-hour period (recommended 6 mEq/l); and (iii) an additional correction factor of 2 mEq/l (if regional citrate anticoagulation [RCA] was used) or 4 mEq/l (if RCA was not used). The additional correction factor of 2 or 4 mEq/l higher than the desired goal of sodium concentration in the dialysate/replacement fluid has been shown to provide an accurate estimation for hyponatremia correction, assuming a delivered urea Kt/V of ~1.2 every 24 hours and that sodium kinetics during RRT are similar to urea kinetics.[7] The use of RCA may contribute to an additional sodium transfer of 9 to 12 mEq per hour and increase in serum sodium levels of ~2 to 3 mEq/l in a 24-hour period (calculations based on Anticoagulant Citrate Dextrose Solution A [ACD-A; sodium concentration of 224 mEq/l] and using CRRT prescription and clinical data of the first 3 patients who were treated under the protocol with hypothetical ACD-A rate [milliliters per hour] ranging from 1.2 to 1.5 times the blood flow). This approach of estimating the contribution of ACD-A to hyponatremia correction in patients receiving CRRT has been also shown by others.[9] If RCA was not used in the CRRT prescription, 50% of replacement fluid was recommended to be given prefilter to decrease filtration fraction and to dilute clotting factors in plasma and therefore attenuate filter clotting.

The CRRT-Hyponatremia Protocol: Patient Eligibility

Only those patients admitted to the ICU who required CRRT and had serum sodium levels less than 120 mEq/l were eligible for the protocol. The lowest patient's serum sodium measurement (nadir) in the 12-hour period before CRRT initiation was used in the initial calculation. After 24 hours of CRRT with hypotonic replacement and dialysate bags, the patient was reassessed, and the sodium concentration of both the replacement fluid and dialysate fluid was adjusted with the equation above using the patient's latest (updated) serum sodium levels. Therapy with hypotonic replacement and dialysate fluid was discontinued once the patient's serum sodium was corrected to a level of 130 mEq/l or greater, at which point the use of commercially available dialysate and replacement fluid bags (140 mEq/l of sodium) was initiated.

The CRRT-Hyponatremia Protocol: Step-by-Step Process and Procedures

The detailed step-by-step process (Figure 1) and procedures are outlined below:

1. Prescriber identifies a patient requiring CRRT with severe hyponatremia, serum sodium (sNa) <120 mEq/l.
2. Prescriber orders CRRT specifying nadir sNa (lowest value in the last 12 hours before initiation of CRRT), correction goal (6 mEq/l in a 24-hour period), dialysate/replacement fluid solutions, and total effluent rate (recommended ~25−30 ml/kg per hour).
3. Pharmacist receives and reviews order.
4. Pharmacist reviews patient's profile and laboratory data. Pharmacist reviews and confirms nadir sNa (patient safety checkpoint #1).
5. Pharmacist proceeds to activate the protocol and the low-sodium CRRT tool:
   a. Enters patient's identifying information (full name, medical record number, date of birth) Q4
   b. Enters nadir sNa
   c. Enters sNa correction goal (6 mEq/l in a 24-hour period)
   d. Enters dialysate/replacement fluid product
   e. Enters total effluent rate of CRRT
6. Pharmacist reviews all calculations from the low-sodium CRRT tool for accuracy (patient safety checkpoint #2):
   a. Goal of Na concentration in the dialysate/replacement fluid
   b. Compounding directions
   c. Concentration of each component in the dialysate/replacement fluid
   d. Number of bags to prepare
7. Pharmacy technician follows compounding directions to prepare bags.
8. Pharmacist reviews compounded bags for accuracy before delivering to the patient (bedside) (patient safety checkpoint #3).
9. Prescriber closely monitors the patient and makes adjustments to the CRRT-Hyponatremia Protocol at least every 24 hours in collaboration with the pharmacist (patient safety checkpoint #4). All concomitant hyponatremia correction maneuvers (e.g., 3% saline intravenous infusion or others) should be discontinued as soon as the CRRT-Hyponatremia Protocol is activated as part of the treatment plan. Special consideration to monitoring of interval improvement in urine output (for patients with AKI) or loss of significant amount of hypotonic fluids (e.g., drains, nasogastric suction, etc.) is critically important to prevent hyponatremia overcorrection. In addition, monitoring of significant hypotonic or hypertonic fluid gain from i.v. medications or enteral feeds should be considered if appropriate.

