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Leading European Nephrology

Clinical Kidney Journal, 2016, vol. 9, no. 2, 205–210

doi: 10.1093/ckj/sfv133
Advance Access Publication Date: 19 December 2015
Original Article

ORIGINAL ARTICLE

Phoxilium® reduces hypophosphataemia and magnesium supplementation during continuous renal replacement therapy

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Abstract

Background: Although associated with severe clinical complications, phosphate remains a neglected ion. Additionally, phosphate balance during continuous renal replacement therapy (CRRT) is complex and multifunctional. The present retrospective study investigated the effects of phosphate-containing CRRT fluid on phosphate homeostasis.

Methods: We retrospectively analysed 112 patients treated with CRRT at Skåne University Hospital, Sweden. The control group was treated with Hemosol® B0 (no phosphate; $n = 36$) as dialysis and replacement fluid, while the study group received Phoxilium® (phosphate; $n = 76$) as dialysis fluid and Hemosol® B0 as replacement fluid.

Results: Hypophosphataemia (<0.7 mM) occurred in 15% of the treatment days in the control group compared with 7% in the study group ($P = 0.027$). Magnesium substitution was reduced by 40% in the study group ($P < 0.001$). No differences in acid–base parameters were detected between the groups.

Conclusions: In this larger cohort, we could confirm that Phoxilium® reduced the episodes of hypophosphataemia during CRRT. A beneficial effect on magnesium balance could also be observed.

Key words: critically ill patients, CRRT, hypophosphataemia, intensive care medicine

Introduction

Electrolyte disorders frequently develop in critically ill patients treated at the intensive care unit (ICU) [1]. The onset of acute kidney injury (AKI), which occurs in up to 15% of ICU patients, further escalates these conditions [2, 3]. Phosphate and magnesium are commonly depleted in critically ill patients, and although frequently overlooked, these ions play key roles in cellular metabolism and are essential in many biological functions [4]. Common conditions predisposing hypophosphataemia and hypomagnesaemia are sepsis, alcohol withdrawal, malnutrition, catecholamines, intravenous glucose infusion, insulin administration, metabolic or respiratory alkalosis, hyperventilation, use of diuretics and rhabdomyolysis [2, 5–8]. Hypomagnesaemia has been reported in up to 65% of the critically ill patients [9]. Hyperphosphataemia is also regularly observed in AKI patients, but often turns into hypophosphataemia shortly after initiation of continuous renal replacement therapy

Received: June 22, 2015. **Accepted:** November 9, 2015

(CRRT) [10]. The technique achieves high clearance of small solutes and can thus deplete the patients of essential electrolytes such as phosphate and magnesium. In the ICU, hypophosphataemia can be expected in up to 80% of the patients and is classified as moderate (0.32–0.71 mM) or severe (<0.32 mM) [11, 12].

Hypomagnesaemia, which is defined as a total serum magnesium concentration <0.70 mM, is a frequent electrolyte abnormality [13]. Animal studies of hypomagnesaemia revealed decreased glomerular filtration rate and renal blood flow, and enhanced post-ischaemic renal injury [14], but this condition is now recognized as a risk factor for the non-recovery of the renal function in ICU patients [15, 16]. Hypophosphataemia, on the other hand, has been associated with respiratory muscle dysfunction, potentially resulting in acute respiratory failure and weaning problems [17]. Low serum phosphate levels can further lead to myocardial dysfunction and arrhythmias, as well as impaired energy metabolism in the myocardium, leading to decreased contractility [18], but corrections of hypophosphataemia are associated with improved cardiac output [19]. Multiple studies show an association between hypophosphataemia and increased mortality in critically ill patients [20–22]. A recent study by Suzuki *et al.* [23] enrolling 2730 critically ill adult patients showed that hypophosphataemia behaves like a general marker of illness severity, but is not an independent predictor of ICU or in-hospital mortality in critically ill patients [23, 24]. It thus remains unclear whether this condition actually contributes to mortality and further investigation is warranted.

