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Preventing Continuous Renal Replacement Therapy-Induced Hypophosphatemia: An Extended Clinical Experience with a Phosphate-Containing Solution in the Setting of Regional Citrate Anticoagulation

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Key Words
Acute kidney injury · Citrate · Continuous renal replacement therapy · Continuous veno-venous haemodiafiltration · Hypophosphatemia · Regional citrate anticoagulation

Abstract
Aims: To evaluate the efficacy and safety of a commercially available phosphate-containing solution for continuous renal replacement therapy (CRRT) in preventing CRRT-related hypophosphatemia. ***Methods:*** In heart surgery patients undergoing continuous veno-venous haemodiafiltration (CVVHDF) with regional citrate anticoagulation (RCA), we combined an 18 mmol/l citrate solution with a phosphate-containing (1.2 mmol/l) dialysate/replacement fluid evaluating the incidence of hypophosphatemia and the need for parenteral phosphorus supplementation. ***Results:*** In 75 patients on RCA-CVVHDF, the mean filter life was 53.9 ± 33.6 h. Regardless of baseline levels, phosphoremia was progressively corrected and maintained in a narrow normality range throughout RCA-CRRT days (after 72 h: 1.14 ± 0.25 mmol/l). Considering the whole CRRT period, 45 out of 975 (4.6%) serum phosphorus determinations met the criteria for mild (<0.81 mmol/l) or moderate (<0.61 mmol/l) hypophosphatemia; severe hypophosphatemia (<0.32 mmol/l) never occurred. After 72 h 88% of the patients were normophosphatemic, 9% hyperphosphatemic and 3% hypophosphatemic. ***Conclusions:*** RCA-CVVHDF with a phosphate-containing solution enabled the maintenance of phosphorus levels within normophosphatemic range in most of the patients, minimizing the occurrence of CRRT-related hypophosphatemia.

Introduction

Hypophosphatemia is common among intensive care unit (ICU) patients [1, 2] with an incidence of up to 80% in patients undergoing continuous renal replacement therapy (CRRT) with standard dialysis/replacement solutions [3–9], especially when highly efficient modalities are employed [4, 5]. Hypophosphatemia may negatively impact on respiratory, central nervous and cardiovascular systems. In particular, severe hypophosphatemia is as-

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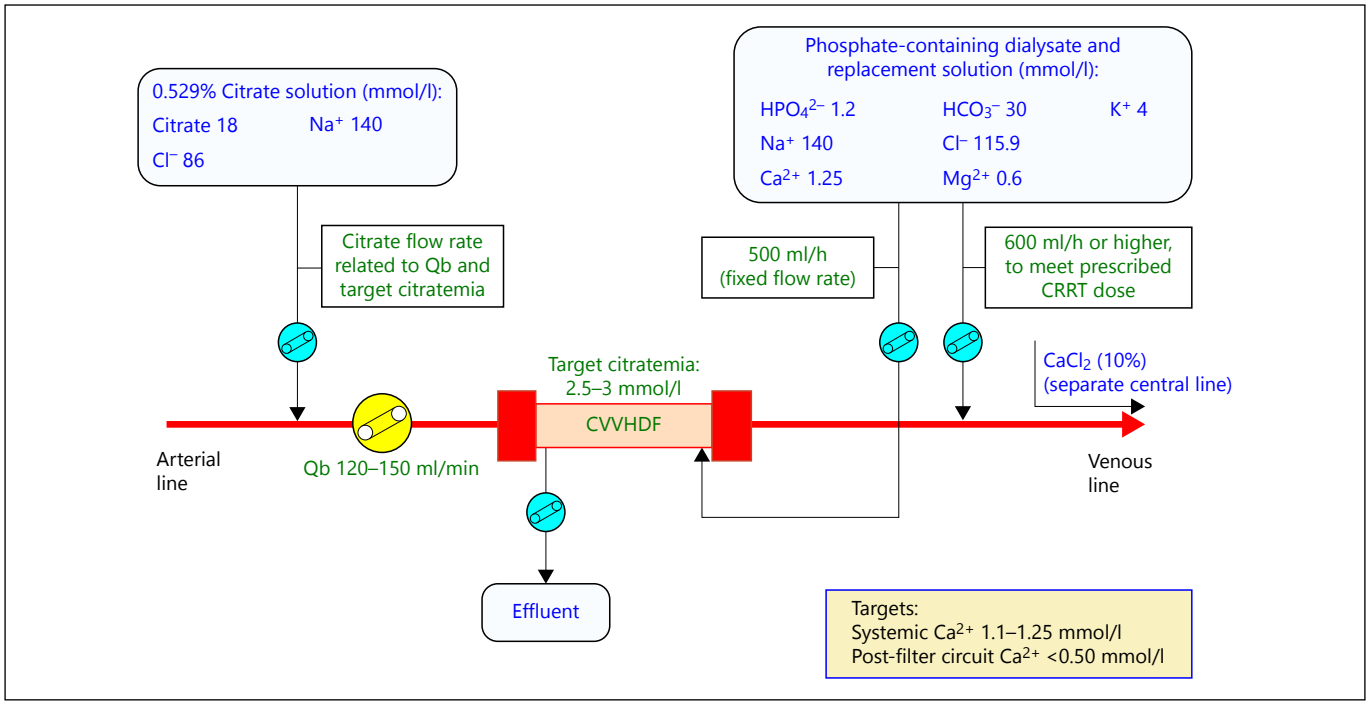

