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Association of Phosphate-Containing versus Phosphate-Free Solutions on Ventilator Days in Patients Requiring Continuous Kidney Replacement Therapy

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Abstract

Background and objectives Hypophosphatemia is commonly observed in patients receiving continuous KRT. Patients who develop hypophosphatemia may be at risk of respiratory and neuromuscular dysfunction and therefore subject to prolongation of ventilator support. We evaluated the association of phosphate-containing versus phosphate-free continuous KRT solutions with ventilator dependence in critically ill patients receiving continuous KRT.

Design, setting, participants, & measurements Our study was a single-center, retrospective, pre-post cohort study of adult patients receiving continuous KRT and mechanical ventilation during their intensive care unit stay. Zero-inflated negative binomial regression with and without propensity score matching was used to model our primary outcome: ventilator-free days at 28 days. Intensive care unit and hospital lengths of stay as well as hospital mortality were analyzed with a *t* test or a chi-squared test, as appropriate.

Results We identified 992 eligible patients, of whom 649 (65%) received phosphate-containing solutions and 343 (35%) received phosphate-free solutions. In multivariable models, patients receiving phosphate-containing continuous KRT solutions had 12% (95% confidence interval, 0.17 to 0.47) more ventilator-free days at 28 days. Patients exposed to phosphate-containing versus phosphate-free solutions had 17% (95% confidence interval, -0.08 to -0.30) fewer days in the intensive care unit and 20% (95% confidence interval, -0.12 to -0.32) fewer days in the hospital. Concordant results were observed for ventilator-free days at 28 days in the propensity score matched analysis. There was no difference in hospital mortality between the groups.

Conclusions The use of phosphate-containing versus phosphate-free continuous KRT solutions was independently associated with fewer ventilator days and shorter stay in the intensive care unit.

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Introduction

Phosphate is a small anion found abundantly in erythrocytes, skeletal bone, and muscle tissue, and it is an important modulator of physiologic homeostasis, including cell membrane structure, bone density, acid-base regulation, metabolism, and oxygen delivery (1–3). Critically ill patients are at risk of hypophosphatemia due to intestinal malabsorption, shock states, vomiting/nasogastric suctioning, rapid uptake due to catabolic states or infection, corticosteroids, volume overload, and extracorporeal removal with KRT (3–6).

Hypophosphatemia is a risk factor for intensive care unit (ICU) morbidity—including prolonged mechanical ventilation and receipt of tracheostomy—especially in critically ill patients with acute respiratory and kidney failure receiving both mechanical

ventilation and continuous KRT (CRRT) (4,6–9). This interplay is not fully understood but could be mediated by rhabdomyolysis, anemia, impaired cardiac contractility, impaired oxygen delivery, and skeletal muscle dysfunction (10,11). Changes in intracellular phosphate concentrations may disrupt protein synthesis, contribute to mitochondrial dysfunction, and lead to skeletal muscle wasting and physical impairment (12–14).

Hypophosphatemia develops in up to 80% of patients receiving CRRT and displays a positive linear relationship with the dose of CRRT (15). CRRT-induced hypophosphatemia has been associated with prolonged respiratory failure, hospital stay, and multiple organ failure (6,8). Extended hypophosphatemia during CRRT has also been associated with higher mortality (5).

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The two primary strategies for managing phosphate during CRRT include: (1) utilizing phosphate-free CRRT solutions plus protocolized phosphate replacement or (2) a preemptive strategy with phosphate-containing CRRT solutions through compounding or the use of commercially available options (16,17). The use of preemptive phosphate replacement with phosphate-containing CRRT solutions has been associated in several studies with a reduction in the severity and duration of hypophosphatemia in patients in the ICU requiring CRRT; however, none of these studies have been large enough to observe an effect on clinical outcomes (4,15,18–21). The aim of this study was to examine the relationship between the receipt of phosphate-containing (versus phosphate-free) CRRT solutions and clinical outcomes of ventilator dependence in a mixed adult patient population in the ICU receiving CRRT and mechanical ventilation.

Materials and Methods

Design and Setting

This study was a single-center, retrospective cohort study conducted at a large tertiary academic medical center with an active CRRT program (~4000 patient-days of CRRT per year) and over 200 ICU beds, with continuous venovenous hemodiafiltration as the predominant CRRT mode. The research was approved by the institutional review board with a waiver of informed consent due to the observational nature of the investigation (institutional review board no. 17-0514-P1G). The Strengthening the Reporting of Observational Studies in Epidemiology checklist for observational studies was followed (Supplemental Material).