The normal phosphate-handling regime at most ICUs is to supplement phosphate according to daily serum phosphates measurements. An infusion of 20 mmol phosphate is usually given over a couple of hours. The phosphate balance in the patient is further complicated as additional phosphate is administered via nutrition at the same time as phosphate is simultaneously cleared via CRRT. Off-label addition of phosphate to CRRT fluids helps prevent hypophosphataemia [25], but runs the risk of solution incompatibility, calcium-phosphate precipitation in alkaline medium, sterile breach and administration errors [25]. Using an industrially produced phosphate-containing solution is, therefore, attractive and convenient.

In our previous study, 14 critically ill patients showed stable serum phosphate levels after treatment with a dialysis fluid containing 1.2 mM phosphate [10]. Here, we retrospectively investigated a larger patient population to further examine the effects of phosphate-containing dialysis fluid on ion homeostasis.

Materials and methods

Study design, patients and CRRT treatments

After acceptance by the Regional Ethical Review Board (Dnr 2011/157, Lund University, Sweden), 68 CRRT patients treated with Hemosol® B0 as pre/post replacement fluid as well as dialysis fluid (the control group; treated 2004–08) and 100 patients treated with Hemosol® B0 as pre/post replacement fluid and Phoxilium® (1.2 mM phosphate; fluid content; Supplementary data, Table S1) as dialysis fluid (the study group; starting from 2008) were identified from the medical records and evaluated. Patients were included only if the raw data were strictly complete. A total of 36 consecutive patients in the control group and 76 patients in the study group were included (Table 1). Patients were excluded if they received intermittent dialysis prior to the ICU stay, if the CRRT treatment lasted <10 h, if they had less than four plasma phosphate analyses in total or if they were under the age of 18 years. The medical records for a majority of the control

Table 1. Patient characteristics

	Control treatment ($n = 36$)	Phoxilium® treatment ($n = 76$)	P
Age (years), median (range)	64.5 (21–82)	67.0 (29–81)	0.166
Weight (kg), median (range)	83 (54–178)	80 (47.5–143)	0.399
Gender, female, *n* (%)	15 (42)	25 (33)	0.370
RIFLE score, numeric 1–5 (%)	2.90	2.98	0.476
RIFLE class, *n* (%)			
R	0	0	
I	5 (14)	6 (8)	
F	25 (69)	63 (83)	
L	0	1 (1.3)	
E	0	2 (2.6)	
Not known	6 (17)	4 (5.3)	
CRRT treatment duration, median time hours (range)	67 (16–106)	84.5 (10–119)	0.060
SOFA score upon CRRT start			
Respiratory	3.0	2.8	0.205
Coagulation	1.7	1.6	0.618
Liver	1.2	1.0	0.369
Circulation	1.8	2.8	**0.005**
CNS	1.4	1.4	0.621
Renal	3.0	3.9	**0.015**
Total	12.2	13.4	**<0.001**
CRRT treatment mode			
Effluent flow (mL/kg/h), median (range)	13.9 (9.3–46.7)	44.6 (19.5–87.2)	**<0.001**
Anticoagulation			
None, *n* (%)	5 (15)	17 (23)	
Heparine, *n* (%)	13 (39)	39 (52)	
Flolan, *n* (%)	3 (9)	8 (11)	
Heparine/flolan, *n* (%)	5 (15)	10 (1)	

Significant values are in bold.

patients were only available in paper format, and therefore, it was not possible to retrieve complete records of >36 control patients. A Gambro Prismaflex® CRRT machine with the CVVHDF modality and a Hospal M100 filter was used in all patients. The CRRT was set according to the patients' conditions and requirements. The replacement fluid was given as 500 mL/h post-filter and the remaining as pre-filter. Intravenous phosphate supplementation was prescribed when serum phosphate was <0.7 mM. Enteral or parenteral nutrition or a combination was given if the patients were haemodynamically stable.

