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Original Article

Acute RRT

High sodium continuous veno-venous hemodialysis with regional citrate anticoagulation and online dialysate generation in patients with acute liver failure and cerebral edema

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Abstract

Introduction: Acute liver failure is associated with a high mortality rate. Induction of plasma hypertonicity with mannitol or hypertonic saline remains the cornerstone in the management of resultant cerebral edema. Significant disadvantages of this approach include poor or unpredictable control of serum sodium concentration and volume expansion, among others.

Methods: We used high sodium continuous veno-venous hemodialysis with regional citrate anticoagulation and online dialysate generation to accurately control the serum sodium in eleven patients with acute liver failure, renal failure, and cerebral edema. We used a Fresenius 2008 K/K2 machine in hemodialysis mode to deliver a blood flow of 60 ml/minute and dialysate flow of 400 ml/minute. Our previously published protocol results in complete removal of infused citrate by the dialyzer. Online clearance calculations were used to model the time required to reach the target serum sodium.

Findings: All patients achieved serum sodium within 2 mEq/L of target without fluctuations or rebound. Nine patients survived without requiring liver transplantation and two died despite reaching the prescribed serum sodium target. We did not encounter any citrate toxicity.

Discussion: We describe a novel approach for delivering continuous osmotherapy to patients with acute liver failure, renal failure, and cerebral edema. In comparison to standard therapy, the described modality enables precise titration of serum sodium without undesirable fluctuations in extracellular fluid volume. A particular advantage is zero delivery of citrate to this vulnerable group of patients with acute liver failure.

Key words: Acute liver failure, cerebral edema, continuous veno-venous hemodialysis, regional citrate anticoagulation, online dialysate generation

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INTRODUCTION

Acute liver failure (ALF) affects approximately 2000 persons annually in the United States[1] and is caused by acetaminophen toxicity in about half of the cases.[2] Acute kidney injury (AKI) develops in 75% of cases caused by

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Table 1 Patients' demographics and clinical settings

Case no.	Age, gender	Etiology of ALF	SOFA score	MELD score	Baseline renal function	Vaso-pressors	MV	ICP monitor
1	43, F	Septic shock	17	39	Normal	Yes	No	No
2	50, F	Budd-Chiari	10	45	Normal	No	No	No
3	24, F	APAP	14	23	Unknown	Yes	No	No
4	40, F	APAP	16	35	Normal	Yes	Yes	Yes
5	34, F	APAP	16	33	Normal	Yes	Yes	Yes
6	42, F	APAP	14	42	Normal	Yes	No	No
7	25, M	APAP	14	45	Unknown	Yes	No	No
8	19, F	APAP	11	51	Unknown	No	No	No
9	36, F	APAP	14	36	Normal	Yes	Yes	Yes
10	54, F	APAP	13	37	Normal	Yes	Yes	Yes
11	44, F	Unknown	9	29	Normal	Yes	Yes	Yes

Patients 2 and 5 did not survive.
ALF = acute liver failure; APAP = *N*-acetyl-para-aminophenol; ICP = intra-cranial pressure; MELD = model for end-stage liver disease score at time of initiation of ol-CVVHD-RCA; MV = mechanical ventilation; SOFA = sequential organ failure assessment. Initial score of more than 11 is associated with a mortality rate >90%, while a score of 8-11 is associated with a mortality rate of 60%.

acetaminophen toxicity and much less with other etiologies.[3,4] Cerebral edema (CE) is one of the most common complications, and occurs in up to 80% of patients with severe encephalopathy.[1] Without liver transplantation, the mortality rate is around 30% usually in the setting of infection and CE.[1,4–7] The etiology of CE is multifactorial and not fully understood. It might result from increased brain water content induced by the accumulation of osmotically active glutamine derived from ammonia in the astrocytes.[8] Rapid dialytic removal of urea and other uremic solutes might also induce or exacerbate CE.[9–11] Several strategies have been implemented to prevent and treat CE, with induction of systemic plasma hypertonicity using hypertonic saline or mannitol therapy being the cornerstone of management. In patients suffering from concomitant kidney injury, plasma hypertonicity can be regulated by adjusting the prescription of continuous renal replacement therapy (CRRT) to achieve and maintain a specific higher systemic sodium level ($[Na]_{Sys}$). Herein, we describe our experience regulating plasma hypertonicity in ALF using a high-sodium online-generated dialysate with 24-hour continuous veno-venous hemodialysis and regional citrate anticoagulation (ol-CVVHD-RCA).