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Fig. 1. RCA-CVVHDF circuit, RCA targets, and composition of citrate solution and phosphate-containing CRRT solution.

sociated with respiratory muscle dysfunction, potentially resulting in difficult weaning from mechanical ventilation, neuromuscular manifestations such as muscle weakness, lethargy, confusion and cardiovascular complications such as myocardial dysfunction and arrhythmias [10]. Therefore, RRT-related hypophosphatemia should be avoided in critically ill patients, and the adoption of any measure aimed at reducing its incidence and severity should be implemented.

The aim was to evaluate in patients undergoing CRRT for cardiac surgery-associated acute kidney injury (CS-AKI) the efficacy and safety of a CRRT protocol specifically designed to reduce the incidence of CRRT-related hypophosphatemia. The effects of the use of a commercially available phosphate-containing CRRT dialysate/replacement fluid combined with a low concentration citrate solution were investigated with special regard to changes in serum phosphorus levels and phosphate supplementation needs throughout CRRT.

Subjects and Methods

We conducted a retrospective analysis on a cohort of patients with CS-AKI who underwent regional citrate anticoagulation (RCA) CRRT for at least 72 h from September 2011 to September 2015 at the Heart Surgery ICU of Policlinico Umberto I, 'Sapienza' University, Rome, Italy. Demographic, clinical and laboratory data was prospectively collected. CRRT was performed by the Prismaflex system (Gambro Lundia AB, Sweden) and polyarylethersulfone haemofilters (HF 1000, 1.15 m^2, Gambro, France). Vascular access was obtained by femoral or internal jugular vein cannulation with a polyurethane or silicone catheter. Since September 2011, we have refined our previously adopted standard RCA protocol [11] with the aim of optimizing buffers balance and to reduce the need for phosphate supplementation. Thus, we developed a continuous veno-venous haemodiafiltration (CVVHDF) protocol by using a 18 mmol/l pre-dilution trisodium citrate solution (Prismocitrate 18/0, Gambro) combined with a calcium- and phosphate-containing solution acting as dialysate and post-dilution replacement fluid (HPO_4^{2-} 1.2, Ca^{2+} 1.25 mmol/l; Phoxilium, Gambro; fig. 1). The citrate solution flow rate was initially set in relation to the blood flow rate to meet a roughly estimated target circuit citrate concentration of 2.5–3 mmol/l in plasma water. Citrate flow rate was modified, if needed, to achieve a circuit Ca^{2+} (c-Ca^{2+}) <0.50 mmol/l. Dialysate flow was maintained at the fixed rate of 500 ml/h. The post-dilution flow rate was adjusted to achieve a prescribed dialysis dose, corrected for pre-dilution, of at least 25 ml/kg/h. Calcium chloride (10%) was infused in a separate central venous line to maintain a target systemic Ca^{2+} (s-Ca^{2+}) of 1.1–1.25 mmol/l. Acid–base parameters, Ca^{2+}, Na^+, K^+ were measured at least every 4 h. Total Ca, P, Mg, coagulation parameters and complete blood count were assessed daily. A total calcium/Ca^{2+} ratio (calcium ratio) >2.5 was considered an indirect sign of citrate accumulation [12]. Clinically relevant metabolic alkalosis was arbitrarily defined as a persistent increase of serum bicarbonate levels >30 mmol/l. Hypophosphatemia was defined as mild (<0.81 mmol/l), moderate (<0.61 mmol/l) or severe (<0.32 mmol/l)