Table 2. Occurrence of phosphate and magnesium imbalances in the groups prior to dialysis treatment as well as during the dialysis treatment

CRRT treatment days	Control treatment, *n* (% of total treatment days)	Phoxilium® treatment, *n* (% of total treatment days)	P
Number of treatment days with p-phosphate <0.7 mM			
Day −1	2 (6.5)	1 (1.8)	0.262
Days 1–5	23 (15.6)	37 (7.43)	**0.027**
Number of patients with *p*-phosphate >1.9 mM			
Day −1	13 (41.9)	22 (38.6)	0.262
Days 1–5	14 (10.9)	23 (7.8)	0.403
Number of treatment days with *p*-magnesium <0.8 mM			
Day −1	6 (21.4)	4 (6.67)	**0.044**
Days 1–5	10 (8.1)	4 (1.36)	0.367
Number of patients with *p*-magnesium >1.4 mM			
Day −1	1 (3.57)	8 (13.3)	0.164
Days 1–5	2 (1.61)	8 (2.72)	0.500

Each day with at least one measurement outside the normal range has been listed in the table. Data are given as number of days and percentage of total number of treatment days in the group, respectively.
Significant values are in bold.

Clinical parameters

Na^+, K^+, Ca^{2+}, Cl^-, pCO_2, base excess, bicarbonate, pH and anion gap were analysed from blood samples from arterial or central venous lines, prior to start of CRRT and regularly every fourth hour. Blood samples for phosphate and magnesium analysis were taken at 5 and 17 o'clock. All blood samples were analysed at the Clinical Chemistry Laboratory, Skåne University Hospital, Lund, Sweden. Baseline clinical parameters, including SOFA scores, RIFLE classification upon the day of CRRT start and data of the delivered CRRT, were registered from the medical records (Table 1). Calculations of assessed strong ion difference (SID_a) and effective strong ion difference (SID_e) were performed as previously described [26].

Statistics

SigmaPlot for Windows version 11.0 was used for statistical analysis (Systat Software Inc.). Normal distributed parameters with equal variance are expressed as average ± SD and parameters without normal distribution and/or unequal variances as median and range. Significant differences were evaluated using Student's *t*-test or Mann–Whitney rank sum test, whichever was applicable. Repeated-measures analysis of variance (ANOVA) or ANOVA on ranks was used for repeated measurements.

Results

Phosphate, magnesium and nutrition

Episodes of hypophosphataemia were present already 24 h after CRRT treatment (76 and 36 observations in the study group and