Study Population

The electronic health record was queried for all patients in the ICU admitted from January 1, 2015 to May 1, 2018 with an order for CRRT. Data were extracted by the study analyst. Patients were excluded from this analysis if they were age <18 or >90 years old, had a CRRT order for the administration of plasmapheresis, received both phosphate-containing and phosphate-free CRRT solutions during their course of CRRT, or had mechanical ventilation initiated >96 hours after the start of CRRT. Patient data were retrieved through discharge. Figure 1 shows the details of the study flow chart.

Independent Variable

The main independent variable of the study was exposure to phosphate-containing versus phosphate-free CRRT solutions during the course of CRRT. Phosphate-containing solutions were commercially available and contained 1 mmol/L phosphate. We were able to identify two well-defined exposure groups following an institution-wide adoption of phosphate-containing CRRT solutions in 2016. The time frames of the two groups are from January 2015 to February 2016 for exposure to phosphate-free solutions and from March 2016 to May 2018 for exposure to phosphate-containing solutions. Other than the change in CRRT solutions, core elements of CRRT delivery, such as devices, prescription, electrolyte replacement, and vascular

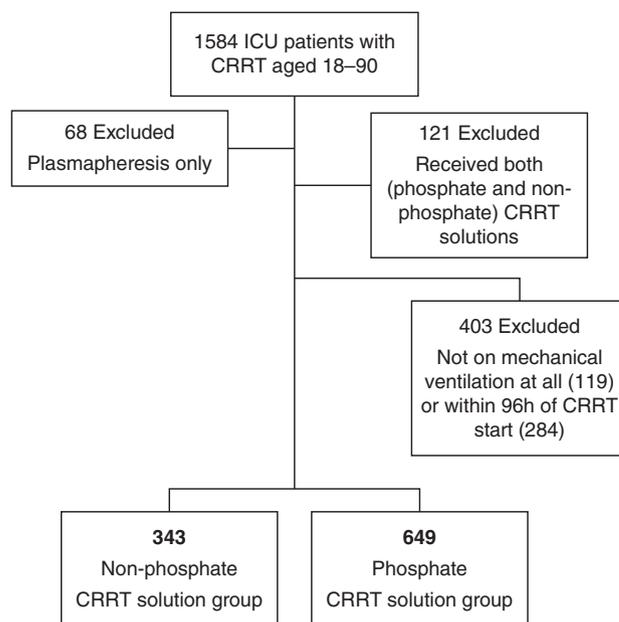


Figure 1. | Consort diagram. CRRT, continuous RRT; ICU, intensive care unit.

access insertion protocols, did not change throughout the study period.

Study Outcomes

The primary outcome of this study was ventilator-free days at 28 days. Ventilator-free days at 28 days were computed from initiation of CRRT through 28 days (days alive and free from ventilator, assigning zero to death). Time on the ventilator was calculated in hours and converted to days by dividing by 24. Any time (in hours) the ventilator was ordered for a patient was counted. This outcome was chosen as we hypothesized that the use of phosphate-containing CRRT solutions will reduce episodes of hypophosphatemia and improve muscle function, ultimately leading to greater ventilator independence. This end point has been extensively validated as a clinically relevant outcome in clinical trials involving patients with acute respiratory distress syndrome (22,23).

Secondary outcomes included total ICU length of stay (days), total hospital length of stay (days), all-cause hospital mortality, need of tracheostomy, incidence of hypophosphatemia (<2.5 mg/dl), and trajectory of serum phosphate levels during the CRRT period.

Statistical Analyses

Multivariable models of ventilator-free days at 28 days were fit by the generalized linear mixed models using the template model builder (glmmTMB) package in R using zero-inflated negative binomial regression, where the zero inflation was fit with the same explanatory variables as the main model. Variables from Table 1 were considered for inclusion in the final model according to univariable analysis and clinical rationale. Final models were adjusted for age, sex, Charlson index, prevalent CKD, sequential organ failure assessment (SOFA) score at ICU admission, total