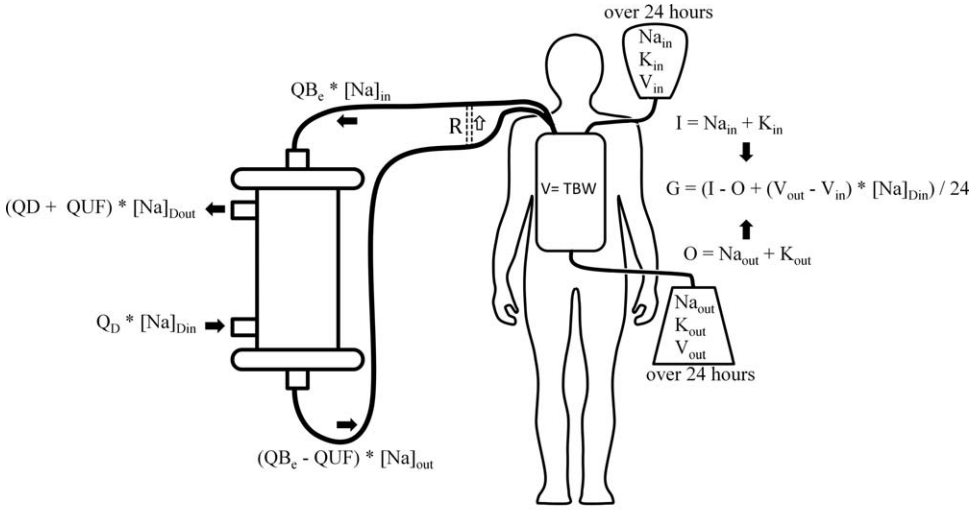
METHODS

Patient selection

Since the implementation of our near-automated ol-CVVHD-RCA program at Henry Ford Hospital[12,13] starting in 2009, we used it to regulate plasma hypertonicity in most patients with ALF, CE, and AKI requiring CRRT. Table 1 summarizes the demographics and clinical settings of 11 consecutive patients who presented between January 2011 and July 2013. Our patients were severely ill with an elevated predicted mortality rate thus ol-CVVHD-RCA was our CRRT modality of first choice. Following an institutional protocol, five patients had an intra-cranial pressure (ICP) monitor inserted after receiving hypertonic saline at the first clinical or radiological signs of CE.

CRRT therapy

As previously described,[12,13] we used a Fresenius 2008K or K2 (Fresenius Medical Care, North America, Waltham, MA, USA) machine in pediatric intermittent hemodialysis (IHD) mode to deliver a blood flow (QB) of 60 mL/min and a dialysate flow (QD) of 400 mL/min. CRRT is achieved by running 9-hour 59-minute IHD sessions separated by a 20-second machine reset procedure. Vascular access was established through central venous hemodialysis catheters. We used the high-flux and high-efficiency Rexeed 15S hemodialyzer (Asahi-Kasei Corp., Tokyo, Japan) which delivers a substantial dose of internal hemofiltration-backfiltration due to its very high ultrafiltration coefficient. The delivered net ultrafiltration rate ranged from 0 to 200 mL/hour (possible 0–500 protocol range), based on individual settings. Online prescription (selection from the machine screen menu) was used to generate a dialysis fluid with a fixed sodium level up to 155 mEq/L (range 130–155). The conductivity of the fresh dialysate was monitored and is a surrogate for the final dialysate sodium concentration. Our 24-hour ol-



Eq. (1) $D_{eff} = [D * (1- R)] / [1 - R * (1- D/QB_e)]$

Eq. (2) $D_{eff} = K_{ecn}$ (measured)

Eq. (3) $TBW_{(t)} = TBW_{(0h)} + (DW_{(t)} - EEW)$

Eq. (4) $[Na]_{Sys(t)} = [Na]_{Din} + ([Na]_{Sys(0h)} - [Na]_{Din}) * e^{-Kecn*t/TBW} + G/K_{ecn} * (1- e^{-Kecn*t/TBW})$

