Phosphate levels in patients treated with low-flux haemodialysis, pre-dilution haemofiltration and haemodiafiltration: post hoc analysis of a multicentre, randomized and controlled trial

Francesco Locatelli1, Paolo Altieri2, Simeone Andrulli1, Giovanna Sau2, Piergiorgio Bolasco3, Luciano A. Pedrini4, Carlo Basile5, Salvatore David6, Luanna Gazzanelli7, Guido Tampieri8, Elisabetta Isola8, Onofrio Marzolla9, Bruno Memoli10, Marino Ganadu11, Ernesto Reina12, Silvio Bertoli13, Rocco Ferrara14, Domenica Casu15, Francesco Logias16, Renzo Tarchini17, Giovanni Mattana18, Mario Passaghe19, Gianfranco Fundoni20, Giuseppe Villa21, Biagio Raffaele Di Iorio22, Giuseppe Pontoriero1 and Carmine Zoccali23

1Department of Nephrology and Dialysis, Azienda Ospedaliera della Provincia di Lecco, Ospedale Alessandro Manzoni, Lecco, Italy, 2Department of Nephrology and Dialysis, Azienda Ospedaliera G. Brotzu, Cagliari, Italy, 3Department of Nephrology and Dialysis, Dipartimento territoriale ASL 8, Cagliari, Italy, 4Department of Nephrology and Dialysis, Ospedale Bolognini, Seriate, Italy, 5Department of Nephrology and Dialysis, Ospedale F. Miulli, Acquaviva delle Fonti, Italy, 6Department of Nephrology and Dialysis, Ospedale Maggiore, Parma, Italy, 7Department of Nephrology and Dialysis, Centro Dialisi della Maddalena, La Maddalena, Italy, 8Department of Nephrology and Dialysis, Ospedale di Ravenna, Ravenna, Italy, 9Department of Nephrology and Dialysis, Centro Dialisi di Melito e Scilla, 10Department of Nephrology and Dialysis, Università Federico II, Napoli, Italy, 11Department of Nephrology and Dialysis, Centro Dialisi di Ozieri, Ozieri, Italy, 12Department of Nephrology and Dialysis, Ospedale di Pinerolo, Italy, 13Department of Nephrology and Dialysis, Ospedale Multimedica, Sesto San Giovanni (MI), 14Department of Nephrology and Dialysis, Ospedale SS Trinità ASL 8, Cagliari, Italy, 15Department of Nephrology and Dialysis, Ospedale Civile, Alghero, Italy, 16Department of Nephrology and Dialysis, Ospedale San Camillo, Sorgono, Italy, 17Department of Nephrology and Dialysis, Azienda Ospedaliera Carlo Poma, Mantua, Italy, 18Department of Nephrology and Dialysis, Ospedale ‘S. Francesco’, Nuoro, Italy, 19Department of Nephrology and Dialysis, ASL 2 of Olbia – P.O. ‘P. Dettori’, Tempio Pausania, Italy, 20Department of Nephrology and Dialysis, Ospedale S. Giovanni di Dio, Olbia, Italy, 21Department of Nephrology and Dialysis, Fondazione Maugeri IROCS, Pavia, Italy, 22Department of Nephrology and Dialysis, Ospedale Agostino Landolfi, Solofra, Italy and 23Department of Nephrology and Dialysis, Azienda Ospedaliera ‘Bianchi Melacrino Morelli’, Reggio Calabria, Italy

Correspondence and offprint requests to: Francesco Locatelli; E-mail: f.locatelli@ospedale.lecco.it

ABSTRACT

Background. Whether convective therapies allow better control of serum phosphate (P) is still undefined, and no data are available concerning on-line haemofiltration (HF). The objectives of the study are to evaluate the effect of convective treatments (CTs) on P levels in comparison with low-flux haemodialysis (HD) and to evaluate the correlates of serum phosphate in a post hoc analysis of a randomized clinical trial.

Methods. This analysis was performed in the database of a multicentre, open label and randomized controlled study in which 146 chronic HD patients from 27 Italian centres were randomly assigned to HD (70 patients) or CTs: on-line pre-dilution HF (36 patients) or on-line pre-dilution haemodiafiltration (40 patients).

Results. CTs did not affect P (P = 0.526), calcium (Ca) (P = 0.849) and parathyroid hormone levels (P = 0.622). P levels were associated with the use of phosphate binders including aluminium-based phosphate binders (P < 0.001) and sevelamer...
(P < 0.001), pre-dialysis bicarbonate levels (P < 0.001) and pre-dialysis blood K levels (P < 0.001). On multivariate analysis (generalized linear model), serum P was again largely un-associated with CTs (P = 0.631). Notably, participating centres were by far the strongest independent correlate of serum P, explaining 45.3% of the variance of serum P over the trial and this association was confirmed at multivariate analysis. Bicarbonate (P < 0.001) and, to a weaker extent, serum K (P = 0.032) were independently related to serum P.