[8], and hyperphosphatemia was defined as serum phosphorus levels >1.45 mmol/l. Nutritional support was provided by enteral and parenteral nutrition with energy and protein intake targets of 25 kcal/kg/day and 1.5 g/kg/day, respectively, and phosphorus intakes of 20–30 mmol/day. Potassium, phosphate and magnesium losses with CRRT were replaced, when needed, respectively with potassium chloride, d-fructose-1,6-diphosphate (FDP; Esafosfina® 5 g/50 ml, Biomedica Foscama, Italy) and magnesium sulphate. In particular, FDP administration was scheduled in case of serum phosphorus levels <0.9 mmol/l.

The study was conducted according to the Declaration of Helsinki and informed consent was obtained from either the patient or a close relative. Ethics Committee approval was not required for this retrospective observational study because data collection, as well as CRRT protocols, were part of routine medical procedures at our Institution.

Statistical Analysis

Data is reported as mean ± SD or median and interquartile range (IQR). Comparisons of continuous variables were performed by Student t test, or one-way analysis of variance with Bonferroni post-hoc test where appropriate. Non-parametric analysis was performed using the Mann–Whitney U test for independent samples. Categorical variables were analyzed with chi-square test or Fisher exact test. All tests were 2-sided (significance level 5%). IBM SPSS statistical software (22.0, SPSS Inc., USA) was used for all analyses.

Results

Seventy-five patients were treated with RCA-CVVHDF for at least 72 h. The mean CRRT duration was 13 ± 11 days (median 9, IQR 5–20). Forty-four out of 75 patients (58.7%) were treated for at least 7 days.

The main clinical characteristics of the patients at the start of CRRT are summarized in table 1. Prescribed dialysis dose, corrected for pre-dilution, was 27.0 ± 2.98 ml/kg/h. Three hundred sixty-nine RCA-CVVHDF circuits were used with a mean filter life of 53.9 ± 33.6 h (median 48, IQR 24–78), for a total running time of 19,891 h. Considering both scheduled and unscheduled CRRT interruptions, down-time periods accounted for 15% of the total treatment period.

Laboratory variables at the start of RCA-CVVHDF and after 72 h of treatment are reported in table 2, along with supplementation needs during CRRT. During RCA, c-Ca^{2+} and s-Ca^{2+} were easily maintained within the intended targets. No episode of clinical relevant hypo- or hypercalcemia was observed. Estimated citrate dose and estimated citrate load were 2.84 ± 0.20 mmol/h (median 2.79) and 13.47 ± 0.81 mmol/h (median 13.73) respectively. Calcium ratio was steadily below the threshold of 2.5. The acid–base status was adequately maintained without the need for additional interventions on RCA-CRRT parameters, and without clinically relevant episode of metabolic alkalosis (table 2). Clinically relevant hypomagnesemia was prevented by magnesium sulphate supplementation. Serum potassium was maintained in the normal range by potassium chloride infusion (table 2).