Figure 1 Top: sodium fluxes across the dialyzer. Due to complete equilibrium with the dialysate $[Na]_{out} = [Na]_{Din}$, any infusion or fluid loss which is not isotonic to $[Na]_{Din}$ will contribute to the arbitrary kinetic construct "sodium generation" G (mEq/h) as defined in the figure; net ultrafiltrate is isotonic and thus is ignored. If all gain and loss of fluid is isotonic to $[Na]_{Din}$ then G will be zero. QB_e effective blood flow for sodium (blood water flow), QD dialysate flow, QUF ultrafiltration flow. All flows are in L/h. $[Na]_{in,out}$ sodium concentration (mEq/L) at the dialyzer blood inlet and outlet, respectively. $[Na]_{Din,Dout}$ sodium concentration (mEq/L) at the dialyzer dialysate inlet and outlet, respectively. $Na_{in,out}$ amount of sodium (mEq/24 h) gained or lost, respectively. $K_{in,out}$ amount of potassium (mEq/24 h) gained or lost, respectively. $V_{in,out}$ volume of water (L/24 h) gained through infusion or lost through drainage or loss of body fluids, respectively. R: access recirculation. Bottom: sodium kinetic equations. Equation 1 derives the K_{eff} (effective urea clearance in L/h) after correcting dialyzer urea clearance (K, in L/h) for access recirculation. In our venous-venous access model there is no cardiopulmonary recirculation. Therefore, as Equation 2 shows K_{eff} can be measured by the K_{ecn}: effective conductivity clearance (L/h) which in turn is near equal to D (effective sodium dialysance in L/h). Equation 3 calculates the $TBW_{(t)}$ (TBW in L at time t) which is equal to the initial $TBW_{(0h)}$ derived from the EEW (estimated euvolemic weight in Kg) using the Watson's formula in addition to any weight gain which is considered 100% water. The latter is the difference between the $DW_{(t)}$ (daily weight at time t in Kg) and EEW. Finally, we derive Equation 4 to predict the patient's systemic sodium concentration. $[Na]_{Sys(t)}$ the systemic sodium concentration at time t (mEq/L). $[Na]_{Sys(0h)}$ the systemic sodium concentration at initiation of dialysis, t: time on dialysis (h). To avoid a more complex kinetic equation we assume that TBW is fixed, still achieving clinically acceptable accuracy. We also assume that the correction factor applied when reporting serum Na concentrations from the clinical laboratory and the Donnan-factor on the dialyzer cancel each other out and therefore can be omitted.

CVVHD-RCA therapy delivers about 3 L of urea clearance and sodium dialysance per hour and therefore was not expected to provide a rapid, immediate increase in $[Na]_{Sys}$. Since CE is a medical emergency that necessitates immediate intervention, all patients initially received either 23.4% saline as intravenous boluses ("saline bullets") or a continuous infusion of 3% saline through a central venous catheter. This maneuver provided the desired acute rise in $[Na]_{Sys}$ and plasma tonicity, with ol-CVVHD-RCA then used to maintain the $[Na]_{Sys}$ within the target range. Weaning of plasma hypertonicity was dictated by radiologic and clinical signs of resolution of CE. Owing to the availability of highly reliable conductivity sensor technology standard on all modern hemodialysis machines, we measured the effective ionic dialysance (K_{ecn})[14] during CRRT every 100 minutes and used it to quantify the volume of systemic blood equilibrating with the fresh dialysate sodium level ($[Na]_{Din}$) while accounting for the variation in plasma protein level, red blood cell permeability, and Donnan factor expected to occur in a critically ill patient. Figure 1 details our sodium kinetic modeling, where Equation 4 was used to predict the

