Published in final edited form as:

Nutr Clin Pract. 2017 April ; 32(2): 245–251. doi:10.1177/0884533616662987.

An institutional change in continuous renal replacement therapy: nutrition support team resolves resultant severe hypophosphatemia

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Abstract

Background—Critically ill patients with acute kidney injury may require parenteral nutrition (PN) and continuous renal replacement therapy (CRRT). Introduction of a phosphate-free premixed renal replacement fluid without system-wide education in May 2011 resulted in increased incidence of hypophosphatemia, necessitating change in practice. Changes included: 1) maximizing phosphate in PN, 2) modifying the CRRT order set, and 3) developing a CRRT competency evaluation for Nutrition Support Team members. This study evaluates the effect of these changes on incidence of hypophosphatemia.

Methods—Phosphate levels and predicated probability of hypophosphatemia were evaluated for patients receiving PN and CRRT over three time periods: prior to implementing the changes (pre-implementation), during change implementation (intermediate), and following implementation (post-implementation). Hypophosphatemia was defined as a serum phosphate level <2.5 mg/dL. Generalized linear mixed models were applied for statistical analysis.

Results—The retrospective study includes 336 measures from 49 patients. Patients in the intermediate and post-implementation periods were not significantly different from each other and

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The contents of this article do not represent the views of the Department of Veterans Affairs or the United States government. This material is the result of work supported with the resources and use of facilities at the William S. Middleton Memorial Veterans Hospital, Madison, WI.

Financial disclosure: The project described was supported in part (RAB) by the Surgical Oncology Research Training Program [grant number T32CA090217].

had significantly higher mean phosphate levels than patients in the pre-implementation period ($p<0.0001$). They were also less likely to develop hypophosphatemia compared to pre-implementation patients [intermediate: OR 0.07, 95% CI (0.03, 0.18), $p<0.0001$; post-implementation: OR 0.09, 95% CI (0.03, 0.27), $p<0.0001$].

Conclusions—Modifications in phosphate dosing together with CRRT education reduced the incidence of hypophosphatemia in PN patients receiving CRRT. Communication of significant changes in clinical care should be shared with all services prior to implementation. Communication and planning between services caring for complex patients is necessary to prevent systems-based problems.

Keywords

Parenteral nutrition; continuous renal replacement therapy; phosphate; hypophosphatemia; renal replacement fluids

Background

Acute kidney injury (AKI) due to shock, sepsis, and often pre-existing kidney dysfunction complicates the management of critically ill patients. AKI aggravates fluid, electrolyte, and acid-base homeostasis in these hypercatabolic patients.^{1,2} Appropriate nutrition support is vital to recovery. While enteral feeding is preferable, clinical circumstances frequently necessitate nutrition delivery as parenteral nutrition (PN). Continuous renal replacement therapy (CRRT) allows delivery of appropriate PN to patients with hemodynamic instability and total fluid overload while supporting them through AKI.^{3,4}

Several forms of CRRT are available for clinical use including continuous venovenous hemodialysis (CVVHD), continuous venovenous hemofiltration (CVVHF or CVVH) and continuous venovenous hemodiafiltration (CVVHDF) as recently reviewed.³ Each technique requires simultaneous administration of renal replacement fluids to account for fluid and electrolyte removal in the effluent. Concurrent administration of PN and CRRT requires cooperation and coordination of nutrition support and nephrology services to ensure fluid and electrolyte balance. Our institution employs a formal Nutrition Support Team (NST) which oversees all PN prescriptions while our Nephrology Service dictates all CRRT prescriptions.