The CRRT-Hyponatremia Protocol: Dialysate and Replacement Fluid Sodium Dilution

Ostermann *et al.* first proposed dilution of commercially available products in 2010 by adding various

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Figure 1. Summary of key process, procedures, and safety checkpoints for the activation and continuation of the CRRT-Hyponatremia Protocol. CRRT, continuous renal replacement therapy.

volumes of sterile water to the replacement fluid.[6,10] In 2014, Yessayan *et al.* proposed a second method of exchanging equal volumes of replacement fluid with sterile water to achieve the desired sodium concentration.[7] Both methods have some disadvantages. The method of dilution by addition to the bag results in a large volume of sterile water added to the standard 5-L dialysate or replacement fluid bag, which may cause the CRRT machine's scale alarm system to trigger or require manipulation or calibration. Furthermore, this method is limited to the volume that will fit in the manufacturer's bag. The second method of exchanging sterile water for a volume of replacement fluid was found to be a much more time-consuming process from a sterile compounding perspective.

For the reasons outlined, a combination of the 2 previous methods was adopted. The capacity and integrity of dialysate and replacement fluid bags were tested and shown to accommodate an additional 1.4 L of fluid. Our CRRT machines (Prismaflex System) were tested with a total volume bag of 6 L for a period of 60 minutes on 3 separate occasions without triggering any scale-based alarms. Therefore, the maximum addition of sterile water allowed per protocol was determined to be 1 L. The volume of sterile water to be added, up to the maximum bag's capacity, to the dialysate fluid or replacement fluid to achieve the desired sodium concentration $[Na^+]$ can be given by the equation:

$$(A)\ \text{Volume to add} = \frac{5\,L \times (\text{initial}\,[Na^+] - \text{desired}\,[Na^+])}{\text{desired}\,[Na^+]}$$

(If less than the maximum additional volume that the bag can accommodate set at 1 L; initial $[Na^+]$ of commercially available dialysate and replacement fluid bags is 140 mEq/L)

When a sodium concentration was unobtainable by sterile water addition alone due to the bag's volume capacity, a portion of fluid was removed from the manufacturer's bag and then replaced with sterile water along with the additional 1 L (maximum of sterile water addition by protocol) as outlined with the equation below. Our hybrid method reduced the required volume to be removed from the manufacturer's bag and thus reduced the time needed to prepare the customized hypotonic fluid. The equations used to calculate volumes for this approach including

rounding to manageable volumes for compounding purposes are provided below:

$$(B)\ \text{Volume to exchange} = 5\,L - \frac{\text{desired}\ [Na^+]}{\text{initial}\ [Na^+]} \times (5\,L + 1\,L)$$

$$*\text{Total volume to exchange and add} = (A) + (B)$$

(Round to the nearest 5 mL; initial [Na^+] of commercially available dialysate and replacement fluid bags is 140 mEq/l)

The removal of dialysate or replacement fluid and addition of sterile water to the bag affects the concentration of the other electrolytes in the bag. Patients may require additional supplementation of these other components, particularly bicarbonate, phosphate, and potassium.[10,11] Regardless of the method used to prepare the dialysate and replacement fluid bags, the final concentration of each electrolyte should be calculated by multiplying its initial concentration by the ratio of the desired and initial sodium concentration of the dialysate or replacement fluid per the equation:

$$\text{Final}\ [\text{Electrolyte}] = \frac{\text{desired}\ [Na^+]}{\text{initial}\ [Na^+]} \times (\text{initial}\ [\text{Electrolyte}])$$

The developed spreadsheet-based tool (Supplementary Figure S1) was designed to complete these calculations based on the patient's nadir serum sodium, correction goal, and correction factor. The tool rounded compounding volumes to the nearest 5 ml and provided specific compounding directions for the pharmacy staff. The tool estimated the quantity of dialysate and replacement fluid bags to be compounded for the patient over a 24-hour period based on the prescribed CRRT effluent rate. In additionally, concentrations of each component of the bag (sodium, potassium, calcium, bicarbonate, etc.), estimated osmolarity, and total volume were provided for transfer to the order and documentation in the patient's electronic health record. This information was then available to all members of the multidisciplinary ICU team caring for the patient.