Regardless of starting values, serum phosphorus was progressively corrected and/or steadily maintained in a narrow normality range throughout RCA-CVVHDF days (fig. 2; table 3). In particular, considering all patients (n = 75) after 72 h of CRRT treatment, serum phosphorus was 1.14 ± 0.25 mmol/l (median 1.10, IQR 0.91–1.36; table 2). Overall prevalence of hypo-, normo- and hyperphosphatemia throughout the first 96 h of treatment is reported in figure 3. Considering serum phosphorus levels at baseline, 12 out of 75 patients (16%) had hypophos-

Table 1. Clinical characteristics of the patients at the start of CRRT

Variable	n = 75
Female gender	23 (30.7)
Age, years	69 (58–74)
Body weight, kg	70 (69–72)
Oliguria	51 (68)
Mean arterial pressure, mm Hg	75 (65–80)
Use of vasopressors or inotropes	51 (68)
Mechanical ventilation	67 (89.3)
Artificial nutrition	75 (100)
APACHE II score	31 (25–34)
SOFA score	13 (11–15)
CV-SOFA score	2 (1–3)
Hemoglobin, g/dl	10.0 (9.0–11.0)
Hematocrit, %	30.0 (27.6–33.3)
White blood cells, $\times 10^3$/μl	12.0 (9.9–15.93)
Platelet count, $\times 10^3$/μl	113 (92–192)
Antithrombin III activity, %	68 (55–80)
aPTT ratio	1.59 (1.30–1.84)
INR	1.30 (1.15–1.60)
Bilirubin, mg/dl	0.88 (0.58–1.47)
Aspartate aminotransferase, IU/l	97 (46–223)
Alanine aminotransferase, IU/l	30 (15–93)
Albumin, g/dl	2.5 (2.2–2.7)
Heart surgery	
Coronary artery bypass grafting	18.7
Coronary artery bypass grafting + valvular surgery	26.7
Valvular surgery	30.7
Ascending aorta replacement	21.3
Others	2.6

Data expressed as median (IQR), n (%) or percentage.

APACHE = Acute physiology and chronic health evaluation; SOFA = sequential organ failure assessment; CV-SOFA = cardiovascular SOFA; aPTT = activated partial thromboplastin time; INR = international normalized ratio.

Table 2. Laboratory variables at RCA-CVVHDF start and after 72 h of treatment, along with supplementation needs during CRRT

Variable (n = 75)	Basal	72 h	
Systemic Ca^{2+}, mmol/l	1.10 (1.02–1.21)	1.17 (1.15–1.21)	<0.0001
Total calcium, mmol/l	2.06 (1.95–2.19)	2.27 (2.15–2.39)	<0.0001
Calcium ratio	–	1.93 (1.84–2.03)	–
Circuit Ca^{2+}, mmol/l	–	0.42 (0.36–0.46)	–
Serum creatinine, mg/dl	2.20 (1.6–3.15)	1.60 (1.00–2.20)	<0.0001
Blood urea nitrogen, mg/dl	41.1 (29.0–56.5)	29.0 (22.4–36.1)	<0.0001
Sodium, mmol/l	141 (138–143)	135 (133–136)	<0.0001
Potassium, mmol/l	4.2 (4.1–4.5)	4.2 (4.0–4.4)	0.021
Phosphorus, mmol/l	1.30 (0.97–1.60)	1.10 (0.91–1.36)	0.027
Magnesium, mmol/l	0.81 (0.74–0.95)	0.82 (0.76–0.86)	0.732
pH, units	7.40 (7.38–7.43)	7.43 (7.39–7.45)	<0.0001
Bicarbonate, mmol/l	23.0 (21.7–24.6)	24.6 (23.6–26.0)	<0.0001
pCO_2, mm Hg	37 (34–40)	37 (34–40)	0.431
Lactate, mmol/l	1.5 (1–2)	1.1 (0.9–1.5)	<0.0001
Supplementation needs during the entire CRRT period			
Calcium chloride infusion, mmol/h		2.31 (2.04–2.65)	
Potassium chloride infusion, mmol/h		2 (0–4)	
Magnesium sulphate, g/day		3 (3–3)	
Need for phosphate supplementation, n (%)		15/75 (20)	
g of phosphorus/day		0.79±1.83	

Data expressed as median (IQR) or mean ± SD or percentage.