For more than a decade prior to 2011, our pharmacy prepared custom renal replacement fluids based upon the prescription of Nephrology (Table 1). These fluids routinely infuse at rates ranging from 2000–3000 mL/hour. Nephrology determined custom renal replacement fluid composition for each patient by measuring serum electrolytes every 4 hours for the first 24 to 48 hours after starting CRRT until a stable regimen was defined and every 8 hours thereafter. In particular Nephrology managed phosphate levels with replacement fluids, so the NST minimized phosphate in PN during CRRT (Table 2). Nationwide electrolyte shortages disrupted this system in 2011.⁵

Our institution introduced a commercially premixed renal replacement fluid (NxStage PureFlow dialysate solutions RFP: 401, 402, 453, 454. NxStage Medical Inc., Lawrence,

MA) in May 2011 in an effort to cope with these electrolyte shortages. However, no commercial replacement fluids contain phosphate,¹ representing a significant change from the individualized renal replacement fluids (Table 3). Unfortunately this system-based change was not universally communicated to clinicians. An investigation into a precipitous increase in episodes of severe hypophosphatemia among PN patients demonstrated CRRT to be a common factor. Further examination revealed the source of these significant electrolyte abnormalities to be the change in renal replacement fluids. Since severe hypophosphatemia can produce significant complications in critically ill patients,^{6,7} this pharmacy change mandated a response by the NST and nephrologists that included increased phosphate dosing in PN (Table 2), modification of the CRRT order set, and development and deployment of an education tool for CRRT competency for all NST members. This retrospective study describes these responses during the transition from the custom mixed to premixed renal replacement fluids in critically ill patients requiring PN and CRRT.

Methods

Adult patients receiving simultaneous PN and CRRT between 1/2/2012 and 6/21/2013 were considered eligible for analysis. CRRT is only administered in our intensive care units. This timeframe captures three specific time periods: 1) the pre-implementation period represents a baseline for study following the introduction of premixed renal replacement fluids prior to consistent phosphate supplementation (1/2–5/19/2012), 2) the intermediate period during which three system-based interventions were implemented (5/20–10/14/2012), and 3) the post-implementation period (10/15/2012–6/21/2013). This study was deemed exempt by the Minimal Risk Institutional Review Board of the University of Wisconsin-Madison and a waiver of authorization and consent was granted (Protocol #: 2013-1232).

During the intermediate period, three system-based interventions were sequentially implemented. First, in May 2012, the NST formally altered prescription practice for CRRT patients to include maximum quantities of phosphate (30 mmol/L) in PN as the standard of care.⁸ This practice differed as PN traditionally provided minimal phosphate (3 mmol/L) for CRRT patients since phosphate was adjusted in the replacement fluids frequently. Second, in August 2012, a scheduled order for 15 mmol of intravenous sodium phosphate every 8 hours or 2 packets (8 mmol/packet) of oral sodium and potassium phosphate replacement 4 times per day was added as a default order for CRRT patients in the CRRT order set. A contingency order for phosphate supplementation previously existed, but there was not always a laboratory draw to supplement against. Third, by October 2012, a formal education and CRRT competency training program was developed at our institution and required of all NST members. The objectives were to 1) review CRRT methods, indications, and solutions, 2) describe macronutrient, micronutrient, fluid, and electrolyte requirements for patients on CRRT, and 3) integrate understanding of CRRT therapy and PN prescription. A written test covering these objectives was required of all clinicians writing PN orders for CRRT patients.

Serum phosphate level and predicted probability of hypophosphatemia were determined for all patients in each time period. Serum phosphate level was measured by blood chemistry drawn per standard CRRT orders and hypophosphatemia was defined as a serum phosphate level <2.5 mg/dL (per our institution during this particular time of national phosphate

shortage). For patients with more than one value in a day, the lowest value obtained was used for that day. The group difference of hypophosphatemia and potentially influencing factors were evaluated across the three time periods (pre-implementation, intermediate, and post-implementation). ANOVA were used to test the group difference demographics including patient age in years, number of intensive care unit (ICU) days, number of ICU days prior to PN initiation, and number of days of PN and CRRT. Linear mixed models were applied to test group difference in amount of dextrose, lipid, and phosphate prescribed in PN, as well as total supplemental phosphate administered. Generalized linear mixed models were adopted to test the group difference in the probability of developing hypophosphatemia determined by the minimal phosphate level. Generalized linear mixed models were applied for statistical analysis to account for the clustered data structure when multiple measurements were taken from the same patient.