$[Na]_{Sys}$.[15] Sodium and potassium total content and total body water (TBW) volume changes derived from the gain or loss of fluids non-isotonic to $[Na]_{Din}$ were included in the calculations and represented by the artificial kinetic term, sodium generation per hour, *G* averaged over a 24-hour period. This was done to account for the non-negligible effect on $[Na]_{Sys}$ of continuous dilute IV fluids (e.g., catecholamines or *N*-acetylcysteine in 5% dextrose-water) often needed in the care of ALF patients. Sodium lost with gastric secretions and stool was practically difficult to account for and was ignored. Urine output was negligible. For mathematical simplicity, we used single-pool fixed-volume sodium kinetic modeling[16] thus we did not account for the changes in TBW induced by fluid administration or body fluid losses naturally or through ultrafiltration. Finally, the pre-filter use of hypernatremic citrate infusion did not affect the return blood sodium level or the $[Na]_{Sys}$ as the protocol ensured that the circuit blood sodium was fully equilibrated to the fresh dialysate fluid sodium level. Systemic citrate accumulation was avoided even in the assumed absence of liver metabolism of citrate as all the infused citrate (>95%) was dialyzed out in a single pass and hence never entered the systemic circulation.

The time, t in hours required to achieve the desired $[Na]_{Sys}$ target was estimated predominantly from an equation using the prescriber set difference between the systemic sodium level and the fresh dialysate sodium level at start of the CRRT modeling period ($[Na]_{Sys(0h)} - [Na]_{Din}$), multiplied by the exponential term $-D_{eff} \times t/V = -K_{ecn} \times t/TBW$ (Figure 1). As we did not expect multi-compartment sodium kinetics during our low efficiency continuous dialysis modality,[16] the single-pool fixed-volume sodium kinetic modeling equation was used:

$$[Na]_{Sys(t)} = [Na]_{Din} + \left([Na]_{Sys(0h)} - [Na]_{Din}\right) * e^{-Kecn * t/TBW} + G/K_{ecn} * \left(1 - e^{-Kecn * t/TBW}\right)$$

where the effective sodium dialysance D_{eff} (L/hour) is replaced by the about equal effective ionic dialysance K_{ecn} (L/hour) which in turn is very accurately and automatically measured by the dialysis machine about every 2 hours during CRRT. The K_{ecn} is about equal to K_{eff} which represents the effective urea clearance and allows us to express the delivered CRRT dose in terms of estimated standard urea Kt/V. A standard urea Kt/V of 1.2 is about equivalent to 30 mL/kg/hour of post-dilution equivalent continuous urea clearance. The t is the time needed to achieve the desired $[Na]_{sys}$ in hours, V the apparent volume of distribution of sodium in L and can be replaced by an estimate of the TBW. The calculation of the artificial kinetic term G in mEq/hour is only needed if the patient is experiencing large fluid gains or losses non-isotonic to the fresh dialysate and can be ignored otherwise. During the ol-CVVHD-RCA with QB of 60 mL/min, we recorded around one-thousand K_{ecn} readings with a mean ± standard error of 55.44 ± 0.1 mL/mn. Assuming a patient with TBW of 45 L and $[Na]_{Sys(0h)}$ of 140 mEq/L without the use of HS, a desired goal serum sodium of 153 mEq/L at 24-hour into ol-CVVHD-RCA ($[Na]_{Sys(24h)}$) and fresh $[Na]_{Din}$ of 155 mEq/L, the NaRR (or the reduction of the sodium difference between systemic sodium at start of the ol-CVVHD-RCA session and the fresh dialysate sodium) will be equal to 0.86, derived from: $([Na]_{Sys(24h)} - [Na]_{Sys(0h)})/([Na]_{Sys(0h)} - [Na]_{Din})$. When using the equation above, t required to reach steady state with $[Na]_{Sys} = [Na]_{Din}$ will be about 27 hours. These kinetic predictions explain our clinical practice of using hypertonic saline initially to acutely raise the $[Na]_{Sys}$ concentration followed by the ol-CVVHD-RCA mostly to maintain the goal $[Na]_{Sys}$. During modeling we ignored the effect of net ultrafiltration (fixed volume kinetic model) as it was expected to be isotonic to the $[Na]_{Din}$ and hence not impact the $[Na]_{Sys}$ significantly. We also did not calculate the difference between the laboratory reported serum sodium level and the blood water sodium concentration nor the impact of the Donnan factor on sodium fluxes on the dialyzer (fortuitously the effects of these latter simplifications essentially cancel out each other). The resulting fixed volume, single-pool sodium dialysance equation is simple enough for routine clinical use and appears to be clinically sufficiently accurate during the conditions of ol-CVVHD-RCA.