phatemia at the start of RCA-CVVHDF, 34 out of 75 (45%) had normal serum phosphorus levels, while 29 out of 75 (39%) were hyperphosphatemic. After 72 h of treatment serum phosphorus was normal in most of the patients (88%), while only a low proportion of them were hyper- (9%) or hypo-phosphatemic (3%; fig. 3). Taking into account the whole CRRT period, excluding samples drawn in the first 48 h of RCA-CVVHDF, only 45 out of 975 (4.6%) serum phosphorus determinations met the criteria for mild (n = 37) or moderate (n = 8) hypophosphatemia; severe hypophosphatemia was never observed. At some time during CRRT, only 15 out of 75 patients (20%) received a low amount of phosphate supplementation (FDP 0.79 ± 1.83 g/day; table 2). In particular, phosphate supplementation was needed in 7 out of 12 patients who were hypophosphatemic at the start of RCA-CVVHDF, in 7 out of 34 normophosphatemic patients and in 1 out of 29 hyperphosphatemic patients. In table 3, serum phosphorus levels at the start and throughout RCA-CVVHDF days are separately reported for patients stratified into 3 groups according to baseline serum phosphorus. Starting from 72 h of treatment time point, comparison of serum phosphorus levels among the 3 groups of patients did not show any statistical difference (p = 0.173; table 3).

Discussion

Hypophosphatemia is a frequent finding among critically ill patients and its incidence can be further increased by the use of prolonged and intensive modalities of RRT [3–9], which achieve a very efficient phosphate clearance [2, 13]. Indeed, in 2 large clinical trials, patients receiving the most intensive RRT modalities experienced a higher incidence of hypophosphatemia [4, 5]. In particular, in the RENAL trial, in which all patients were treated with CRRT, the reported incidence of hypophosphatemia in the low- and high-intensity groups was 54 and 65.1% respectively [5].

Among other complications, severe hypophosphatemia has been associated with respiratory muscle weakness with a higher incidence of prolonged respiratory failure requiring tracheostomy [7]. Furthermore, it has recently reported a link between CRRT-induced hypophosphatemia and a relevant reduction in red blood cell 2,3-diphosphoglicerate concentration, leading to a leftward shift in the O_2-haemoglobin dissociation curve and reduced oxygen unloading in peripheral tissues with a higher risk for in-hospital death [14]. Therefore, RRT-related hypophosphatemia should be avoided in critically ill patients, and the adoption of phosphate-containing