Table 1. Baseline characteristics of unmatched and matched cohorts

Patient Characteristics	Entire Cohort, <i>n</i> =992	Phosphate-Free Continuous KRT Solution, <i>n</i> =343	Phosphate- Containing Continuous KRT Solution, <i>n</i> =649	Propensity Score Matched Phosphate-Free Continuous KRT Solution, <i>n</i> =303	Propensity Score Matched Phosphate- Containing Continuous KRT Solution, <i>n</i> =303
Study periods	—	1/2015–2/2016	3/2016–5/2018	1/2015–2/2016	3/2016–5/2018
Demographics					
Age, yr, median (IQR)	56 (13)	56 (13)	57 (14)	58 (48–65)	59 (49–66)
Men, <i>n</i> (%) ^a	579 (58)	218 (64)	361 (56)	182 (60)	176 (58)
Race, <i>n</i> (%) ^a	White 912 (92), Black 76 (8), other 3 (0.4)	White 313 (91), Black 28 (8), other 2 (1)	White 599 (92), Black 48 (7), other 2 (1)	White 278 (92), other 25 (8)	White 278 (92), other 25 (8)
BMI, median (IQR) ^a	33 (12)	33 (10)	33 (13)	31 (26–38)	30 (25–38)
Comorbidity					
Charlson index, mean (SD) ^a	2.2 (1.8)	2.3 (1.9)	2.1 (1.7)	2.1 (1.7)	2.2 (1.7)
Elixhauser index, mean (SD)	4.6 (1.8)	4.5 (1.6)	4.6 (1.8)	4.4 (1.6)	4.7 (1.8)
Prevalent CKD (ICD-10 diagnosis), <i>n</i> (%) ^a	452 (46)	170 (50)	282 (43)	144 (48)	142 (47)
Acuity of illness					
Admission to MICU, <i>n</i> (%) ^a	664 (67)	211 (62)	453 (70)	197 (65)	192 (63)
Admission ICU, <i>n</i> (%)					
Medical/pulmonary	664 (67)	211 (62)	453 (70)		
Surgical/trauma	75 (8)	27 (8)	48 (7)		
Cardiothoracic	92 (9)	43 (13)	49 (8)		
Cardiac/nonsurgical	87 (9)	40 (12)	47 (7)		
Transplant	38 (4)	12 (4)	26 (4)		
Surgical/general	27 (3)	9 (3)	18 (3)		
Neurosurgery/ neurology	9 (1)	1 (0)	8 (1)		
SOFA at ICU start, mean (SD) ^a	13 (3)	13 (4)	13 (3)	12.6 (3.5)	12.6 (3.3)
Vizient expected LOS	14 (8–19)	15 (10–23)	14 (8–19)		
Total effluent CRRT dose, ml/kg per h, median (IQR) ^a	36 (11)	36 (13)	37 (10)	33 (28–43)	35 (31–40)
Cumulative fluid balance from ICU admission to CRRT start, ml, median (IQR) ^a	680 (0–3007)	1179 (0–3546)	545 (0–2520)	1050 (0–3376)	793 (0–2952)
Cumulative fluid balance from ICU admission to CRRT stop, ml, median (IQR)	622 (–15–2254)	635 (–165–2343)	662 (0–2197)	614 (–91–2306)	614 (0–1780)
Cumulative fluid balance from ICU admission to ICU discharge, ml, median (IQR)	382 (–52–2155)	369 (–65–2024)	402 (–52–2230)		
Days from ICU admission to CRRT start, median (IQR)	1.5 (0.5–3.8)	1.7 (0.5–4.6)	1.4 (0.5–3.6)	1.6 (0.5–4.1)	1.8 (0.6–4.2)
Days on CRRT, median (IQR) ^a	7 (3–12)	7 (2–12)	7 (3–11)	7 (2–11)	7 (3–12)
Ventilator days prior to CRRT	0.31 (9.4)	0.02 (6.1)	0.47 (3.3)		

IQR, interquartile range; BMI, body mass index; ICD-10, International Classification of Diseases 10th revision; MICU, medical intensive care unit; ICU, intensive care unit; SOFA, sequential organ failure score; LOS, length of stay; CRRT, continuous KRT.
^aVariables included in the propensity score matching and variables considered for the primary multivariable model.