RESULTS

The duration of high sodium ol-CVVHD-RCA treatment ranged from 4 to 13 days. Within 24 hours of start, all patients had their sodium levels at or around the specified target. Severe hypernatremia or unexpected changes in $[Na]_{Sys}$ did not occur in any patient. Similarly, the $[Na]_{Sys}$ was maintained throughout the duration of therapy, and was not significantly lowered despite the large loads of free water used to deliver antibiotics and/or continuous infusions of pressors and antidotes such as *N*-acetylcysteine in hypotonic IV fluids. Figure 2 provides details regarding the actual $[Na]_{Sys}$, the $[Na]_{Sys}$ goal, and the prescribed fresh dialysate sodium concentration $[Na]_{Din}$. Using the ol-CVVHD-RCA approach, we did not encounter any complication related to citrate accumulation or toxicity such as ionized hypocalcemia or abnormally high

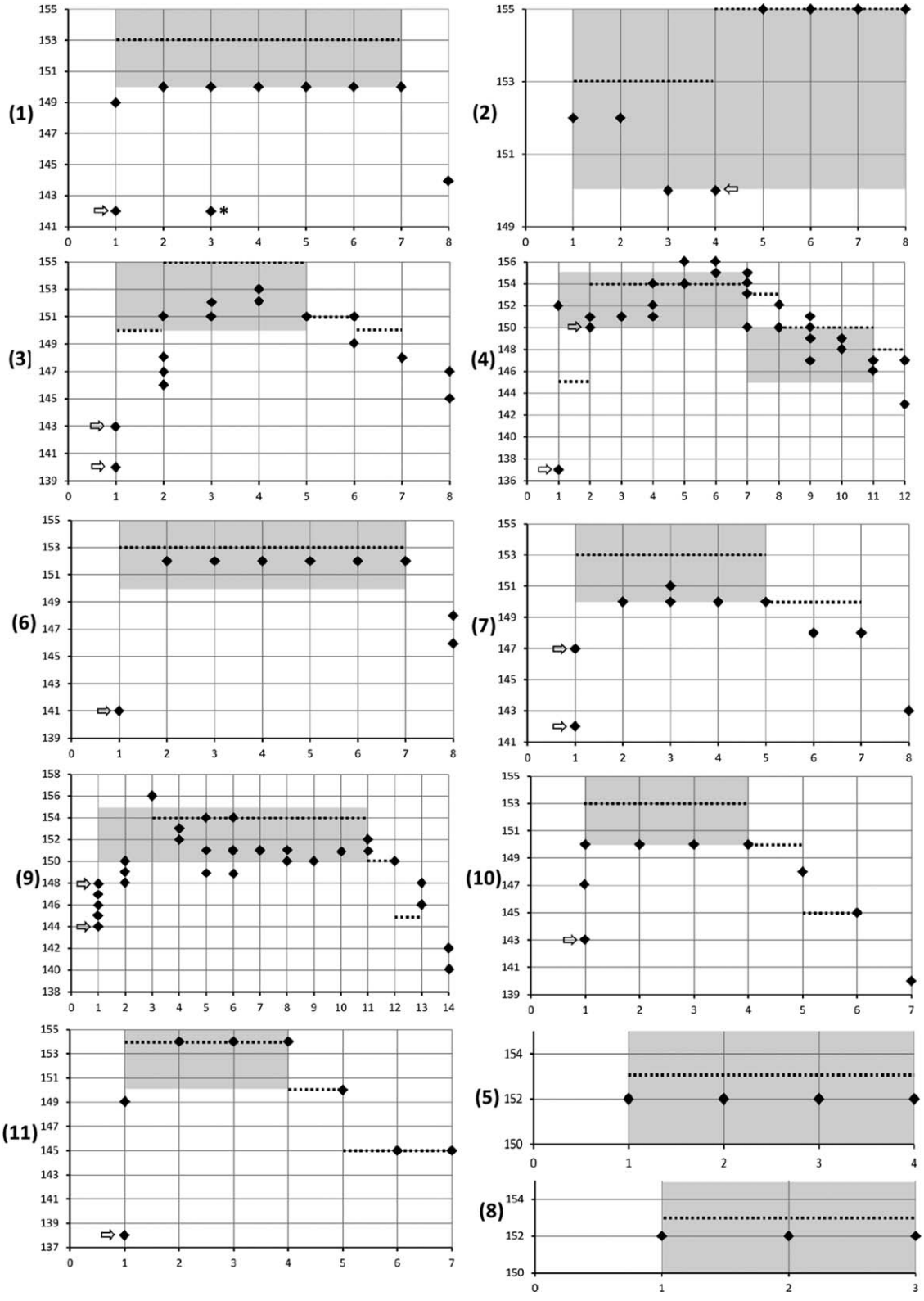

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Figure 2 Individual serum, dialysis fluid, and target sodium levels. X-axis indicates time in days and Y-axis denotes serum sodium concentration (mEq/L). Filled diamonds (◆) and broken (- - -) lines indicate achieved serum sodium levels and dialysate sodium concentrations, respectively. Solid arrows indicate administration of 20 mL of 23.4% saline bolus. Shaded areas indicate desired serum sodium concentration range. Note that identical serum sodium values throughout a day are superimposed. The decrease in the dialysate sodium indicates the weaning from osmotherapy and the disappearance of the broken line indicated the stopping of CVVHD-RCA. Patients (2) and (5) died. Patients (5) and (8) depicted in the right lower corner underwent the shortest duration of therapy. * sodium level likely a laboratory error; rechecked immediately and was 150 mEq/L.

total-to-ionized calcium ratio. One hundred and sixty serum ionized calcium levels out of 162 were within normal laboratory reference of 1 to 1.3 mmol/L. Two values of 0.91 and 1.33 mmol/L were of no clinical significance. For patients who had an ICP monitor, we did not observe any increase in the ICP at the start or throughout the ol-CVVHD-RCA therapy, including patients who received this treatment the longest (Table 2). The modality-related downtime was 53.5 hours of 1902 prescribed hours, accounting for 2.81%. The patient suffering from Budd-Chiari syndrome as well as one patient with acetaminophen toxicity