Conclusions. In comparison with low-flux HD, CTs did not significantly affect serum P levels. Participating centres were the main source of P variability during the trial followed by treatment with phosphate binders, serum bicarbonate and, to a weak extent, serum potassium levels (ClinicalTrials.gov Identifier: NCT011583309).

Keywords: haemodialysis, on-line haemodiafiltration, on-line haemofiltration, phosphate, convective therapies

INTRODUCTION

Hyperphosphataemia is one of the most frequent alterations in patients with kidney failure and represents a crucial element in mineral bone disorders in this population. Inhibition of 1-alpha-hydroxylation of 25-hydroxyvitamin D3 via the fibroblast growth factor-23 pathway by high serum phosphate and the ensuing calcitriol deficiency may result in hyperparathyroidism and bone disease [1]. On the other hand, hyperphosphataemia entails an excess risk for vascular damage and death in this population, and a recent meta-analysis focusing on biomarkers of bone and mineral disorders in chronic kidney disease (CKD) patients [2] has identified phosphate as the most solid predictor of adverse clinical outcomes in CKD. Correction and prevention of hyperphosphataemia is a fundamental component of the management of patients with kidney failure, and both phosphorus binders and restricted dietary phosphorus intake are formally recommended by current guidelines [3].

Because phosphate is an intracellular anion primarily removed by diffusion, it is not effectively reduced by conventional dialysis. Larger dialyser surface area, higher blood and dialysate flows and higher glucose and bicarbonate levels in the dialysate have been inconsistently associated with better phosphate removal [4–6]. Observations in patients entering daily nocturnal dialysis strongly suggest that long dialysis may fully correct hyperphosphataemia [7]. However, such a possibility is limited by logistic and cost considerations in most dialysis centres and for this reason the addition of convective removal to standard removal by diffusion with haemodiafiltration (HDF) has been proposed as an alternative to long dialysis. In this respect, in 1999 Zehnder et al. [8] reported that HDF may allow better control of hyperphosphataemia but two subsequent papers failed to confirm this finding [5–6, 9]. A recent audit in a large dialysis network reported slightly lower serum phosphate levels in patients on HDF than in haemodialysis (HD) patients despite shorter treatment session times [10]. However, the lack of control for potential confounders like the use of phosphate binders, diet and bias by indication make data interpretation in this audit problematic. From a methodological point of view, the analysis of the problem in a clinical trial designed to compare standard HD with convective techniques may limit bias and provide important information for testing the hypothesis that convection allows significant additional removal of phosphate when compared with standard dialysis.

Within the framework of the CONVESTUDY [11], a randomized trial comparing standard low-flux HD with two convective techniques (on-line pre-dilution haemofiltration (HF) and on-line pre-dilution HDF) in terms of haemodynamic stability and various clinical end points, we performed an analysis aimed at establishing whether these techniques have a differential effect on phosphate (P) and parathyroid hormone (PTH) levels. This paper describes the effects of these techniques on the main biomarkers of calcium-phosphate metabolism in the CONVESTUDY.

METHODS

Study design

This is a post hoc analysis of a multicentre, open label and randomized trial involving 27 Italian dialysis centres and comparing low-flux HD with on-line pre-dilution HF and/or on-line pre-dilution HDF (CONVESTUDY) [11]. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of each centre. All of the patients gave their written informed consent before enrolment.

Details of the study protocol have been published elsewhere [12]. Eligible patients were randomly assigned by e-mail to receive low-flux HD or convective treatments (CTs) (1:1) to on-line pre-dilution HF or on-line pre-dilution HDF using a central computer-generated randomization list stratified by centre. After a 2-month run-in period, the planned 2 years of the experimental phase were divided into two periods: a fixed 3-month adaptation period and a subsequent 21-month evaluation period. According to the protocol, the patients who did not complete the adaptation period were excluded from the modified intention-to-treat (ITT) analysis.

Participants

Patients aged 18–80 years were considered eligible if they had been undergoing thrice-weekly HD or HDF for at least 6 months, had a body weight of <90 kg and were in stable clinical condition. The patients with clinically relevant infections, malignancies, active systemic diseases, active hepatitis or cirrhosis, unstable diabetes, diuresis of >200 mL/24 h or a dysfunctional vascular access with a blood flow rate of <300 mL/min were excluded from the study.

Extracorporeal treatments and drug therapy

The HD, HF and HDF machines were all equipped with a dialysis fluid ultrafiltration system for the production of ultra-pure dialysate [with each millilitre containing <0.1 colony-forming units (CFU) and <0.03 endotoxin units (EU)] and sterile non-pyrogen substitution fluid (<0.001 CFU/L and <0.03 EU/mL), which was checked at monthly intervals. Blood flow rate was 300–400 mL/min and treatment time of 3–4.5 h per session. HD was performed using a low-flux membrane and a dialysate flow rate of 500 mL/min; HF using a synthetic high-flux
membrane and an infusate/blood flow ratio of 1 and HDF using a synthetic high-flux membrane with an infusate/blood flow ratio of 0.6 and a dialysate plus infusate rate of 700 mL/min.

