Prospective study of the short-term effect of 1.75 mmol/L calcium concentration dialysate on hemodialysis patients

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Abstract

Objective: The purpose of the current study was to determine the influence of a 1.75 mmol/L calcium (Ca) concentration dialysate (DCa 1.75) during maintenance hemodialysis (MHD) therapy for patients with chronic kidney disease, mineral, and bone disorders (CKD-MBD) on biochemical indices and clinical prognosis.

Methods: Four hundred eighty-three MHD patients from three hemodialysis centers were enrolled. During 24 months of follow-up (January 2011 to December 2012), 289 patients from Center 1 who used 1.50 mmol/L Ca concentration dialysate (Dca 1.50) between January and December 2011 and DCa 1.75 between January and December 2012 were included in the high Ca group. The remaining 194 patients from the other centers who used Dca 1.50 for hemodialysis between January 2011 and December 2012 were included in the ordinary Ca group. The following CKD-MBD biochemical indices were monitored: blood Ca; blood phosphorus (P); intact parathyroid hormone (iPTH); and bone-specific alkaline phosphatase (BAP). The metastatic calcification index included calcification of aortic arch scoring (AoACS), abdominal aorta calcification (AAC), and cardiac valve calcification (CVC). The study end points included all-cause mortality (ACM), cardiovascular and cerebrovascular diseases (CCVDs), fractures, and new metastatic calcifications. The changes between the two groups in the observed indices were compared.

Results: Two hundred eighty-four patients in the high Ca group (98.3%) and 194 patients in the ordinary Ca group (100.0%) completed an average follow-up of 21.3±5.6 months. After DCa 1.75 was used, the blood Ca in the high Ca group increased [(2.39±0.22) mmol/L vs. (2.34±0.21) mmol/L, t=–2.910, P=0.004] compared to the previous year, and increased [(2.39±0.22) mmol/L vs. (2.30±0.16) mmol/L, t=5.187, P<0.001] compared to the ordinary Ca group in the same year. The blood P and iPTH decreased [(1.78±0.39) mmol/L vs. (1.89±0.42) mmol/L, t=2.909, P=0.004 and (306.5±298.6) pg/ml vs. (425.7±365.1) pg/ml, t=8.377, P<0.001, respectively] compared with the previous year, and decreased [(1.78±0.39) mmol/L vs (1.86±0.39) mmol/L, t=–2.016, P=0.044 and (306.5±298.6) pg/ml vs. (366.6±341.0) pg/ml, t=–2.113, P=0.035, respectively] compared with the ordinary Ca group in the same year. There was no difference in AoACS between the two groups before and after the change in DCa in the high Ca group (P>0.05). In 2011, there were 13 CCVDs, 2 fractures, and 13 new metastatic calcifications in the ordinary Ca group compared to 8 CCVDs, 3 fractures, and 16 new metastatic calcifications in the high Ca group; there were no statistically significant differences in the incidence of end point events between the two groups (χ²=2.747, P=0.098). In 2012, the values for the ordinary Ca group were 13, 2, and 19, respectively, while the values for the high Ca group were 8, 1, and 19, respectively, which indicated a statistically significant difference in the incidence of end point events between the two groups (χ²=4.391, P=0.036).
Conclusion: Short-term use of DCa 1.75 significantly reduced the blood P and iPTH levels in MHD patients, significantly increased the blood Ca level, did not increase the proportion of new cardiovascular calcifications, and decreased the overall incidence of end point events.

Keywords: Hemodialysis dialysate, Dialysate, Calcium, Phosphorus, Parathyroid hormone

Introduction
Chronic kidney disease, mineral, and bone disorders (CKD-MBD), a common complication of patients on maintenance hemodialysis (MHD), not only causes renal osteodystrophy [1, 2], but increases the risk of cardiovascular disease (CVD) and all-cause mortality (ACM) [2–5] through metastatic calcifications. The key factor to control CKD-MBD is to control blood calcium (Ca), blood phosphorus (P), and parathyroid hormone (PTH) levels within the target ranges. The current hemodialysis centers in China, however, have failed to control the above-mentioned indices within the desired ranges. The Beijing Hemodialysis Quality Control and Improvement Center, for example, reported that 8.8% of the above-mentioned indices achieved standard targets in 2011 [6]. Under circumstances of a domestic lack of more effective means, high Ca dialysate (Ca ion concentration=1.75 mmol/L [DCa 1.75]), as an effective measure of reducing PTH levels [7], has been suggested. Considering that DCa 1.75 might lead to PTH over-inhibition, hypercalcemia, and metastatic calcifications, this study conducted a multi-center, prospective, and parallel control study to demonstrate the effectiveness and safety of the short-term clinical use of DCa 1.75.