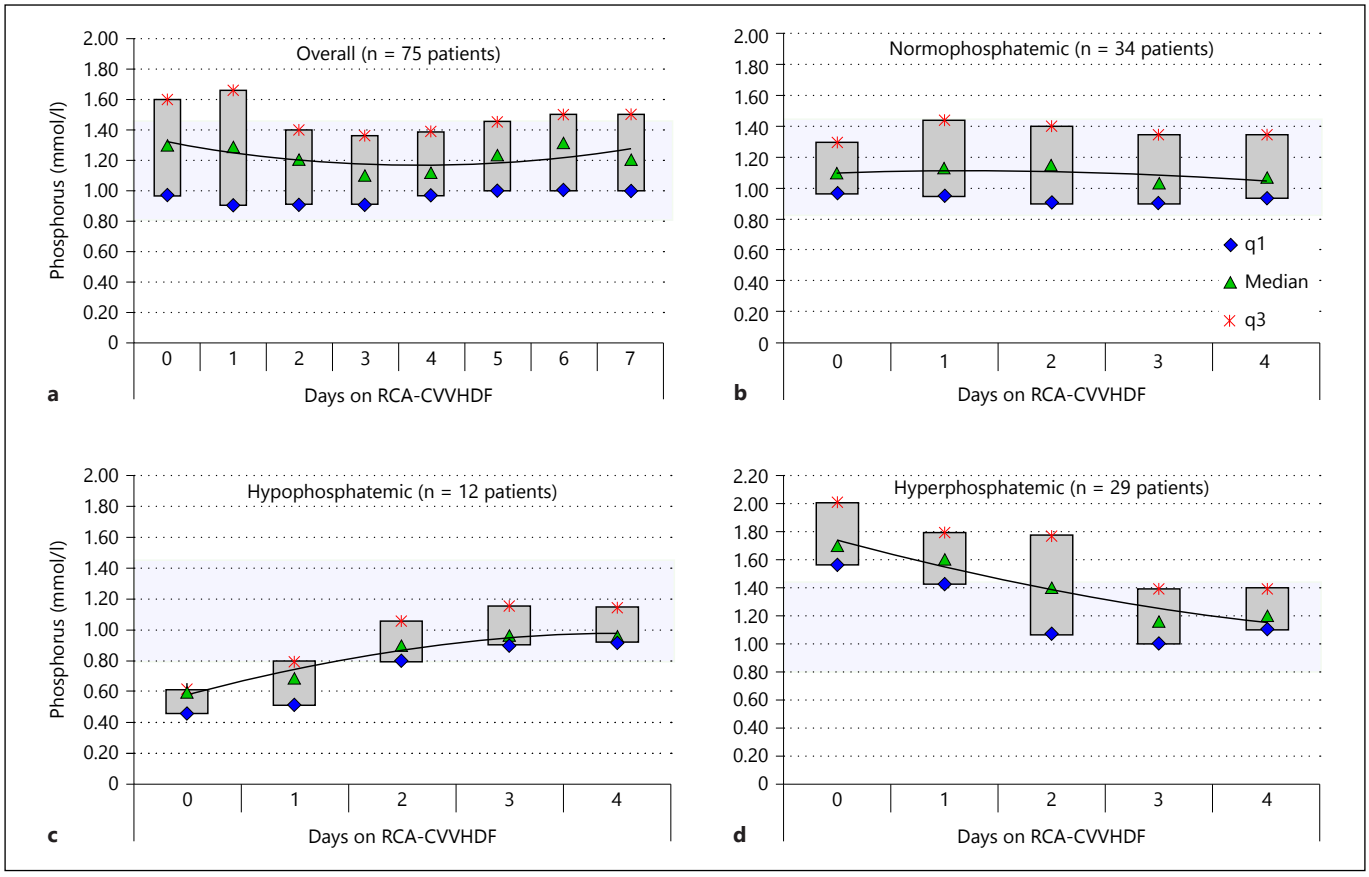

Fig. 2. a–d Serum phosphorus levels trend throughout RCA-CVVHDF days in all patients and in subgroups of patients stratified according to baseline values. The shaded area represents the range of normophosphatemia (0.81–1.45 mmol/l). Data is reported as median and IQR (q1–q3).

Table 3. Serum phosphorus levels at the start and throughout RCA-CVVHDF days

Days on RCA-CVVHDF	Serum phosphorus levels, mmol/l			p value	Overall (n = 75)
	low (n = 12)	normal (n = 34)	high (n = 29)		
Basal	0.54±0.13	1.12±0.18	1.81±0.28	<0.0001	1.29±0.51
Day 1	0.67±0.18	1.23±0.42	1.57±0.29	<0.0001	1.28±0.46
Day 2	0.92±0.22	1.14±0.29	1.47±0.50	<0.0001	1.23±0.42
Day 3	1.05±0.21	1.12±0.26	1.21±0.24	0.173	1.14±0.25
Day 4	1.05±0.22	1.12±0.27	1.25±0.24	0.084	1.16±0.26

Data expressed as mean ± SD.

The patients are stratified according to basal serum phosphorus levels (low <0.81 mmol/l; normal 0.81–1.45 mmol/l; high >1.45 mmol/l).