Routine patient care, the dialysate/infusate composition and the prescription of medications were decided by attending nephrologists. Therapy with phosphate binders was registered considering separately the use of aluminium-based phosphate binders (yes versus no), the calcium-based phosphate binders (scored as no therapy, dose ≤2 g/day, >2 g/day) and sevelamer (scored as no therapy, dose ≤3.2 g/day, >3.2 g/day). Therapy with oral or i.v. vitamin D was considered as a dummy variable (0/1). Drug compliance was not specifically addressed.

Laboratory data and dialysis dose

Pre-dialysis levels of haemoglobin (Hb) serum electrolytes (including sodium, potassium, bicarbonate, calcium, phosphate), urea and creatinine were checked monthly; urea and sodium were also evaluated monthly at the end of the session. Iron status and the levels of C-reactive protein and albumin were checked every 3 months. Intact PTH levels were checked every 6 months. All laboratory samples were analysed by standard techniques in laboratories of nephrology centres participating in the CONVESTUDY.

Equilibrated Kt/V (eKt/V) and equilibrated normalized protein catabolic rate (ePCRn) values were calculated monthly using the procedures and simplified equations of Daugirdas [13].

Statistical analysis and outcome measures

The descriptive analysis was based on the median values and interquartile ranges (IQRs) or mean values and standard deviations of the normally distributed continuous variables, and counts and percentages of the categorical variables. Baseline differences in clinical and laboratory variables between the three groups were tested using Mann–Whitney U-test for continuous variables, and the χ² test for categorical variables. A separate analysis was made for P and PTH levels. The general linear model for repeated measures of analysis of variance was used to test the effect of the experimental treatments (HF and HDF) in comparison with the reference treatment (HD) and to identify predictors related to P and PTH levels over the trial. The tested covariates were the participating centre, age, the type and dosage of phosphate binders, bicarbonate levels, eKt/V, the ePCRn total calcaemia, PTH and potassium levels. The major inter-subject factor was the randomly assigned group. The group effect was tested using the group-by-time interaction, with the HD group being considered the reference. The effect size was estimated by means of the partial η² value associated with each predictor. All statistical analyses were made using SPSS for Windows, release 18.0.

The primary outcome of this study was the evaluation of the effect of pure (HF) and/or mixed convection (HDF) in comparison with diffusion (HD) on P levels, as estimated by the changes in P levels between the 2-month run-in period and the 21-month evaluation period, adjusted for the relevant associated covariates.

RESULTS

Baseline characteristics

A total of 146 patients were enrolled, centrally randomized to HD (70 patients), HF (36 patients) or HDF (40 patients) and followed up for a median of 1.5 years (IQR 0.8–2.2).

Table 1 summarizes the baseline clinical and laboratory characteristics of the three groups which were similar in terms of gender, body weight, comorbidities, dialysis vintage and dialysis treatment time, whereas there were minor differences among groups for age and the proportion of diabetes. At baseline (Table 1), there were no between-group differences in the biochemical variables related to the dialysis dose for small molecular weight solutes (estimated by means of eKt/V), Hb, calcaemia, phosphataemia, PTH, bicarbonate, kalaemia and plasma albumin. The therapy with phosphate binders and/or vitamin D was not different among the three study groups (P = 0.356 and P = 0.815, respectively).

The CONSORT diagram of the study is reported in Figure 1. Fifteen patients (10.3%) died during the study, with no difference between the groups (P = 0.403). The causes of death were infection (four patients), acute myocardial infarction (three patients), cachexia (two patients), pulmonary embolism (two patients) and post-operative complications, cardiovascular disease, acute pulmonary oedema and acute cerebral bleeding (one patient each). Thirteen patients (8.9%) received a cadaveric kidney transplant with no difference between the groups (P = 0.273). Only 10 patients (6.8%: 4 patients in the HD, 1 patient in the HDF and 5 patients in the HF group) (P = 0.127) dropped out during the 3-month adaptation period. The main analysis therefore involved 136 patients (93.2%), 66 on HD, 39 on HDF and 31 on HF (Figure 1). Baseline characteristics of the 136 studied patients were not different from the population as a whole (146 patients, data not shown).

As per the protocol, the eKt/V remained unchanged in patients randomized to HD [baseline: 1.27 (IQR 1.15–1.44); during the trial: 1.28 (IQR 1.14–1.44)]. As expected, eKt/V decreased (P < 0.001) in those randomized to HF [from 1.22 (IQR 1.13–1.40) to 1.11 (IQR 0.98–1.23)]. Patients in the HDF arm had a slightly lower eKt/V at baseline [1.20 (IQR 1.13–1.37)] in comparison with other groups. During the trial, eKt/V in this group rose to 1.37 (IQR 1.21–1.50) (P < 0.001). Overall eKt/V did not differ significantly during the trial (P = 0.968).