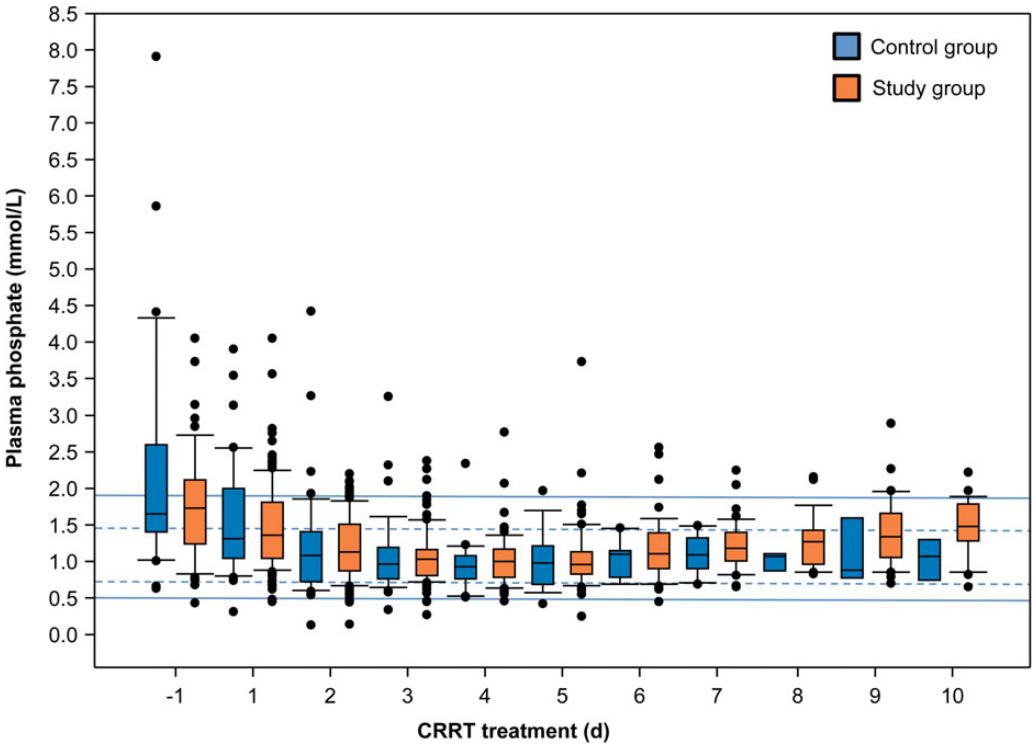

Fig. 1. Phosphate level modification during CRRT treatment.

the control group, respectively). The number of treatment days resulting in hypophosphataemia (phosphate <0.7 mM) during the study period was significantly lower: 37/502 treatment days (7.4%) in the Phoxilium® treated group versus 23/147 (15.6%) in the control group (P = 0.027) (Table 2, Figures 1 and 2). There were no significant differences in the phosphate supplementation between the groups: 11 mmol/day in the control group versus 8 mmol/day in the study group, P = 0.11 (Figures 2 and 3). A total of 41.9% of the patients in the control group and 38.6% (P = 0.262) of the patients in the study group showed hyperphosphataemia (phosphate >1.9 mM) prior to CRRT due to the AKI state. Once the CRRT started, the incidences of hyperphosphataemia were low in both treatment groups (Table 2).

Magnesium supplementation was significantly lower in the study group: 1.2 mmol per treatment day for treatment group compared with 3.7 mmol per treatment day for the control group (P < 0.001), although the number of treatment days with hypomagnesaemia (magnesium <0.8 mM) and hypermagnesaemia (magnesium >1.4 mM) did not differ (Table 2, Figure 2).

There was no difference in total given calories between the study group and the control group (20.2 ± 6 and 19.9 ± 10 kcal/24 h/kg, respectively; P ≤ 0.464, in both groups; 29.5% of the total nutrition was given via the enteral route).

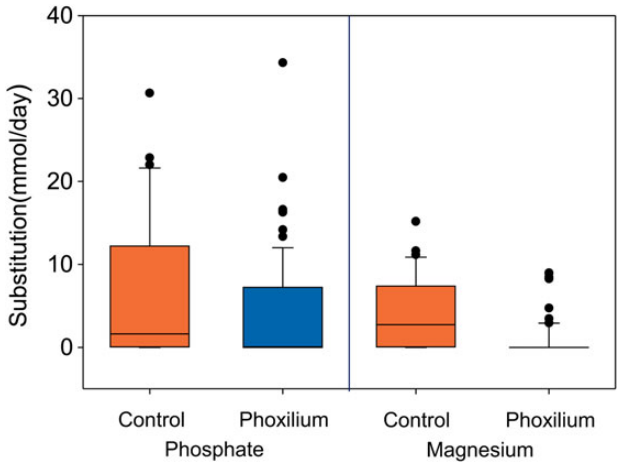

Fig. 2. Phosphate/magnesium supplementation in both groups.