CRRT solutions could decrease its incidence in patients with AKI. For this purpose, we developed a protocol for minimizing CRRT-induced hypophosphatemia through the combination of a recently introduced, commercially available, phosphate-containing CRRT solution that can be used as dialysate and post-dilution replacement fluid, with a low concentration, isotonic in sodium, citrate solution for RCA. The feasibility and safety of adding phosphate to conventional CRRT fluids have been previously and successfully tested in adult and pediatric patients [3,

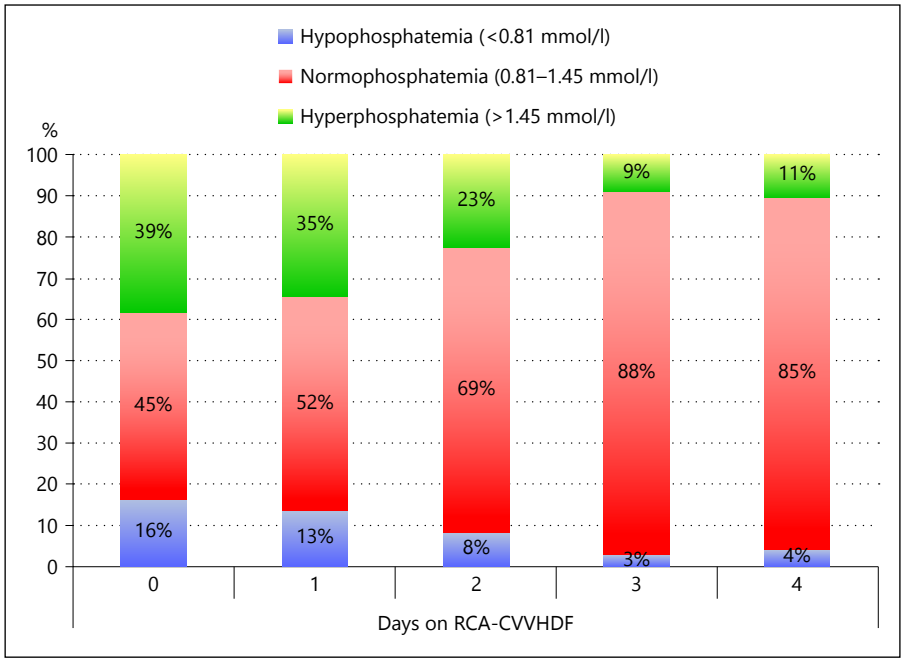

Fig. 3. Distribution of patients in relation to phosphatemia throughout RCA-CVVHDF days.

6]. More recently, the efficacy of a commercially available phosphate-containing solution in preventing hypophosphatemia has been reported in CVVHDF [8, 15] or CVVH [16]. The use of a phosphate-containing CRRT solution in the specific setting of RCA was described for the first time by our own group in a single case report on CS-AKI patients undergoing RCA-CVVH. This approach enabled the prevention of hypophosphatemia, in addition to avoiding the need for phosphate supplementation [17]. The protocol was further refined and successfully tested in 2 small case series in RCA-CVVH and RCA-CVVHDF modalities [18, 19]. The RCA-CVVHDF modality is now routinely adopted at our Institution; in this study conducted in 75 CS-AKI patients undergoing prolonged CRRT periods, we report the main findings derived from 4 years of its extended use. All patients were treated for at least 72 h, and most of them were treated for more than 7 days. To our knowledge, this is the longest treatment period until now reported with the use of a phosphate-containing CRRT solution in the setting of RCA.

In our study, 39 and 16% of patients were respectively hyper- and hypophosphatemic before the start of RRT. While hyperphosphatemia could be mainly related to the presence of worsening renal function in the course of AKI, the causes of hypophosphatemia could not be easily recognized in our selected population of CS-AKI patients. On the other hand, independently from RRT, it is well known that multiple causal factors may lead to the occurrence of hypophosphatemia in critically ill patients [20] and most of them are present in the cardiac surgery patient (e.g., post-operative state, fluid expansion with intracellular redistribution, use of diuretics). Moreover, higher illness severity scores, the need for mechanical ventilation, and a lower minimum serum albumin level have been identified as independent risk factors for ICU-acquired hypophosphatemia in a cohort of general ICU critically ill patients [1]. However, although some of these risk factors were present in most of our patients, the design and the sample size of the study do not allow us to confirm their relation with the development of RRT-unrelated hypophosphatemia.