Dietary protein intake, estimated by ePCRn at baseline and monthly during follow-up, was not different among groups at baseline and during follow-up (P = 0.994). As shown in Table 2, the use of phosphate binders tended to decrease over follow-up from 90.4 to 83.0%, while the use of the active forms of vitamin D remained constant in the three groups. Plasma bicarbonate (20.3 + 2.5 mmol/L) and potassium levels (5.53 + 0.65 mmol/L) were similar at baseline in the three study arms (P = 0.987 and P = 0.733, respectively) and did not change during the trial (P = 0.667 and P = 0.867, respectively).

Total median reinfusion in pre-dilution mode was equal to 60.4 L per HF session (IQR 50.2–69.9), 106% of dry body weight and 39.9 L per HDF session (IQR 28.2–51.0), 64% of

Table 1 summarizes the baseline clinical and laboratory characteristics of the three groups which were similar in terms of gender, body weight, comorbidities, dialysis vintage and dialysis treatment time, whereas there were minor differences among groups for age and the proportion of diabetes. At baseline (Table 1), there were no between-group differences in the biochemical variables related to the dialysis dose for small molecular weight solutes (estimated by means of eKt/V), Hb, calcaemia, phosphataemia, PTH, bicarbonate, kalaemia and plasma albumin. The therapy with phosphate binders and/or vitamin D was not different among the three study groups (P = 0.356 and P = 0.815, respectively).

The CONSORT diagram of the study is reported in Figure 1. Fifteen patients (10.3%) died during the study, with no difference between the groups (P = 0.403). The causes of death were infection (four patients), acute myocardial infarction (three patients), cachexia (two patients), pulmonary embolism (two patients) and post-operative complications, cardiovascular disease, acute pulmonary oedema and acute cerebral bleeding (one patient each). Thirteen patients (8.9%) received a cadaveric kidney transplant with no difference between the groups (P = 0.273). Only 10 patients (6.8%: 4 patients in the HD, 1 patient in the HDF and 5 patients in the HF group) (P = 0.127) dropped out during the 3-month adaptation period. The main analysis therefore involved 136 patients (93.2%), 66 on HD, 39 on HDF and 31 on HF (Figure 1). Baseline characteristics of the 136 studied patients were not different from the population as a whole (146 patients, data not shown).

As per the protocol, the eKt/V remained unchanged in patients randomized to HD [baseline: 1.27 (IQR 1.15–1.44); during the trial: 1.28 (IQR 1.14–1.44)]. As expected, eKt/V decreased (P < 0.001) in those randomized to HF [from 1.22 (IQR 1.13–1.40) to 1.11 (IQR 0.98–1.23)]. Patients in the HDF arm had a slightly lower eKt/V at baseline [1.20 (IQR 1.13–1.37)] in comparison with other groups. During the trial, eKt/V in this group rose to 1.37 (IQR 1.21–1.50) (P < 0.001). Overall eKt/V did not differ significantly during the trial (P = 0.968).

Dietary protein intake, estimated by ePCRn at baseline and monthly during follow-up, was not different among groups at baseline and during follow-up (P = 0.994). As shown in Table 2, the use of phosphate binders tended to decrease over follow-up from 90.4 to 83.0%, while the use of the active forms of vitamin D remained constant in the three groups. Plasma bicarbonate (20.3 + 2.5 mmol/L) and potassium levels (5.53 + 0.65 mmol/L) were similar at baseline in the three study arms (P = 0.987 and P = 0.733, respectively) and did not change during the trial (P = 0.667 and P = 0.867, respectively).

Total median reinfusion in pre-dilution mode was equal to 60.4 L per HF session (IQR 50.2–69.9), 106% of dry body weight and 39.9 L per HDF session (IQR 28.2–51.0), 64% of
dry body weight and the reinfusion volume was maintained constant throughout the trial.

**Effect of CTs on phosphate, calcium and PTH**

Baseline values of P, Ca and PTH were not different in the three study groups (Table 1) and remained quite stable across the trial in the HD group as well as in the HF and HDF group (Figure 2). CTs did not affect P (P = 0.526), calcium (P = 0.849) and PTH levels (P = 0.622).

At univariate analysis, P levels were associated directly with the use of phosphate binders including aluminium-based phosphate binders (P < 0.001) and sevelamer (P < 0.001) and with pre-dialysis serum K levels (P < 0.001), and they were associated inversely with age (P < 0.001) and pre-dialysis bicarbonate levels (P < 0.001).