In addition, a multiple-predictor mixed model was applied to test the effects of the serum phosphate level and the probability of hypophosphatemia based on phosphate administered via PN and as supplemental phosphate while parsing out the effects of potential covariates including age, PN administered dextrose, PN administered lipid, and the serum phosphate measured the previous day. The application of mixed models was again to account for the clustered data structure as multiple measures were taken from the same patients. Tukey-Kramer test was used to control for the inflation of type I error rate associated with multiple comparisons of group difference. A p -value < 0.05 was considered statistically significant.

Results

During our time periods, 49 adult patients received PN during CRRT administration with a cumulative total of 336 serum phosphate measurements. Sixteen patients were evaluated during the pre-implementation period (81 measurements), 14 patients during the intermediate period (129 measurements), and 21 patients during the post-implementation period (126 measurements). Two patients received PN and CRRT during both the pre-implementation and intermediate periods. Of note, there were no burn or palliative patients in our study.

General demographics regarding patient care team, diagnosis, complicating diagnoses and care withdrawal/death at the time of PN and CRRT therapy are listed in Table 4. Patient-specific demographics including patient age, ICU days, ICU days prior to NST consultation, and days of PN and CRRT treatment are listed in Table 4. The only significant difference was in days of simultaneous PN and CRRT treatment between pre-implementation and intermediate groups ($p=0.02$) which was driven by two patients requiring therapy for over 20 days.

PN components including dextrose, lipid, and phosphate were evaluated in addition to phosphate administered as either intravenous or oral supplements (Figure 1 and 2). The intermediate group had significantly more phosphate administered in PN than the pre-implementation group ($p=0.004$) although there were no differences between either of these groups and the post-implementation group. When summed, the total amount of phosphate received daily significantly differed between the post-implementation and the pre-

implementation groups ($p=0.037$) and the overall difference between total phosphate among groups was also significant ($p=0.047$). There were no significant differences in glucose or lipid in PN between groups for the overall test or any ad-hoc pairwise comparison.

Mean phosphate levels during the intermediate and post-implementation periods remained significantly higher than those of patients in the pre-implementation period (Figure 3). No significant differences in mean phosphate levels occurred between the intermediate and post-implementation periods ($p = 0.99$).

During the pre-implementation period, there were 42 episodes of hypophosphatemia with 3 of those being severe episodes (serum phosphate < 1.0 mg/dL). Nine and 12 episodes of hypophosphatemia occurred during the intermediate and post-implementation periods, respectively, with no severe episodes during either period.

Patients in the intermediate and post-implementation periods were less likely to develop hypophosphatemia than patients in the pre-implementation period [OR = 0.07, 95% CI = (0.03, 0.18), $p < 0.0001$; and OR = 0.09, 95% CI = (0.03, 0.27), $p < 0.0001$, respectively]. There was no difference in likelihood to develop hypophosphatemia between intermediate and post-implementation periods [OR = 0.76, 95% CI = (0.25, 2.36), $p = 0.63$].

Discussion

Critically ill patients requiring PN and CRRT are complex, with fluid and electrolyte imbalances, acid-base disturbances, and hypercatabolism demanding diligence in their care.^{1,9,10} A change to prescribing premixed renal replacement fluids in conjunction with insufficient communication resulted in an increased incidence of hypophosphatemia among patients receiving both PN and CRRT. While no severe clinical complications occurred from these episodes, this experience highlights the impact of national drug shortages on patient care and the importance of communication and education on a systems level when multiple providers are caring for complex patients.

The first and most crucial step in this process was identification of the problem. Electrolytes are easily filtered during CRRT.³ An individualized system of providing renal replacement fluids containing electrolytes sufficient to maintain homeostasis was converted to use of premixed fluids without phosphate due to drug shortages in accordance with published recommendations.^{5,11,12} However, this change precipitated an increase in hypophosphatemia in this patient population, raising concern for patient safety while attempting to cope with national drug shortages.^{13,14} Fortunately, the NST recognized an increase in severe electrolyte disturbances which were occurring in CRRT patients, and only then were the premixed replacement fluids identified as the precipitating factor. Unfortunately no safeguards had been instituted to prompt system-wide education to all services impacted by this change. Almost certainly, other services were impacted.