CRRT effluent rate, time from ICU admission to CRRT start, ventilator days prior to CRRT start, CRRT duration, and admission to medical ICU. The SOFA score was calculated automatically at the time of data extraction from the

electronic health record. A similar approach was used for secondary outcomes of ICU length of stay and hospital length of stay. Missing data were imputed for sensitivity analyses using the multiple imputation by chained

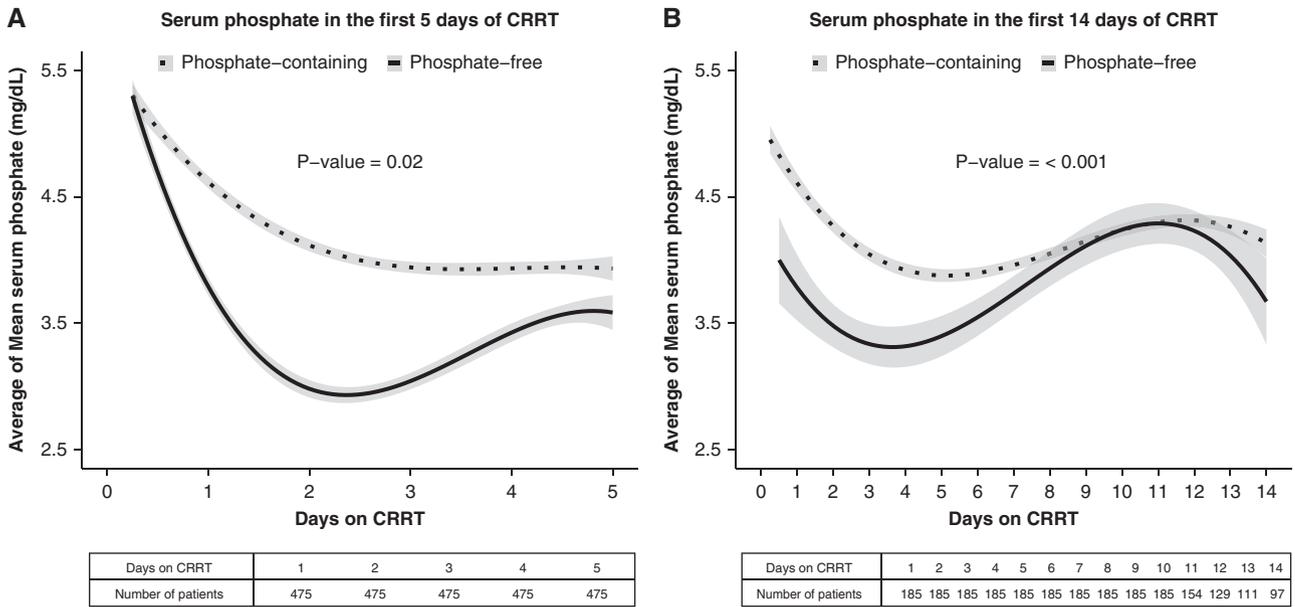


Figure 2. | Serum phosphate trajectory over 5 and 14 days of therapy. Unadjusted natural cubic splines of serum phosphate trajectories generated by averaging each patient’s 6-hour mean of measurements. (A) Represents the first 5 days of CRRT and (B) represents the first 14 days of CRRT in the whole cohort. The trajectories of serum phosphate levels of the two CRRT solution types were evaluated individually by autoregressive integrated moving average (ARIMA). The *P* value denotes the *F* test comparison of ARIMA model parameters between the two groups. The shaded area on either side of the line denotes 95% confidence intervals.

equations approach implemented in R. Five imputed datasets were generated. Means and 95% confidence intervals (95% CIs) for parameter estimates are reported. For evaluation of the trajectory of serum phosphate levels according to solution type, we fitted unadjusted natural cubic splines

to display the average of each patient’s 6-hour mean of serum phosphate measurements. Observations were restricted to patients will full data available through days 5 and 10. Knots were placed at the start and end of the observation day of CRRT, and extreme values (≥ 97.5 and ≤ 2.5

Table 2. Unadjusted study outcomes according to the continuous KRT solution group