**DISCUSSION**

This analysis of the CONVESTUDY shows that, at constant phosphate binders and active vitamin D use, serum phosphate during long-term treatment with convective (HF and HDF) and standard low-flux dialysis remains quite similar in patients randomized to these extracorporeal therapies. The main

Table 1. Clinical and laboratory characteristics of enrolled patients at baseline.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>HD</th>
<th>pre-HF</th>
<th>pre-HDF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>146</td>
<td>70</td>
<td>36</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.646</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>84 (57.5)</td>
<td>43 (61.4)</td>
<td>19 (52.8)</td>
<td>22 (55.0)</td>
<td></td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>62 (42.5)</td>
<td>27 (38.6)</td>
<td>17 (47.2)</td>
<td>18 (45.0)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.9 ± 11.9</td>
<td>63.0 ± 10.7</td>
<td>66.8 ± 12.1</td>
<td>62.8 ± 13.4</td>
<td>0.086</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>64.1 ± 10.9</td>
<td>64.7 ± 9.7</td>
<td>60.9 ± 9.6</td>
<td>66.0 ± 13.2</td>
<td>0.115</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>83 (56.8)</td>
<td>39 (55.7)</td>
<td>20 (55.6)</td>
<td>24 (60)</td>
<td>0.894</td>
</tr>
<tr>
<td>Diabetes, no. (%)</td>
<td>26 (17.8)</td>
<td>12 (17.1)</td>
<td>3 (8.3)</td>
<td>11 (27.5)</td>
<td>0.091</td>
</tr>
<tr>
<td>Dialysis vintage (years)</td>
<td>3.0 (1.4–7.7)</td>
<td>2.5 (1.2–9.0)</td>
<td>4.1 (1.4–7.7)</td>
<td>3.1 (1.5–6.1)</td>
<td>0.636</td>
</tr>
<tr>
<td>Dialysis time (min)</td>
<td>240 (210–240)</td>
<td>240 (210–240)</td>
<td>240 (210–240)</td>
<td>240 (221–240)</td>
<td>0.650</td>
</tr>
<tr>
<td>Urea at start of session (mg/dL)</td>
<td>169 ± 36</td>
<td>170 ± 37</td>
<td>166 ± 41</td>
<td>169 ± 29</td>
<td>0.851</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>11.5 ± 1.5</td>
<td>11.5 ± 1.3</td>
<td>11.3 ± 1.2</td>
<td>11.8 ± 1.2</td>
<td>0.135</td>
</tr>
<tr>
<td>Total calcium (mg/dL)</td>
<td>9.11 ± 0.69</td>
<td>9.05 ± 0.61</td>
<td>9.19 ± 0.74</td>
<td>9.15 ± 0.79</td>
<td>0.591</td>
</tr>
<tr>
<td>Calcium–phosphorous product (mg/dL)²</td>
<td>44.9 ± 11.9</td>
<td>44.6 ± 12.4</td>
<td>45.2 ± 12.0</td>
<td>45.1 ± 11.2</td>
<td>0.965</td>
</tr>
<tr>
<td>PTH (ng/mL)</td>
<td>241 (110–392)</td>
<td>234 (101–357)</td>
<td>241 (133–454)</td>
<td>252 (109–485)</td>
<td>0.517</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>20.3 ± 2.5</td>
<td>20.3 ± 2.4</td>
<td>20.3 ± 2.2</td>
<td>20.2 ± 2.7</td>
<td>0.989</td>
</tr>
<tr>
<td>K (mEq/L)</td>
<td>5.54 ± 0.65</td>
<td>5.51 ± 0.60</td>
<td>5.62 ± 0.66</td>
<td>5.52 ± 0.73</td>
<td>0.700</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.95 ± 0.42</td>
<td>3.93 ± 0.46</td>
<td>3.94 ± 0.37</td>
<td>3.98 ± 0.40</td>
<td>0.958</td>
</tr>
<tr>
<td>eKt/V</td>
<td>1.28 ± 0.20</td>
<td>1.31 ± 0.20</td>
<td>1.27 ± 0.15</td>
<td>1.23 ± 0.24</td>
<td>0.317</td>
</tr>
<tr>
<td>ePCrụ (g/kg/day)</td>
<td>1.12 ± 0.22</td>
<td>1.15 ± 0.23</td>
<td>1.09 ± 0.22</td>
<td>1.11 ± 0.19</td>
<td>0.425</td>
</tr>
<tr>
<td>On phosphate binders (%)</td>
<td>131 (89.7)</td>
<td>61 (87.1)</td>
<td>34 (94.4)</td>
<td>36 (90.0)</td>
<td>0.502</td>
</tr>
<tr>
<td>With two or more phosphate binders (%)</td>
<td>79 (54.1)</td>
<td>37 (52.9)</td>
<td>25 (69.4)</td>
<td>17 (42.5)</td>
<td>0.060</td>
</tr>
<tr>
<td>On aluminium-based phosphate binders (%)</td>
<td>20 (13.7)</td>
<td>10 (14.3)</td>
<td>3 (8.3)</td>
<td>7 (17.5)</td>
<td>0.500</td>
</tr>
<tr>
<td>On calcium-based phosphate binders (%)</td>
<td>83 (56.8)</td>
<td>41 (58.6)</td>
<td>22 (61.1)</td>
<td>20 (50.0)</td>
<td>0.572</td>
</tr>
<tr>
<td>On sevelamer (%)</td>
<td>75 (51.4)</td>
<td>32 (45.7)</td>
<td>22 (61.1)</td>
<td>21 (52.5)</td>
<td>0.319</td>
</tr>
<tr>
<td>On active vitamin D (%)</td>
<td>69 (47.3)</td>
<td>35 (50.0)</td>
<td>17 (47.2)</td>
<td>17 (42.5)</td>
<td>0.750</td>
</tr>
</tbody>
</table>