In total, three formal changes were implemented by the NST and Nephrology. First, the NST prescribed maximum quantities of phosphate in the PN of patients receiving PN and CRRT as it was the patient's consistent source of phosphate delivery. Since maximum concentration of phosphate in PN is 30 mmol/L at our institution,⁸ additional scheduled

supplemental phosphate was prescribed per a change in the CRRT order set. Nephrology modified the CRRT order set to include scheduled supplemental phosphate as a default order even for patients not receiving PN. The final intervention involved development and deployment of a lecture and exam-based educational competency for NST members providing PN to CRRT patients to fill knowledge gaps that were previously unrecognized.

Since not all NST members had the same understanding of CRRT, an educational program was developed and successful completion was required prior to writing PN orders independently for patients on CRRT. The components of the educational program included: 1) dialysis principles for both diffusion and convection along with molecule size clearance for diffusion versus convection; 2) indications for CRRT, and goals and types of CRRT; 3) dosing of CRRT to deliver optimal clearance of solute; 4) types of anticoagulation and alterations in CRRT composition with use of citrate anticoagulation; 5) machine, fluid, and blood circuits; 6) nutrition assessment in AKI with calorie, protein, and micronutrient needs with continuous dialysis; 7) the function of all solutions employed in CRRT and how they may impact serum electrolytes or serum glucose; 8) coordination with Nephrology of electrolyte supplementation by PN versus boluses and scheduled doses; 9) transitioning from PN to EN; and 10) how and when to transition from CRRT to hemodialysis with subsequent PN solution modifications. A NST dietitian (CEK) developed the curriculum in conjunction with Nephrology and taught the didactic portion of the course. Subsequently, the trained NST members (CEK & CSC) mentored newly trained NST members in writing PN orders during CRRT. Once the learners demonstrated understanding, they completed a written competency exam that incorporated questions addressing PN calculations for different CRRT scenarios. After demonstrating competence in PN ordering and successfully completing the exam, NST members were approved to independently write PN orders for CRRT patients. Previously, no such educational tool was in place.

This study aims to evaluate the effect of these three changes in preventing hypophosphatemia in patients receiving PN and CRRT. The pre-implementation period was significantly different than the intermediate and post-implementation periods such that patients in the intermediate and post-implementation periods had significantly higher average phosphate levels and were significantly less likely to develop hypophosphatemia than patients in the pre-implementation period. However, results from the intermediate and post-implementation periods were not significantly different. Together these results suggest that the implemented changes had an immediate effect on the incidence of hypophosphatemia. Again, definition and understanding of the problem were essential to its correction.

There are several limitations to our study. First, this retrospective study cannot determine whether other responses beyond these NST changes affected the incidence of hypophosphatemia among these patients. However, once the NST recognized the problem and implemented the first response to the problem, there was an immediate impact so it seems likely that the NST changes had a direct effect. Perhaps even more severe episodes of hypophosphatemia would occur had a PRN order for supplemental phosphate not been in effect. Second, there was a time period when NST members were inconsistent in altering the phosphate in PN during our pre-implementation period. If anything, this practice would

decrease the number of episodes of hypophosphatemia during our pre-implementation period. Additionally we did not assess how our change in practice affected the incidence of hyperphosphatemia or if calcium levels were affected. Episodes of hyperphosphatemia (serum phosphate > 4.5 mg/dL) were present in all groups, however the most common cause of hyperphosphatemia in this patient population was CRRT pump malfunction, which was not evaluated nor correlated with the incidence of hyperphosphatemia. Finally, hypophosphatemia was not evaluated in enterally fed patients on CRRT; no conclusions about overall phosphate requirements in this population can be made from this study.

Conclusions

At our institution, a change to commercial renal replacement fluids for patients on CRRT led to an increase in hypophosphatemia. Once this change was recognized as the source of hypophosphatemia, measures implemented by the nutrition and nephrology services almost immediately corrected this systems-based problem. These measures included maximizing phosphate in PN, adding supplemental phosphate to the standard CRRT order set, and development and deployment of a competency for administering PN to CRRT patients. This study highlights how drug shortages and resultant minor systems changes can affect multiple services and patient care. Widespread communication and education are necessary when dealing with complex patients.