died despite maintaining target $[Na]_{Sys}$ levels. Among the 9 patients who survived, none required liver transplantation. Seven patients had normalization of their serum creatinine and liver function tests, while the remaining 2 had partial improvement in both organ functions and were discharged without requiring outpatient dialysis and were lost to follow-up.

DISCUSSION

The regeneration of hepatocytes in patients surviving ALF starts after 3 days[17] with restoration of liver function occurring within 10 days.[18] Optimal organ support is crucial within this 10-day window while awaiting liver recovery, especially managing any concomitant AKI and CE. Frequently used agents such as mannitol and hypertonic saline are associated with various adverse events, including volume expansion and rebound CE especially during sudden withdrawal without prior weaning.[19–25] In this paper, we assume that osmotherapy delivered through the modification of the replacement/dialysate fluid sodium level offers numerous advantages over the conventional methods. The desired $[Na]_{Sys}$ can be smoothly maintained with less risk of hypernatremia, and gradually reversed at the end of therapy with less risk for rebound CE. In addition, the volume overload and the metabolic disturbances resulting from the renal failure itself or from the induced hypernatremia, such as metabolic acidosis, hypokalemia, or hyperkalemia, can be easily addressed and managed. The use of a modified dialysate sodium concentration has been previously reported for the management of dysnatremias.[26–28] In a 5 L bag, the sodium concentration can be raised from 140 to 154 mEq/L by the addition of 17.5 mL of 23.4% hypertonic saline (sodium concentration of 4 mEq/mL). This approach has three major drawbacks: significant financial cost of CVVH compared to the much less expensive ol-CVVHD-RCA, an additional workload imposed on the pharmacy personnel who perform the mixing, and the risk of contamination and errors during the injection of HS into the fluid bags. The last concern is highly significant as fatal errors during the compounding of replacement fluid bags have been reported.[29] For these reasons, many hospital pharmacies prohibit the modifications of CRRT fluid bags. Moreover, the weaning phase of hypernatremia when the target serum sodium $[Na]_{Sys}$ is gradually decreased might be difficult with the need for repetitive calculations. All of these