Some continuous variables such as dialysis vintage and PTH are skewed to the right and thus represented by median and IQR. P-values were obtained from χ²- or Kruskal-Wallis test for categorical and continuous variables, respectively.

**FIGURE 1:** Flow chart of evaluated patients.
sources of P variability during the trial were participating centres, treatment with phosphate binders, serum bicarbonate and, to a weak extent, serum potassium levels. Overall, this analysis suggests that, as applied in everyday clinical practice, convection added to diffusion is unlikely to improve the control of steady-state serum phosphate over time when compared with standard low-flux HD. Since we did not measure whole-body phosphate pool we cannot rule out the possibility that CTs reduced the whole-body P burden, without affecting serum P. Furthermore, this study further highlights the relevance of local clinical policies in the control of hyperphosphataemia.

Individuals on a normal phosphate diet (25–40 mmol/day) absorb ∼15–35 mmol/day of phosphate. If phosphate excess is to be eliminated by dialysis, this treatment should subtract 35–81 mmol per dialysis in patients on standard thrice-weekly regimens. HD with high-flux membranes removes ∼30 mmol over a 4-h treatment [17]. Given the huge pill burden demanded by the use of phosphate binders (four 400-mg calcium acetate tablets are needed to remove 1 mmol of phosphate) efforts at enhancing extracorporeal phosphate removal represent an important clinical research goal.

Table 2. Therapy with various types of phosphate binders at baseline and during follow-up.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total n = 136</th>
<th>HD n = 66</th>
<th>Pre-HF n = 31</th>
<th>Pre-HDF n = 39</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Follow-up</td>
<td>Baseline</td>
<td>Follow-up</td>
<td>Baseline</td>
<td></td>
</tr>
<tr>
<td>On phosphate binders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With two or more phosphate binders</td>
<td>90.4</td>
<td>83.0</td>
<td>87.9</td>
<td>76.9</td>
<td></td>
</tr>
<tr>
<td>On aluminium-based phosphate binders</td>
<td>54.4</td>
<td>48.9</td>
<td>53.0</td>
<td>46.2</td>
<td></td>
</tr>
<tr>
<td>On calcium-based phosphate binders</td>
<td>14.0</td>
<td>12.6</td>
<td>13.6</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td>On sevelamer</td>
<td>58.1</td>
<td>52.6</td>
<td>59.1</td>
<td>44.6</td>
<td></td>
</tr>
<tr>
<td>On active o.s. or i.v. vitamin D</td>
<td>50.0</td>
<td>41.5</td>
<td>45.5</td>
<td>38.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On aluminium-based phosphate binders</td>
<td>47.8</td>
<td>51.9</td>
<td>50.0</td>
<td>53.8</td>
<td></td>
</tr>
<tr>
<td>On calcium-based phosphate binders</td>
<td>0.893</td>
<td>0.886</td>
<td>0.631</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>On sevelamer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On active o.s. or i.v. vitamin D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P-values were obtained from binary multiple logistic regression, using the interaction of the type of treatment (HD, pre-HF and pre-HDF) by period (baseline and follow-up). The corner ‘HD treatment at baseline’ was used as the reference category. Although the results of table suggests some differences, convective therapies were not associated with a significant variation in the use of any binder drug.

Table 3. Independent correlates of phosphate levels over the trial in dialysis patients (generalized linear model)

<table>
<thead>
<tr>
<th>Variable</th>
<th>β coefficient</th>
<th>P-value</th>
<th>Partial η² model (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period effect</td>
<td>0.893</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Group difference</td>
<td>0.886</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>CTs effect</td>
<td>0.631</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Participating centre</td>
<td>0.005</td>
<td>0.208</td>
<td>45.3</td>
</tr>
<tr>
<td>Bicarbonate(mEq/L)</td>
<td>-0.125</td>
<td>&lt;0.001</td>
<td>0.058</td>
</tr>
<tr>
<td>Kalaemia (mmol/L)</td>
<td>0.259</td>
<td>0.032</td>
<td>0.022</td>
</tr>
<tr>
<td>Aluminium-based phosphate binders (yes versus no)</td>
<td>0.781</td>
<td>&lt;0.001</td>
<td>0.055</td>
</tr>
<tr>
<td>Sevelamer (for each unit score increase)</td>
<td>0.392</td>
<td>&lt;0.001</td>
<td>0.075</td>
</tr>
<tr>
<td>Calcium-based phosphate binders (for each unit score increase)</td>
<td>0.274</td>
<td>0.034</td>
<td>0.021</td>
</tr>
<tr>
<td>Calcaemia (mg/dL)</td>
<td>-0.171</td>
<td>0.130</td>
<td>0.011</td>
</tr>
<tr>
<td>Total</td>
<td>0.459</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There was no CTs effect (P = 0.631).