SOFA and RIFLE

Sub-analysis of the total SOFA scores (12.2 versus 13.4, P < 0.001, Table 1) indicated difference between the groups in the circulation and in the renal organ systems. The SOFA scores from the circulation show that the study group had significantly lower blood pressure levels throughout the study period, indicating that these patients were more shocked (Table 1). The renal organ system SOFA scores also differ significantly, but the RIFLE class upon CRRT start was the same (Table 1).

Potassium, calcium and acid–base parameters

Data can be found in Supplementary data, Table S2; [K^+] and [Ca^{2+}] showed no difference during CRRT treatment between

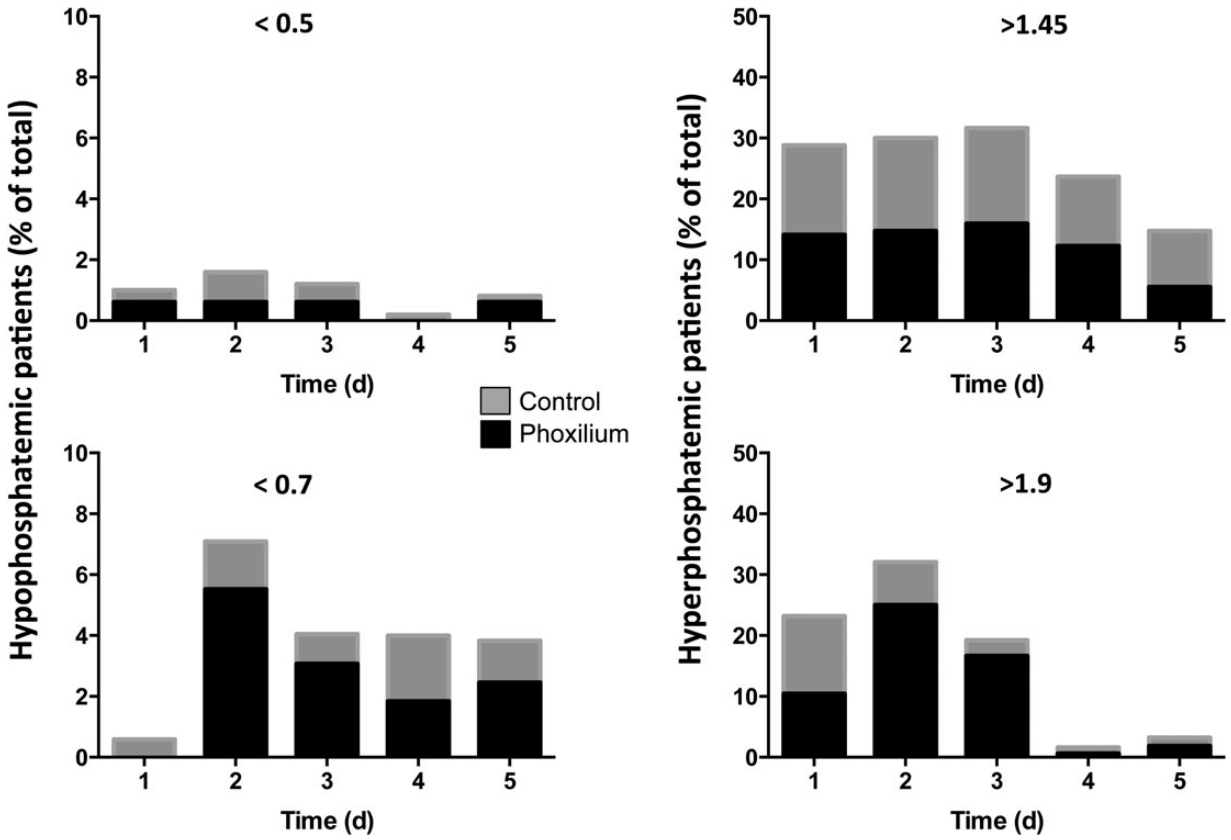

Fig. 3. Phosphate variations in patients treated for >72 h with CRRT.

the groups. There were no differences in direct, measured acid–base parameters such as base excess and anion gap, nor in the calculated parameters such as SID_a and SID_e during CRRT. However, the bicarbonate level was slightly higher in the control group (22.7 ± 2.95 versus 23.7 ± 3.93; $P < 0.001$).