Study Outcomes	Phosphate-Free Continuous KRT Solution, <i>n</i> =343	Phosphate-Containing Continuous KRT Solution, <i>n</i> =649	<i>P</i> Value
Primary outcome			
Ventilator-free days at 28 d, median (IQR)	21 (16–25)	22 (17–25)	0.20 ^a
Secondary outcomes			
Total hospital LOS, d, median (IQR)	16 (5–25)	12 (5–22)	0.01 ^a
Total ICU LOS, d, median (IQR)	10 (3–23)	8 (3–15)	0.01 ^a
Hospital mortality, <i>n</i> (%)	213 (62)	426 (66)	0.23 ^b
Other outcomes			
Total days on ventilator, median (IQR)	6 (2–12)	4 (2–8)	0.01 ^a
Hypophosphatemia <2.5 mg/dl, <i>n</i> (%)	194 (58)	135 (22)	0.01 ^b
Severe hypophosphatemia <1 mg/dl, <i>n</i> (%)	6 (2)	79 (1)	0.37 ^b
Median phosphate level during CRRT, mg/dl, median (IQR)	3.7 (3.1–4.7)	4.4 (3.7–5.3)	0.01 ^a
Minimum phosphate level during CRRT, mg/dl, median (IQR)	2.3 (1.8–3.9)	3.4 (2.6–4.6)	0.01 ^a
Total phosphate replacement during CRRT, mmol, median (IQR)	62 (0–302)	0 (0–8)	0.01 ^a
Median ionized calcium	3.15 (1.16)	3.4 (1)	0.01 ^c
Positive ketones, <i>n</i> (%)	53 (43)	90 (40)	0.60 ^b
Tracheostomy, <i>n</i> (%)	25 (7)	19 (3)	0.01 ^b
Discharge disposition, <i>n</i> (%)			
Alive/home	196 (32)	186 (29)	0.27 ^b
Rehabilitation facility	19 (6)	33 (5)	
Other	5 (2)	3 (1)	

Continuous data are reported as median (IQR), and categorical data are reported as counts and percentages. IQR, interquartile range; LOS, length of stay; ICU, intensive care unit; CRRT, continuous KRT.

^aWilcoxon rank sum test.

^bChi-squared test.

^cIndependent samples *t* test.

Table 3. Multivariable models of the continuous KRT solution group (phosphate containing versus phosphate free) as the main independent variable and study outcomes as the dependent variables in the whole and matched cohort

Variable	Total Cohort					Matched Cohort		
	Estimate (% Change)	Model 95% Confidence Interval	P Value	Imputation Mean	Imputation 95% Confidence Interval	Estimate (% Change)	Model 95% Confidence Interval	P Value
Ventilator-free days at 28 d								
Phosphate versus phosphate-free group	0.11 ^a (12%)	0.05 to 0.17	<0.001 ^{b,c}	0.100	0.10 to 0.10	0.14 (15%)	0.07 to 0.21	<0.001 ^b
ICU LOS								
Phosphate versus phosphate-free group	-0.19 (-17%)	-0.08 to -0.30	<0.001 ^{b,c}	-0.142	0.14 to -0.14	—	—	—
Hospital LOS								
Phosphate versus phosphate-free group	-0.22 (-20%)	-0.12 to -0.32	<0.001 ^{b,c}	-0.148	-0.15 to 0.15	—	—	—

Estimates are shown for nonimputed and imputed models. ICU, intensive care unit; LOS, length of stay.
^aModel interpretation: exponentiating the phosphate coefficient $\exp(0.11)=1.12$; thus, the phosphate treatment is associated with more ventilator-free days (at 28 days) by 12% on average after adjusting for everything else.
^bThe model was adjusted for age, sex, race, Charlson index, prevalent CKD, sequential organ failure score, total continuous KRT (CRRT) effluent rate, ventilator days prior to CRRT, CRRT duration, and admission to medical ICU.
^cThe model was constructed with zero-inflated negative binomial logistic regression, with multiple imputation of missing data included in parentheses.

percentiles) were excluded to avoid implausible extrapolation of trajectories. The serum phosphate trajectories of the two CRRT solution groups were evaluated individually by autoregressive integrated moving average, and autoregressive integrated moving average model parameters were compared by *F* test. Statistical analyses were done using R version 3.6.2 (24,25).

Sensitivity Analyses

Propensity Score Matching. A propensity score was estimated by fitting a logistic regression model to predict the individual's probability of receiving a phosphate-free CRRT solution with a set of *a priori*-selected clinical parameters as the model covariates. These variables included age, sex, race, body mass index, Charlson index, CKD, SOFA score at ICU admission, cumulative fluid balance from ICU admission to CRRT start, time from ICU admission to CRRT start (days), CRRT duration (days), and admission to medical ICU. Missing data were imputed with median values for continuous variables. Individuals in the phosphate-containing and phosphate-free CRRT solution groups were matched by a caliper distance equal to 0.30 times the SD of the logit of the propensity score. Ventilator-free days at 28 days were modeled on the matched dataset using a zero-inflated negative binomial model, with adjustment for the same covariates as the primary analysis.