FIGURE 2: Phosphate, calcium and PTH levels at baseline and during the follow-up among the three treatment groups. The median values labelled as ‘follow-up’ were obtained from each patient during the 21-month evaluation phase. The values of the 3-month adaptation phase were excluded.
phosphate binders constitute the cornerstone for controlling hyperphosphataemia in dialysis patients. Furthermore, increasing dialysis phosphate removal is set as a specific treatment goal in patients with hyperphosphataemia in the same guidelines. In particular, the efficacy of daily, nocturnal dialysis is emphasized [16]. However, renal physicians face relevant organizational and financial difficulties in performing longer and/or more frequent dialysis schedules.

CTs have been proposed as an interesting possibility to enhance extracorporeal removal of phosphate in dialysis patients [8, 18–19] but evidence in support of this proposal remains scanty and controversial. Zehnder et al. [8] compared P clearance in 16 patients treated for 1 week with high-flux HD followed by a 1-week treatment with on-line HDF and found that HDF produces a marked (33%) increase in P clearance. The sequential design is an inherent limitation of the Zehnder study, which does not allow a firm conclusion on the issue. Lorno et al. [20] performed a randomized trial in 22 HD patients assigned to post-dilution on-line HDF (4 h) or to high-flux HD of identical duration. The P removal was marginally higher in HDF than in high-flux HD, but this effect was restricted to patients with slight hyperphosphataemia (5.0–5.5 mg/dL), and the apparently higher phosphate removal by HDF did not translate into a measurable reduction in serum phosphate. A secondary analysis of the CONTRAST study [21] tested the hypothesis that HDF on line may have a favourable impact upon P control in dialysis patients. This study failed to show a clear benefit of HDF when compared with standard HD (mean difference in serum phosphate: −0.17 mg/dL; confidence interval −0.44/ +0.11 mg/dL) and only after adjusting for phosphate binders use did a marginal difference favouring HDF over HD (−0.36 mg/dL) materialize in this analysis. Two recent randomized clinical studies primarily aimed to investigate the effect of convective therapies on mortality failed to show an effect of these treatments on phosphate control [22–23].

Our finding that CTs do not determine any advantage in terms of serum phosphate levels control is in keeping with current knowledge about the kinetics of phosphate removal. Phosphate has a multi-compartmental distribution with a complex kinetics [24], and time is the critical variable to increase phosphate removal during extracorporeal treatments [17]. Our findings are in keeping with studies [17, 25] emphasising that time rather than membrane type or the type of extracorporeal treatment (HDF versus HD) is the critical, modifiable variable which may allow better control of hyperphosphataemia in dialysis patients.

Perhaps, the most interesting finding in our study is the large variability of P plasma levels across participating centres, accounting for ≈45% of the variability in serum phosphate. Differences in the timing of the pre-dialysis blood sample or the duration or intensity of the dialysis sessions could explain the inter-centre variability in serum P. However, adding to the generalized model the timing of the samples (first or second dialysis of the week), dialysis duration and the intensity of dialysis as estimated by the blood flow rate, none of these variables were independently related to phosphate levels. Moreover, adding these covariates and removing the centre effect, their prediction power did not change, suggesting that the centre effect cannot be explained by these covariates. This high variability across participating centres suggests that there is much room for improving P control simply by multiplying efforts to improve the implementation of current guidelines [15], i.e. by promoting the application of adequate diet, better use of phosphate binders and, whenever possible, longer dialysis. Serum P associated inversely with plasma bicarbonate and directly with serum K, further underscores the need for considering the acid-base and nutritional status for the interpretation of prevailing serum P levels in dialysis patients.

A limitation to our study is that since we did not measure whole-body phosphate pool we cannot fully rule out the possibility that CTs could have reduced the whole-body P burden, without affecting serum P. Furthermore, this study further highlights the relevance of local clinical policies in the control of hyperphosphataemia. The use of a modified ITT analysis could be another potential limitation of our study, although it was pre-specified in the protocol. Moreover, there was an imbalance in baseline patient characteristics because the HF-treated patients were older. Finally, the relative small number of included patients did not allow other post hoc analyses.
A point of strength of our study is that it is the first time that the use of various types of phosphate binders has been accurately investigated in the context of convective therapies and with a multivariate approach, combining their action with other confounders. In agreement with other studies [26], we found that phosphate binders (90.4%) and active forms of vitamin D (47.8%) were largely used in dialysis patients. The use of these drugs may be an important source of confounding in the interpretation of prevailing serum P levels in patients on CTs when compared with those on standard dialysis. However, in our study there were no differences in the use of these drugs in the three arms of this study, thus avoiding this possibly confounding factor [27]. Furthermore, multivariate analysis adjusting for these drugs as well as for serum calcium, another variable that emerged as a possible confounder [28] further confirmed that CTs do not portend any advantage in controlling serum P levels.