Table 2 Intra-cranial pressure values before and during ol-CVVHD-RCA

Case No	At insertion of ICP monitor	At initiation of ol-CVVHD-RCA	6 h	1 d	2 d	3 d	4 d	5 d	6 d	7 d
4	18	18	15	10	6	8	7	9	7	
5	19	5	13	5	95	111				
9	17	5	9	8	2	3	4	4	9	6
10	22	10	19	12	18	14				
11	17	19	19	5	8	2	2			

Intra-cranial pressure (ICP) values in mmHg of five patients who had an ICP monitor insertion. Data represents ICP at the time of insertion of the ICP monitor, at the initiation of ol-CVVHD-RCA, after 6 h, and up to 7 d. All patients received hypertonic saline before the insertion of the ICP monitor due to radiographic signs of cerebral edema and at initiation of ol-CVVHD-RCA. Patient 5 did not survive.

represent possibilities for additional error and wasting of incompletely utilized fluid bags. This ol-CVVHD-RCA protocol offers numerous advantages over conventional continuous RRT (CRRT), including much less cost, simpler logistics of therapy delivery, and less risk of dosing errors. This method warrants less frequent laboratory testing given the general stability of the $[Na]_{Sys}$, and helps the intensive care team focus on addressing some of the other complex issues. The weaning phase of hypernatremia specifically proved smoother, with the target sodium and bicarbonate in the fresh dialysate adjusted as needed through simply pressing a few buttons on the machine screen. It is important to emphasize that citrate should not be used in patients with ALF unless the single pass dialyzer removal of citrate exceeds at least 80% (95–98% in the current protocol). In addition, the dialysis modality used should have the least possible downtime to avoid dangerous fluctuations in the serum sodium levels. A key feature of our model is the ability to measure K_{ecn} repeatedly and provide feedback about vascular access and dialyzer performances in delivering the prescribed sodium dialysance. This is a crucial safety measure that eliminates the risk of fluctuations in serum sodium level or life-threatening citrate accumulation and toxicity in our vulnerable patients with ALF. Additionally, the precise delivery of hypernatremic therapy with this model requires strict quality control of every step of dialysate generation, which starts with the acid and bicarbonate concentrate mixing process (performed by two trained technicians working together) and ends with the final proportioning on the dialysis machine. Dialysis technicians were available on-site 24/7 to answer any conductivity alarms.

CRRT in general might be the preferred method for delivering both renal replacement therapy and high plasma tonicity control in patients with ALF, owing to the common occurrence of circulatory dysfunction resulting in fragile hemodynamics. If IHD or higher intensity hemofiltration (shift-therapy) are used for the management of the co-existing renal failure, they may worsen the intra-cranial hypertension through the dialysis disequilibrium phenomenon, and through the induction of hypotension, which leads to a decrease in the cerebral perfusion pressure and a reflex cerebral vasodilation, thereby raising the ICP.[30,31] These changes may occur within the first hour of treatment, before any major changes in plasma osmolality have occurred. Despite CRRT being reported to avoid this problem,[32,33] an increase in ICP as early as 3 hours after initiation of CVVH and SLED has been reported.[34] The absence of such findings in our patients might be owing to the extremely low blood flow (60 mL/mn) and sodium dialysance or urea clearance of $\leq$ 55 mL/min.

CONCLUSION

The use of high sodium ol-CVVHD-RCA in general might be superior to the conventional approach in the management of CE in the context of ALF and AKI. Our model in particular is an effective, simple, and safe alternative for maintaining and weaning a high target $[Na]_{Sys}$. Although it offers many advantages over conventional therapies, our data cannot advocate the use of hypernatemia in patients with CE but rather provides a reliable method of delivery if this approach is to be pursued. This model is expected to be further studied and small improvements to be made with more experience. Finally, more data is needed to clarify whether this proposed model will provide any morbidity or mortality benefit beside optimizing and simplifying the treatment of CE in the described settings.

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