Addressing Intensive Care Unit Practice Variations. To evaluate possible changes in ICU practice during the two study periods, which may have influenced the primary outcome, we compared ICU and hospital length of stay in all critically ill adult patients in the ICU who did not receive CRRT within the two CRRT solutions periods: from January 2015 to February 2016, which was the period of phosphate-free solutions use, and from March 2016 to May

2018, which was the period of phosphate-containing solutions use.

Results

Clinical Characteristics

A total of 992 critically ill adult patients were included in the analysis: 343 patients (10 patient-days of CRRT) in the phosphate-free CRRT solution group and 649 patients (9 patient-days of CRRT) in the phosphate-containing CRRT solution group. The patients were primarily men (58%) and White participants (92%). The majority of patients (667 of 992; 67%) were admitted to the medical ICU. The mean (SD) SOFA score at ICU admission was 13 (3), and the Charlson comorbidity index was 2.2 (1.8). Patients were on CRRT for a median of 7 (interquartile range [IQR], 3–11.5) days. When compared with patients in the phosphate-containing CRRT solution group, patients in the phosphate-free CRRT solution group were more frequently men (64% versus 56%), were less frequently admitted to the medical ICU (62% versus 70%), and had higher cumulative fluid balance from ICU admission to CRRT start (median of 1179 ml; IQR, 0–3546 versus 545 ml; IQR, 0–2520). When cumulative fluid balance was calculated from ICU admission to the end of CRRT, it was not different between the two groups (median of 635 ml; IQR, -165–2343 in the phosphate-free versus 662 ml; IQR, 0–2197 in the phosphate groups). There were no statistically significant differences in SOFA scores, comorbidity scores, time from ICU admission to CRRT start, CRRT dose, or duration of CRRT between the two groups (Table 1).

Serum Phosphate Trajectories According to the Continuous Kidney Replacement Therapy Solution Group

As depicted in Figure 2, trajectories of patients' serum phosphate concentrations exhibited overall lower levels of

serum phosphate in patients exposed to phosphate-free versus phosphate-containing CRRT solutions groups ($P=0.05$ and $P=0.004$) when evaluating the first 5 and 14 days of CRRT, respectively. Further, incident hypophosphatemia was more frequent in the phosphate-free CRRT solution group when compared with the phosphate-containing CRRT solution group (Table 2).

Study Outcomes

Receipt of phosphate-containing CRRT solutions was associated with fewer days of mechanical ventilation: median of 4 (2–8) versus 6 (2–12), respectively ($P<0.001$). Similarly, patients exposed to phosphate-containing versus phosphate-free CRRT solutions had less requirement of tracheostomy and shorter length of stay in the ICU and the hospital (Table 2).

After multivariable adjustment, exposure to phosphate-containing versus phosphate-free CRRT solutions was associated with 12% more ventilator-free days at 28 days (95% CI, 0.05 to 0.17; $P<0.001$ and 95% CI, 0.03 to 0.09; $P<0.001$) (Table 3). Patients exposed to phosphate versus phosphate-free solutions had 17% fewer days in the ICU (95% CI, -0.08 to -0.30 ; $P<0.001$) and 20% fewer days in the hospital (95% CI, -0.12 to -0.32 ; $P<0.001$) (Table 3).

Hospital mortality was similar in both groups: 66% in those receiving phosphate-containing CRRT solutions versus 62% in those receiving phosphate-free CRRT solutions ($P=0.23$) (Table 2).

Sensitivity Analyses

The results of the zero-inflated negative binomial regression models (ventilator-free days at 28 days, ICU length of stay, and total hospital length of stay) with imputation of the full dataset are similar to the nonimputed estimates (Table 3). When the multivariable analysis was restricted to a propensity matched cohort of 606 critically ill adult patients ($n=303$ in each CRRT solution group), the use of phosphate-containing versus phosphate-free CRRT solutions was associated with 15% more ventilator-free days at 28 days (log mean 0.14; 95% CI, 0.07 to 0.21; $P<0.001$) (Table 3). The covariate balance plot with standardized mean differences is reported in Supplemental Figure 1. Unadjusted study outcomes according to the CRRT solution group of the matched cohort are found in Supplemental Table 1.

There were no indicators of ICU practice variations influencing the primary outcome during the two study periods as determined by length of stay in non-CRRT critically ill adults. Median hospital length of stay was 7 (3–14) versus 7 (3–13) days ($P=0.10$) and median ICU length of stay was 2 (1–5) versus 2 (1–5) days ($P=0.80$) in the periods of phosphate-free and phosphate-containing CRRT solutions usage in the ICU, respectively.