Subjects and methods
Study subjects
The study was conducted between January 2011 and December 2012. This study selected MHD patients who received treatment in three hemodialysis centers (Beijing Friendship Hospital Affiliated to Capital Medical University [Center 1], Beijing Chaoyang Hospital Affiliated to Capital Medical University [Center 2], and Beijing Fuxing Hospital Affiliated to Capital Medical University [Center 3]). The inclusion criteria were as follows: (1) MHD duration >3 months; (2) good general health with a life expectancy >2 years; and (3) initial age of renal replacement therapy ≥18 years of age. The exclusion criteria were as follows: (1) new fracture within the last 3 months; (2) patients undergoing parathyroidectomy within the last 3 months due to secondary hyperparathyroidism (SHPT); (3) patients administered Ca-sensing receptor agonists (e.g., Cinacalcet Hydrochloride), vitamin D analogues (e.g., paricalcitol and maxacalcitol) or non-Ca-aluminum phosphate binders (e.g., lanthanum carbonate, and sevelamer hydrochloride); (4) patients with acute myocardial infarctions, strokes, and other cardiovascular and cerebrovascular diseases within the past 3 months; and (5) patients with poor compliance who do not have routine follow-up evaluations.

Dialysis method
All centers centralized the liquid supply system for configuration of the dialysate. Between January and December 2011, the following formula was used: Ca, 1.5 mmol/L; sodium, 135.0 mmol/L; magnesium, 2.0 mmol/L; potassium 2.5 mmol/L; and bicarbonate, 35.0 mmol/L. Between January and December 2012, patients from Center 1 used DCa 1.75 (high Ca group); the other ingredients remained unchanged. Patients from Centers 2 and 3 continued to use the original dialysate (ordinary Ca group). Each patient underwent dialysis 2–3 times per week for 4–5 h each time with a blood pump speed of 250–300 mL/min and a KT/V>1.2.

The observation indices
General situation: The general status of the patients included age, gender, the primary disease, and the dialysis time.

Detection of CKD-MBD biochemical indices: During the follow-up, the CKD-MBD biochemical indices of the patients, including blood Ca, blood P, intact PTH, alkaline phosphatase (ALP), and bone-specific (BAP), were determined. Blood Ca and blood P were measured every 3 months and BAP every 6 months. Every 3 months, serum was collected from
patients before dialysis and stored at –80°C for the simultaneous detection of iPTH and BAP at the end of the follow-up period. Measurement of iPTH was performed with a chemiluminescence method (Siemens Healthcare Diagnostics Products Limited, Glyn Rhonwy, Llanberis, United Kingdom) and BAP was determined using an enzyme immunoassay (EIA; Osteolinks BAP, Quidel Corpora Serum, San Diego, CA, USA).

Other indices included hemoglobin, albumin, creatinine, and total cholesterol, which were measured every month.

The above indices were detected using an automatic blood analyzer and an automatic biochemical analyzer in the experimental center of each unit, taking the average index at each time as the annual value using the following formula: corrected Ca (mg/dL) = serum Ca (mg/dL) + 0.8×[4.0-albumin (g/L)] to correct blood Ca; the blood Ca concentration is 1 mg/dL = 0.2495 mol/L.

Metastatic calcification assessment indices: Metastatic calcification assessment indices included calcification of aortic arch scoring (AoACS), abdominal aorta calcification (AAC), and cardiac valve calcification (CVC), and the progress of each index compared to the baseline level was determined to be a new metastatic calcification. Every 6 months, chest X ray examinations were obtained for determination of AoACS, abdominal lateral X-ray examinations for assessment of AAC, and ultrasound cardiogram examination for assessment of CVC [8]. AoACS and AAC were estimated by two imaging physicians and the average value was calculated; the CVC was estimated by the ultrasonic image professionals from each unit.