RESULTS

The CRRT-Hyponatremia Protocol: Patient Data

Data of the first 3 patients who were treated under the CRRT-Hyponatremia Protocol are reported. All of these patients were admitted to the ICU, had severe hyponatremia (serum sodium <120 mEq/l), and required CRRT for AKI management. Patient characteristics are detailed in Table 1. Targeted and gradual hyponatremia correction was achieved in all patients. One patient survived the hospitalization and was discharged on hemodialysis with poor chances of renal recovery due to severe AKI on underlying advanced CKD. One patient died in the hospital, and the other patient was transferred to inpatient hospice. None of the patients had end-stage renal disease at baseline (Table 1). Two patients were prescribed CVVHDF, and 1 patient received CVVH. There were no complications or adverse events related to the CRRT-Hyponatremia Protocol. Specific details about the CRRT prescription for each patient are reported in Table 2. RCA was not used in any of the CRRT prescriptions for these 3 patients. Therefore, no firm conclusions can be drawn in relation to the use of RCA in this context.

In Table 3, we compared the estimated sodium dilution targets using (i) the single-pool urea kinetic modeling proposed by Yessayan *et al.*,[7] customized to each individual CRRT prescription; and (ii) the simplified method of sodium dilution applied in our CRRT-Hyponatremia Protocol, which used the desired goal of sodium correction in a 24-hour period plus the addition of a correction factor of 2 mEq/l (if RCA was used) or 4 mEq/l (if RCA was not used). A non−clinically significant median difference of 1.7 mEq/l in the sodium dilution target between the 2

Table 1. Clinical characteristics of the first 3 patients treated under the CRRT-Hyponatremia Protocol Q10

	Patient 1	Patient 2	Patient 3
Age, yr	47	70	64
Gender	Female	Male	Male
Comorbidity	HTN, PAD	COPD, HTN, liver cirrhosis	A-fib, CHF, DM, DVT
ICU admission diagnosis	Acute respiratory failure	Acute liver failure due to alcohol intoxication	Acute respiratory failure, sepsis
CKD at baseline	CKD stage 4	No	No
AKI diagnosis	ATN/ischemic nephropathy	ATN + HRS	ATN
Urine output at time of CRRT initiation	Anuric	Anuric	Anuric
Volume status	Hypervolemia	Hypervolemia	Hypervolemia
Hospital LOS, days	21	11	9
ICU LOS, days	17	10	2
Hospitalization outcome	Discharge on HD	Inpatient hospice	Hospital death

A-fib, atrial fibrillation; AKI, acute kidney injury; ATN, acute tubular necrosis; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; DM, diabetes mellitus; DVT, deep venous thrombosis; HD, hemodialysis; HRS, hepatorenal syndrome; HTN, hypertension; ICU, intensive care unit; LOS, length of stay; PAD, peripheral artery disease.

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Table 2. CRRT prescription of the first 3 patients treated under the CRRT-Hyponatremia Protocol

	Patient 1	Patient 2	Patient 3
Weight, kg	77.9	102.7	113.0
Hematocrit, %	27.5	22.0	28.0
CRRT modality	CVVHDF	CVVH	CVVHDF
CRRT solution	Phoxillum BK 4/2.5	Phoxillum BK 4/2.5	Phoxillum BK 4/2.5
Total days of CRRT	4	2	1
Total days of customized sodium solution	2	2	1
Filter type	HF 1400	HF 1400	HF 1400
Blood flow, ml/min	250	250	250
Dialysate fluid rate, ml/h	750	—	2000
Replacement fluid rate, ml/h	1500 (50% prefilter)	2000 (50% prefilter)	2000 (50% prefilter)
Fluid removal rate, ml/h	150	100	0
Anticoagulation	None	None	None
Prescribed effluent dose, ml/kg per h	30.8	20.4	35.4
Effective effluent dose, ml/kg per h[a]	28.8	18.8	32.4

CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration.
[a]Corrected for prefilter dilution.

methods was observed in the 3 patients ($P = 0.44$). Finally, Figure 2 represents the observed serum sodium correction in relation to the predicted (per protocol) correction and the sodium dilution target of the dialysate/replacement fluid bags.