Acknowledgments

The authors have no conflicts of interest to declare.

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Figure 1.

Quantity of phosphate administered in PN and quantity of sodium or potassium phosphate administered as a supplement.

NS: $p > 0.05$ for overall test. * $p < 0.05$ between pre-implementation and intermediate group

PN: parenteral nutrition. IV: intravenous

Figure 2.
Quantity of dextrose and intravenous lipid administered in PN. Values are presented $\pm$ standard error of the mean.

Figure 3.

Daily serum phosphate level. Values are presented $\pm$ standard error of the mean. NS: $p > 0.05$.

Example of composition of individually compounded renal replacement fluids administered at our institution prior to the introduction of premixed renal replacement fluids. Renal replacement fluids were administered as a combination of the following three bags in addition to other supplements.

Table 1

Bag	Sodium mEq/L	Potassium mEq/L	Calcium mEq/L	Bicarbonate mEq/L	Magnesium mEq/L	Chloride mEq/L	Glucose mg/dL	Phosphate mmol/L
A	155	5.5	0	0	0	170	0	1
B	125	0	0	12.5	0	0	0	0
C	78	5.5	0	0	0	82	0	1

Table 2

Electrolyte composition of typical parenteral nutrition prescription for patients on continuous renal replacement therapy during the pre-implementation, intermediate, and post-implementation periods.

Electrolyte	pre-implementation	intermediate and post-implementation
Sodium (mEq/L)	130	40
Potassium (mEq/L)	12	14
Calcium (mEq/L)	0	6
Magnesium (mEq/L)	4	4
Phosphate (mmol/L)	3	30

Composition of premixed NxStage PureFlow Dialysate Fluids administered at our institution during all time periods. Renal replacement fluids are administered as a combination of the following four products in addition to other supplements.

Table 3

	Sodium mEq/L	Potassium mEq/L	Calcium mEq/L	Bicarbonate mEq/L	Magnesium mEq/L	Chloride mEq/L	Glucose mg/dL	Phosphate mmol/L
A	140	4	3	35	1	113	100	0
B	140	0	3	35	1	109	100	0
C	130	2	0	25	1.5	108.5	100	0
D	130	4	0	25	1.5	110.5	100	0

Table 4

Patient demographics. Service refers to team caring for patient at time of PN and CRRT. Admitting diagnosis represents primary diagnosis at time of ICU admission. Complicating diagnoses were selected based on known influence on serum phosphate level. Care withdrawn/mortality represent death immediately following PN and CRRT therapy only.

Demographics	Pre-Implementation	Intermediate	Post-Implementation	ANOVA
Age (years)	55.6 ± 14.2	57.8 ± 12.2	57.8 ± 14.7	NS
ICU days (days)	18.5 ± 9.7	24.9 ± 17.8	20.8 ± 11.4	NS
ICU days prior to NST consultation (days)	1.8 ± 14.6	2.4 ± 10.4	6.9 ± 9.9	NS
Days of PN+CRRT (days)	4.9 ± 3.2	9.4 ± 3.9*	6.2 ± 3.9	NS
Service				
Medical ICU	13	10	8	
Surgical ICU	2	3	10	
Cardiothoracic ICU	1	1	3	
Admitting Diagnosis				
Sepsis	6	5	6	
ESLD	2	4	6	
Heart Failure	0	2	3	
Respiratory Failure	2	1	2	
Trauma	1	0	0	
Other	5	2	4	
Complicating Diagnosis				
Alcoholism	2	1	2	
Malnutrition	1	1	1	
Traumatic Brain Injury	0	0	0	
Burn	0	0	0	
Care Withdrawn/Mortality	8/16	6/14	8/21	

NS= p>0.05 for overall test

* p <0.05 between pre-implementation and intermediate group

ICU: Intensive care unit. NST: nutrition support team. PN: parenteral nutrition. CRRT: continuous renal replacement therapy. ICU: Intensive care unit. ESLD: end stage liver disease.