Discussion

The primary aim of the present study was to retrospectively investigate the phosphate levels in a larger study population receiving CRRT. In our previous study of 14 patients, we showed that a phosphate-containing dialysis fluid covered the phosphate needs and resulted in stable serum concentrations [10]. In the present study, in a larger cohort, we could confirm that the phosphate-containing dialysis fluid reduced episodes of hypophosphataemia. Recently, several studies successfully investigated the possibility to use phosphate-containing replacement fluid during citrate anticoagulation [27–29]. In one of those studies involving totally 40 patients undergoing prolonged CVVHDF treatment, Morabito *et al.* [28] observed that phosphate-containing dialysate prevented CRRT-induced hypophosphataemia. Furthermore, Phoxilium® was also recently used as both replacement and dialysis fluid, and we could confirm that this set-up occasionally leads to mild hyperphosphataemia [10, 26, 30]. Minor hyperphosphataemia is usually not considered to be a problem in CRRT patients and is not considered to be associated with increased risks. As we only used Phoxilium® as dialysis fluid, a possibility to improve the phosphate concentrations would be to also include Phoxilium® as replacement fluid or to use fluids with slightly lower phosphate content as both dialysis and replacement fluid.

The reduction in magnesium supplementation despite higher treatment intensity in the study group indicates that the higher magnesium content in Phoxilium® is beneficial. Another important concern was the content of 4 mM potassium that could induce a risk for potassium overload, but hyperkalaemia was not observed in either of the two study groups. Phoxilium® also contains less calcium than Hemosol® B0, which could affect acid–base balances in critically ill patients [26, 30]. However, in our large study cohort, we did not observe increased frequency of hypocalcaemia or metabolic acidosis. Neither did we observe any differences in base excess, anion gap, SID_a or SID_e during treatment between the groups, but bicarbonate level was slightly lower in the study group. This finding could be a result of the lower bicarbonate content in Phoxilium®: 30 mM compared with 32 mM found in Hemosol® B0.

In this study, there was a temporal bias for choice of treatment as we were not able to randomize the patients. The dialysis dose and the clearance were higher in the study group than in the control group, possibly reflecting the trend over the years towards increased dialysis dose in AKI patients. The increased clearance in the study group was also due to the increased SOFA scores in this population, indicating that there was an inclusion bias, possibly by different admission criteria for ICU over time. Sub-analysis revealed that this difference arose in the circulation and in the renal organ systems. Assessing the SOFA scores from the circulation shows that the study group had significantly lower blood level pressures throughout the study period, indicating that these patients were more shocked. The renal organ system SOFA scores also differed significantly, but the RIFLE class upon CRRT start was the same. However, we found that hypophosphataemia was significantly less frequent in the study group during treatment, despite equal phosphate supplementation and increased clearance.

In conclusion, we can confirm that Phoxilium® improves the phosphate balance and reduces the need for magnesium supplementation for CRRT patients. In addition, we could not detect any impact of the fluid on acid–base balance, the calcium balance or the potassium balance.

Supplementary data

Supplementary data are available online at http://ckj.oxfordjournals.org.

Conflict of interest statement

The results presented in this paper have not been published previously in whole or in part. Part of the data has been presented as an abstract at the 19th Annual CRRT congress, San Diego, USA, 2014. The ICU department at Skåne University Hospital, Lund, paid an ordinary price for Phoxilium® used in the study. Gambro approved a Research Grant, which was paid to the ICU department of Skåne University Hospital. O.C. was a Gambro employee during the study. Gambro did not have any insight in how the Research Grant has been used. An independent statistician monitored the raw data and the statistics.

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Clinical Kidney Journal
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