Discussion

This study found an independent association between the receipt of phosphate-containing CRRT solutions and a higher number of ventilator-free days at 28 days when compared with the receipt of phosphate-free CRRT solutions in critically ill adult patients requiring CRRT and

mechanical ventilation. We also found a reduction in ICU and hospital lengths of stay in patients who received CRRT with phosphate-containing solutions. Patients receiving phosphate-free CRRT solutions exhibited more incident hypophosphatemia and overall lower serum phosphate levels during CRRT when compared with those receiving phosphate-containing CRRT solutions. Our findings are supported by prior work in this area describing the notably higher incidence of hypophosphatemia with the use of phosphate-free (versus phosphate-containing) CRRT solutions in critically ill patients in the ICU (4,15,19–21).

Our findings complement prior studies, which demonstrated a relationship between incident hypophosphatemia and adverse clinical outcomes. A prospective observational study by Demirjian *et al.* (6) evaluating patients with AKI receiving CRRT found an association between hypophosphatemia and prolonged respiratory failure requiring tracheostomy (odds ratio, 1.81; 95% CI, 1.07 to 3.08). This observation was more pronounced when CRRT and hypophosphatemia duration were prolonged, suggesting that the interplay of severity and duration of hypophosphatemia may be especially detrimental (6). Two additional studies found that incident hypophosphatemia during CRRT was associated with 7 additional days of mechanical ventilation (8) and independently associated with mortality (5). Our results suggest that these outcomes can be mitigated through the continuous repletion of phosphate *via* phosphate-containing CRRT solutions; however, our study, like others, was nonrandomized and therefore subject to bias. A prospective, blinded, randomized controlled trial would provide definitive evidence of this relationship.

Prior studies have found an association between hypophosphatemia during CRRT and higher mortality (26–28). Although our study did not show a difference in hospital mortality between the two phosphate solutions groups, we did find a higher number of days alive and free from ventilator in the phosphate-containing CRRT solution group as compared with the phosphate-free CRRT solution group. Patients receiving CRRT with phosphate-containing solutions were able to be liberated from mechanical ventilation earlier, which may have a desirable effect on organ recovery and rehabilitation. There are some options to clinicians to achieve a phosphate-containing CRRT solution, including compounding individual bags and using stock solutions. Another option to mitigate hypophosphatemia during CRRT involves careful monitoring and preemptive replacement of phosphate before significant hypophosphatemia occurs (16). In our study, the trajectory analysis of serum phosphate levels during CRRT revealed overall lower levels of serum phosphate during the course of CRRT with the use of phosphate-free (versus phosphate) CRRT solutions. Effective preemptive thresholds for phosphate replacement should be carefully determined to favor a “proactive” approach rather than a “reactive” (replace as needed) approach, which could be subject to delays in phosphate replacement in some cases. Despite many patients requiring CRRT for AKI and having a presumably elevated phosphate initially, hypophosphatemia is common after a patient starts therapy. A study of the relationship between the prevention of hypophosphatemia during CRRT by the use of phosphate-containing CRRT solutions and/or proactive phosphate replacement protocols on

clinical and patient-centered outcomes should be a research priority in critical care nephrology.

A possible explanation of our finding of reduced mechanical ventilation days may be related to the interaction of hypophosphatemia and diaphragmatic muscle weakness (29,30), which has been associated with longer duration of mechanical ventilation and death in patients in the ICU (31–33). Hypophosphatemia decreases oxygen delivery to skeletal muscle, reducing contractility (34). In a formative experiment, Aubier *et al.* (35) demonstrated that hypophosphatemia was strongly associated with transdiaphragmatic pressure (diaphragm contraction) measured during electrical stimulation of the phrenic nerve (34). It is reasonable to hypothesize that hypophosphatemia-induced diaphragm weakness impairs respiratory function, possibly prolonging mechanical ventilation and increasing the need for tracheostomy and the risk of mortality as some studies have shown (32). Importantly, this is a modifiable risk factor in critically ill patients requiring CRRT (18,19). Differing trajectories of serum phosphate levels by patients in the two CRRT solutions groups, as depicted in Figure 2, further support this hypothesis.