DISCUSSION

We report a single-center quality improvement project that resulted in the development and implementation of the CRRT-Hyponatremia Protocol for customized and slow correction of severe hyponatremia (serum sodium < 120 mEq/l) in ICU patients requiring CRRT. We described our experience with the first 3 patients treated under our protocol and provided details about the process and procedures from the initial prescription until protocol deactivation. Our report adheres to SQUIRE guidelines and recommendations.[12]

Proponents of and Hindrances to Successful Implementation

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Successful implementation of the CRRT-Hyponatremia Protocol relied on several factors. Most importantly was the strong multidisciplinary collaboration among nephrologists, pharmacists, intensivists, and ICU nurses. This constructive and sustained interaction produced a standardized tool that identified patients eligible for the protocol, checked and verified automated calculations, ensured appropriate compounding directions, and provided details about the dialysate and replacement fluid solutions for all members of the patient-care team. The key elements of the development and successful implementation of the CRRT-Hyponatremia Protocol are summarized in Table 4.

A pharmacy with a compliant sterile compounding space as well as staff trained in aseptic techniques is vital to safely manipulating the dialysate and replacement fluid bags. The quality and integrity of the commercially available bags is also important. Not all manufacturers produce a bag that can accommodate or withstand the additional weight of the additional fluid. Careful consideration should be made concerning the quality of the bags for this reason. If additional volume is to be added to the bag, the team must test the compatibility of these bags with the CRRT machines to ensure that

Table 3. Estimated sodium dilution target for the initial day of the CRRT-Hyponatremia Protocol activation

	Estimated sodium dilution by urea kinetic modeling method (initial day)[a]		Simplified method for CRRT-Hyponatremia Protocol (initial day)[b]	
Patient 1	Nadir sNa, mEq/l	117	Nadir sNa, mEq/l	117
	Goal of correction (mEq/l in 24 h)	6	Goal of correction (mEq/l in 24 h)	6
			Correction factor (mEq/l)	6 + 4 = 10
	Sodium dilution target (mEq/l)	117 + 8.0 = 125.0	Sodium dilution target (mEq/l)	127
Patient 2	Nadir sNa, mEq/l	105	Nadir sNa, mEq/l	105
	Goal of correction (mEq/l in 24 h)	6	Goal of correction (mEq/l in 24 h)	6
			Correction factor (mEq/l)	6 + 4 = 10
	Sodium dilution target (mEq/l)	105 + 11.3 = 116.3	Sodium dilution target (mEq/l)	115
Patient 3	Nadir sNa, mEq/l	119	Nadir sNa, mEq/l	119
	Goal of correction (mEq/l in 24 h)	6	Goal of correction (mEq/l in 24 h)	6
			Correction factor (mEq/l)	6 + 4 = 10
	Sodium dilution target (mEq/l)	119 + 8.3 = 127.3	Sodium dilution target (mEq/l)	129

CRRT, continuous renal replacement therapy.
[a]Using single-pool urea kinetic modeling and the actual CRRT prescription for each patient. Sodium dilution target $[Na^+]$ = nadir serum $[Na^+] + \frac{\text{desired } \Delta \text{ serum}[Na^+]}{1 - e^{-D \times 24\,h/V}}$, where D = effective effluent dose of CRRT in a 24-h period in liters and V = volume of distribution (total body water) of the patient in liters (0.5 × weight for females and 0.6 × weight for males, using weight determined on the initial day of the CRRT-Hyponatremia Protocol activation).
[b]Simplified method for the CRRT-Hyponatremia protocol (goal of correction in a 24-h period [mEq/L] + correction factor of 2–4 mEq/L)