Regardless of starting values, serum phosphorus was progressively corrected throughout RCA-CVVHDF days. Over the course of treatment, serum phosphorus levels fell in a progressively narrower range, with an increase in the proportion of patients with phosphorus values in the normal range. Indeed, within a few days of RCA-CVVHDF, most of the patients (>85%) had normal serum phosphorus levels, with only a low proportion of them having hyper- or hypophosphatemia. In this regard, the differences in baseline serum phosphorus, that were used to stratify the patients into 3 groups (hypo-, normo- and hyperphosphatemia), disappeared after 72 h from the time the treatment started.

Considering the whole treatment period, mild to moderate hypophosphatemia was observed in less than 5% of

serum phosphate determinations, while severe hypophosphatemia never occurred. A low amount of phosphate supplementation (FDP <1 g/day) was needed only in 20% of patients. It should be underscored that protocol-guided supplementation was sporadically needed, and mainly required in patients already hypophosphatemic at the start of CRRT.

Stressing the importance of strategies aimed at preventing, rather than curing, hypophosphatemia, Yang et al. [9] recently reported that the ratio of CVVH therapy days with hypophosphatemia to total CVVH days was independently associated with global outcome. The authors highlighted that parenteral phosphate supplementation failed to prevent CVVH-related hypophosphatemia in a majority of the patients underlining that the use of CRRT phosphate-containing solutions could represent a more appropriate option. Indeed, as confirmed by our experience, in which mild to moderate hypophosphatemia occurred in only 45 out of 975 phosphate determinations, this strategy appears to be able to steadily maintain safe serum phosphorus levels during CRRT irrespective of the baseline levels.

At variance with previous reports, in which the same phosphorus-containing solution was used to provide the full CRRT dose [16], the present study did not show any clinically relevant trend towards hyperphosphatemia and/or metabolic acidosis. Mild hyperphosphatemia was in fact observed in only 9% of patients after 72 h of RCA-CVVHDF, while metabolic acidosis never occurred. Hence, we could speculate that the use of the phosphorus-containing solution as roughly as 50–60% of the total CRRT dose may explain the lower incidence of hyperphosphatemia; moreover, the buffer supply provided by the 18 mmol/l citrate solution, by compensating for the lower than usual bicarbonate concentration (30 mmol/l) in the phosphate-containing solution, may have accounted for a better acid–base control.

Along with the above described benefits related to the use of a phosphorus-containing solution, the use of citrate as the main anticoagulation strategy in a clinical setting characterized by a very high bleeding risk allowed us to ensure prolonged filter life. Therefore, on the bases of these findings and according to the more recently published guidelines on AKI and related commentaries [21–24], the adoption of the described RCA-CVVHDF protocol has been extended in our centre to all CS-AKI patients without contraindications for citrate [25]. It should be in any case underlined that the efficacy of our low citrate dose RCA protocol, in terms of filter life, cannot be generalized to other populations and may be worthy to be tested in other clinical settings (e.g. septic patients in the general ICU).

Study Limitations

Besides being retrospective in nature, this was a single-centre study that enrolled a selected population of CS-AKI patients undergoing CRRT. In addition, we acknowledge the lack of a control group treated with conventional CRRT solutions. However, as we describe the longest RCA-CVVHDF treatment reported to date with a phosphate-containing solution in the setting of RCA in a relatively large and homogeneous cohort of critically ill patients, we feel that this study provides consistent data on the efficacy and safety of our protocol.

Conclusions

The adoption of a commercially available phosphate-containing CRRT solution in the setting of RCA-CVVHDF enabled the possibility to meet the double target of minimizing CRRT-induced hypophosphatemia and to ensure an adequate circuit life in the absence of electrolyte and acid–base derangements. During a prolonged CRRT period, hypophosphatemia was effectively prevented or corrected in most of the patients throughout treatment days. Irrespective of baseline values, serum phosphorus levels were steadily maintained in a progressively narrower range without new episodes of severe hypophosphatemia, and with a negligible occurrence of hyperphosphatemia. The trend of phosphorus levels towards a narrow normality range led to a very high proportion of patients with normal serum phosphorus levels within few days since the start of RCA-CVVHDF.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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