In addition to the effects on contractility, phosphate is an important regulator of oxygen delivery. Hypophosphatemia decreases erythrocyte 2,3-diphosphoglycerate, which, in turn, can decrease the dissociation of oxygen from hemoglobin by altering the oxygen-hemoglobin affinity curve (36). Tightly bound oxygen to hemoglobin is unavailable for delivery to the peripheral tissues, thus blunting this beneficial adaptive response to tissue hypoxia and acidemia, which is crucial to the mitigation of tissue necrosis during critical illness and has been implicated in the causal pathway for greater morbidity in critically ill patients (3,34). Sharma *et al.* (34) found a significant association between the duration of CRRT and the reduction of mean 2,3-diphosphoglycerate levels, which was observed independent of serum phosphate levels. Finally, animal models of hypophosphatemia have shown significant reduction in muscle ATP synthesis by oxidative phosphorylation in the mitochondria, suggesting that hypophosphatemia may have a profound effect on diaphragm and skeletal muscle function (12).

Strengths of our study are the inclusion of consecutive patients receiving CRRT who were also receiving mechanical ventilation, thus reflecting a population with multiorgan failure in need of extracorporeal organ support. This enhances external validity to a heterogeneous ICU population that would frequently receive CRRT. By excluding those who received both solution types, we controlled for a treatment crossover effect. Adopting the use of phosphate-containing CRRT solutions as a standard practice at our institution limited the indication bias inherent to observational studies comparing different exposures. We tested widely available commercial CRRT solutions, which can be readily applied to clinical practice and are a real-world intervention for patients on CRRT. Further, this work supports the hypothesis that hypophosphatemia is causally related to adverse outcomes and sets the groundwork for future prospective trials.

Our study has several limitations. First, observational studies are prone to confounding, which can often be unmeasured. Our exposure variable—CRRT solution type—was evaluated in two different periods of time in the

ICU, which could be subject to practice variations. We attempted to account for this by demonstrating that the length of ICU stay was similar in non-CRRT patients treated in these two periods of time. Second, we were unable to control or perform subgroup analyses according to ICU diagnoses, CRRT indications, or degree of baseline lung injury. However, our CRRT protocol did not significantly change during the course of the study, including indications, dose, or access. Importantly, we controlled for multiple patient-specific and acute illness parameters in the presented multivariable models and matched cohort analysis. Third, retrospective data are subject to systematic biases, including documentation or extraction errors. Lastly, the nonexperimental design of this study limits the conclusions and should be viewed as hypothesis generating. In addition, the study design prohibits conclusions to be drawn on the effect of phosphate-containing solutions in a nonmechanically ventilated population or in those in whom mechanical ventilation was initiated outside our study exposure window.

In critically ill adult patients requiring CRRT and mechanical ventilation, the utilization of 1 mmol/L phosphate-containing CRRT solutions was associated with a significant reduction in days on the ventilator and in the ICU. Patients exposed to phosphate-free CRRT solutions exhibited more incident hypophosphatemia and overall lower levels of serum phosphate during CRRT. These results highlight the importance of mitigating hypophosphatemia and maintaining optimal serum phosphate levels during CRRT as potential interventions that can affect respiratory function and clinical outcomes in this debilitated population. These findings should be validated with randomized clinical trials to establish the effect of preventing hypophosphatemia during CRRT on relevant clinical and patient-centered outcomes.

Disclosures

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Author Contributions

J.A. Neyra, A.J. Stromberg, and M.L. Thompson Bastin conceptualized the study; S.N. Nerusu and M.L. Thompson Bastin were responsible for data curation; S.N. Nerusu and M.L. Thompson Bastin were responsible for investigation; L.J. Liu and A.J. Stromberg were responsible for formal analysis; J.A. Neyra, A.J. Stromberg, and M.L. Thompson Bastin were responsible for methodology; J.A. Neyra and M.L. Thompson Bastin wrote the original draft; and S.M. Bagshaw, K.D. Liu, L.J. Liu, K.P. Mayer, P.E. Morris, S.N. Nerusu, J.A. Neyra, A.J. Stromberg, M.L. Thompson Bastin, and R. Wald reviewed and edited the manuscript.

Supplemental Material

This article contains the following supplemental material online at <http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.12410921/-/DCSupplemental>.

Supplemental Material. STROBE checklist.

Supplemental Table 1. Unadjusted study outcomes on the matched cohort according to the CRRT solution group.

Supplemental Table 2. CRRT solutions used.

Supplemental Table 3. Phosphate replacement protocols throughout the study period.

Supplemental Figure 1. Plot representing the covariate balance of propensity score matching between critically ill adults exposed to phosphate- versus nonphosphate-containing CRRT solutions.

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