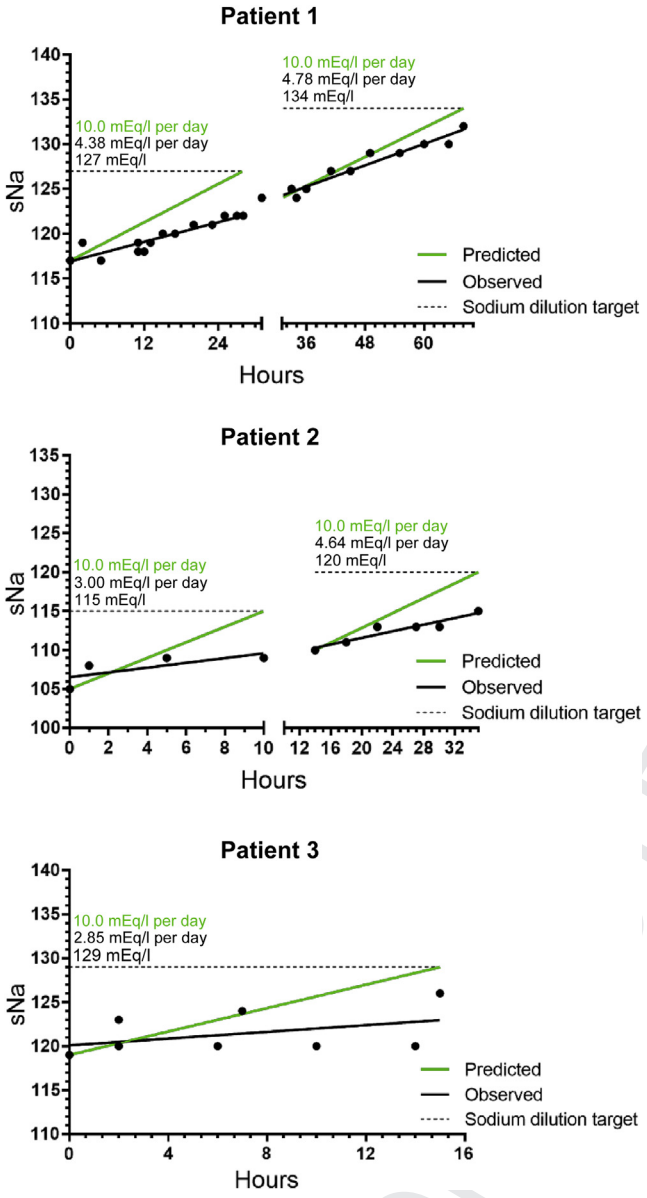

Figure 2. Observed serum sodium correction in relation to the predicted (per protocol) correction and sodium dilution target of the dialysate/replacement fluid bags. These data correspond to the first 3 patients treated under the CRRT-Hyponatremia Protocol. Green line represents the predicted change in serum sodium levels according to the sodium dilution target. Black line represents the observed change in serum sodium levels in each patient.

additional weight and volume do not interfere with inline safety measures and calibration of the scales.

Education was provided to all members of the patient-care team and was essential to the effective implementation of this protocol. Specifically, education regarding bag overfill and negligible concentration changes was provided to prescribers to ensure standardization for use of this therapy. Recognizing the presence of the additional fluid (sterile water) is needed in order to estimate the unintended dilution of other dialysate and replacement fluid constituents that are

Table 4. Key elements for the successful implementation of the CRRT-Hyponatremia Protocol

1. Identification of the need for the protocol and assembling of a multidisciplinary team to develop and implement the protocol
2. Collaboration among nephrologists, pharmacists, pharmacy technicians, intensivists, and ICU nurses through effective channels of communication
3. Development of an electronic spreadsheet–based CRRT tool to standardize the process of calculating and ordering custom-made hypotonic fluids for CRRT
4. Focus on safety measures such as sterile compounding space, integrity of manufacturer bags, and compatibility of manipulated bags with available CRRT machines
5. Development of a special electronic order set that incorporates a 24-h timeout alert and a clinical decision support system with a link to the protocol
6. Close patient and CRRT monitoring, including interval improvement in urine output, concomitant administration of hypertonic or hypotonic intravenous fluids, hypotonic fluid loss, and review of CRRT flowsheets
7. Education to clinicians (prescribers), pharmacy personnel, ICU nurses, and all members of the patient-care multidisciplinary ICU team
8. Data capturing through electronic health records for all patients who are included in the protocol; this is essential to monitor patient safety, protocol utilization, and sustainability of the protocol

CRRT, continuous renal replacement therapy; ICU, intensive care unit.

important for CRRT. In addition, nursing education was vital to the success of this therapy, as ICU nurses in our institution are tasked with management of the CRRT machines at the bedside. Close communication among the prescriber, the pharmacist, and the ICU nurse caring for the patient was essential in order for the patient to receive the correct therapy in a timely manner.

The monitoring of clinical and CRRT parameters should be established through collaboration among ICU nurses, pharmacists, nephrologists, and intensivists prior to protocol activation. A safeguard 24-hour limit (Figure 1) was built into the CRRT order set to prompt review of the CRRT prescription based on updated patient laboratory parameters, as well as to guide future therapy. In addition, the pharmacist monitoring treatment should contact the nephrology/ICU team to ensure that the CRRT prescription has been reviewed and renewed. In general, this modality of custom-made (sodium dilution) solution is limited to 72 hours, but can be extended based on discussion between members of the ICU team.