In conclusion, the results of this study do not support the hypothesis that CTs, either HDF or HF, may allow better control of hyperphosphataemia in patients on extracorporeal treatments. The fact that the participating centres were the most relevant factors explaining the variability of serum phosphate, further emphasizes the need for multiplying efforts to improve compliance to current guidelines (KDIGO) recommendations for phosphate control in dialysis patients.

ACKNOWLEDGEMENTS

We would like to thank all of the physicians, nurses and patients of the participating centres for their support, and Gambro Hospal for its logistic support for investigator meetings.

CONFLICT OF INTEREST STATEMENT

All of the authors declare that they have no conflict of interest related to this study.

REFERENCES

APPENDIX

STEERING COMMITTEE

Francesco Locatelli (Chairman: Lecco); Paolo Altieri (Co-chairman: Cagliari); Simeone Andrulli (Lecco); Carlo Basile (Acquaviva delle Fonti); Piergiorgio Bolasco (Cagliari); Salvatore Di Filippo (Lecco); Mariano Feriani (Mestre); Luciano Alberto Pedrini (Seriate); Salvatore David (Parma); Antonio Santoro (Bologna); Francesco Pizzarelli (Firenze); Carmine Zoccali (Reggio Calabria).

DATABASE AND CLINICAL RECORD FORM

Simeone Andrulli (Lecco); Piergiorgio Bolasco (Cagliari); Salvatore Di Filippo (Lecco).

QUALITY CONTROL

Giovanna Sau (Cagliari); Simeone Andrulli (Lecco).

STATISTICAL ANALYSIS

Simeone Andrulli (Lecco).

LIST OF PARTICIPATING CENTRES

Cagliari, S. Michele: Altieri Paolo, Sau Giovanna, Menneas P. Amalia, Mereu M. Cristina, Matta Valeria, Sardara Roberto.

Lecco, A. Manzoni: Locatelli Francesco, Manzoni Celestina, Di Filippo Salvatore, Andrulli Simeone, Bigi Maria Carla, Pontoriero Giuseppe.

Pavia, Fondazione Maugeri: Segagni Siro, Villa Giuseppe, Montagna Giovanni, Dell’Acqua Franca, Tomaselli Maria.

Solofra: Di Iorio Biagio Raffaele.

Quartu Sant’Elena: Bolasco Piergiorgio, Scotto Patrizia, Frongia M. Angelica, Peddio Giuseppe.

Napoli, Federico II: Memoli Bruno, Capuano Alfredo, Serio Vittorio.


Acireale: Battaglia Giovanni, Milone Filippo, Urso Salvatore, Garozzo Maurizio, D’Antonio Grazia, Saraceno Margherita.

Alghero: Casu Maria Domenica, Piras Angelo.

Cagliari, SS. Trinità: Ferrara Rocco, Pillosu Isabella.

Aosta: Alloitti Sandro, Nebioli Pier Eugenio, Pelli Valentina, Paroli Virna.

Tempio Pausania: Passaghe Mario, Chiarelli Giorgio, Cossu Rita.

Nuoro: Cadinu Francesco, Mattana, Cadunia, Pusceddu Rita, Pala Rosalia, Fadda Susanna.

Sorgono e Isili: Logias Franco, Esposito Maria Paola, Musu Antonietta, Murru Marco, Tolu Antioco, Noli Loretta, Onali Franco, Serra Salvatore.

Melito e Scilla: Marzolla Onofrio, Barreca Eleonora.

Pinerolo: Malcangi Ugo, Reina Ernesto.

Ravenna: Fusariol Maurizio, Montanari Augusto, Isola Elisabetta, Rosetta Vasi.

Olbia: Fundoni Gianfranco, Burrail Lucia.


Acquaviva delle Fonti: Basile Carlo, Antonelli Maurizio, Avella Anna Maria, Lassandro Michele.

Parma: Buzio Carlo, David Salvatore.

Mantova: Tarchini Renzo, Marseglia C.D., Bottini E., Talassi E., Baruffaldi M.

Mestre: Feriani Mariano, Fracasso Agostino, Genchi Rosanella, Boldrin Luigi.

Milano, Multimedica: Bertoli Silvio, Teodoli Silvia, Maio Giovanni, Arienti Alberto.

La Maddalena: Gazzanelli Luanna, Renga Salvatorica.

Ozieri: Ganadu Marino, Calvisi Luciabella.

Received for publication: 5.7.2013; Accepted in revised form: 20.1.2014