It is important to note that there are other methods for the management of severe hyponatremia in patients requiring CRRT that are based on customization of the CRRT circuit rather than manipulation (sodium dilution) of the dialysate/replacement fluid bags.[8,9] These methods are based primarily on the addition of 5% dextrose solution (D5W, 0 mEq/l of sodium) to the post-filter replacement fluid, with the goal of achieving an end-circuit sodium concentration that prevents hyponatremia overcorrection.[8,9] Nonetheless, all proposed methods for effective and safe hyponatremia correction in patients receiving CRRT are based on the prescribed effluent dose and do not account for downtime and filter degradation or clotting. Therefore,

close monitoring of these patients is mandatory. Most importantly, none of these mathematical methods have been fully validated in clinical trials examining not only the goal and rate of sodium correction but also patient-centered outcomes.

In conclusion, we have demonstrated a multidisciplinary approach for the development and successful implementation of the CRRT-Hyponatremia Protocol, which is based on the use of customized dialysate and replacement fluid solutions for the gradual correction of severe hyponatremia (serum sodium <120 mEq/l) in ICU patients who require CRRT. Our protocol was derived from single-pool urea kinetic modeling and utilized a hybrid technique of volume exchange and addition of sterile water for sodium dilution of commercially available dialysate and replacement fluid bags. We have reported data pertaining to the first 3 patients who were treated under this protocol and have described proponents and hindrances to successful implementation. Nonetheless, our protocol requires specific logistics that may not be available or feasible in other institutions. Importantly, it is not known whether the use of customized dialysate and replacement fluid solutions for the gradual correction of severe hyponatremia in ICU patients requiring CRRT has a significant impact on patient outcomes. Further research and quality improvement initiatives are needed in this susceptible population.

DISCLOSURE

JAN disclosed consulting agreements with Baxter Healthcare Inc. (Deerfield, IL) that are not related to this project. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Figure S1. CRRT-Hyponatremia Protocol spreadsheet-based tool for standardized process and accurate compounding of dialysate and replacement fluid bags.
Supplementary material is linked to the online version of the paper at www.kireports.org.

REFERENCES

1. Palmer BF. Hyponatremia in the intensive care unit. *Semin Nephrol*. 2009;29:257–270.
2. Pokaharel M, Block CA. Dysnatremia in the ICU. *Curr Opin Crit Care*. 2011;17:581–593.
3. Sterns RH, Hix JK, Silver S. Treatment of hyponatremia. *Curr Opin Nephrol Hypertens*. 2010;19:493–498.
4. Martin RJ. Central pontine and extrapontine myelinolysis: the osmotic demyelination syndromes. *J Neurol Neurosurg Psychiatry*. 2004;75(suppl 3):iii22–iii28.
5. Neyra JA, Goldstein SL. Optimizing renal replacement therapy deliverables through multidisciplinary work in the intensive care unit. *Clin Nephrol*. 2018;90:1–5.
6. Vassallo D, Camilleri D, Moxham V, Ostermann M. Successful management of severe hyponatraemia during continuous renal replacement therapy. *Clin Kidney J*. 2012;5:155–157.
7. Yessayan L, Yee J, Frinak S, Szamosfalvi B. Treatment of severe hyponatremia in patients with kidney failure: role of continuous venovenous hemofiltration with low-sodium replacement fluid. *Am J Kidney Dis*. 2014;64:305–310.
8. Hasegawa M, Taki F, Shimizu K, et al. A case of continuous venovenous hemofiltration for anuric acute kidney injury with severe hyponatremia: a simple method involving flexible adjustment of sodium replacement solution. *Kidney Int Rep*. 2016;1:85–88.
9. Rosner MH, Connor MJ Jr. Management of severe hyponatremia with continuous renal replacement therapies. *Clin J Am Soc Nephrol*. 2018;13:787–789.
10. Ostermann M, Dickie H, Tovey L, Treacher D. Management of sodium disorders during continuous haemofiltration. *Crit Care (London, England)*. 2010;14:418.
11. Bender FH. Successful treatment of severe hyponatremia in a patient with renal failure using continuous venovenous hemodialysis. *Am J Kidney Dis*. 1998;32:829–831.
12. Ogrinc G, Davies L, Goodman D, et al. SQUIRE 2.0 (Standards for Quality Improvement Reporting Excellence): revised publication guidelines from a detailed consensus process. *Am J Crit Care*. 2015;24:466–473.