Follow-up of end point events: The patients in the two groups were followed between January 2011 and December 2012. The follow-up end point events included ACM, non-fatal cardiovascular and cerebrovascular diseases (CCVD), fractures, and new metastatic calcifications. If any end point event occurred, the patient continued to follow-up until the end of the study, and the blood biochemical examination results during the follow-up were included in the statistical analysis. At the same time as the follow-up evaluation, all adverse events were recorded.

The research project was approved by the Ethics Committee of Beijing Friendship Hospital Affiliated to Capital Medical University. This study conformed to the Declaration of Helsinki guidelines, and all patients signed informed consent.

The statistical method
SPSS 13.0 was used to perform statistical analyses. The repeated measurements of the indices for each patient were averaged annually before analysis. The continuous variables are expressed as the \( \bar{x} \pm s \), and the comparison between the two groups used an independent sample t-test or \( \chi^2 \) test. A \( P < 0.05 \) was considered statistically significant.

Results
General situation
The three centers included 483 MHD patients, among whom 289 were included in the high Ca group and 194 (106 in Center 2 and 88 in Center 3) were in the ordinary Ca group, accounting for 91.7% (289/315), 87.6% (106/121), and 81.5% (88/108) of all MHD patients undergoing dialysis in each center in January 2011. Two hundred eighty-four (98.3%) patients in the high Ca group and 194 (100.0%) patients in the ordinary Ca group conformed to the study program and completed the follow-up. Five patients in the high Ca group were transferred to another center for MHD treatment.

A comparison between the two groups with respect to gender, age, primary disease, and the average duration of dialysis showed that the differences were not statistically significant (\( P > 0.05 \); Table 1).

Comparison of CKD-MBD biochemical indices
In 2012, the average Ca correction level of the high Ca group increased compared with 2011, and increased compared with the ordinary Ca group in the same year (\( P < 0.05 \)). The blood P and iPTH levels in the high Ca group decreased compared with the 2011 levels and decreased compared with the ordinary Ca group in the same year (\( P < 0.05 \)). The difference between the two groups with respect to all other blood biochemical indices during the 2 years were not statistically significant (\( P > 0.05 \); Table 2).

Comparison of metastatic calcification assessment indices between the two groups
The AoACS in the two groups was not significantly different during the 2 years of follow-up (\( P > 0.05 \); Table 2).
Comparison of end point events between the two groups

All 478 patients who conformed to the study program and completed the follow-up had 3–24 months of follow-up without any end point event, thus an average of 21.3±5.6 months without a death end point event. There were 42 patients (8.8%) with CCVDs, 8 patients (1.7%) with fractures, and 63 patients (13.2%) with new metastatic calcifications. The comparison between the high Ca group and the ordinary Ca group in end point events each year during the follow-up was not statistically different ($P>0.05$). The difference in the total incidence of end point events between the high Ca group and the ordinary Ca group in 2011 were not statistically significant ($\chi^2=2.747$, $P=0.098$). In 2012, the incidence of end point events in the high Ca group was lower than the ordinary Ca group; the difference was statistically significant ($\chi^2=4.391$, $P=0.036$; Table 3). No end point events occurred in the 5 patients who were transferred during the follow-up period. There was no adverse events (nausea, vomiting, headache, uncontrolled blood pressure, new arrhythmias, or previous arrhythmia exacerbations) that were related to DCa 1.75.

Discussion

Most of the blood purification centers in China implement the purification standards of the Kidney Disease Outcomes Quality Initiative (K/DOQI), as recommended by the American Kidney Foundation [9]. Beginning in 2003, DCa has been reduced from 1.75 mmol/L to 1.5 mmol/L, but in the past 10 years the CKD-MBD clinical indices have not improved significantly. It has been shown that the ratio of blood Ca, blood P, and iPTH of domestic MHD patients reaching the standards is significantly lower than the 2007 Dialysis Outcomes and Practice Patterns Study (DOPPS) 3 and 2010 DOPPS 4 [10]. The clinical data generated by this research center over the past 10 years has also shown that the proportion of patients in whom the 3 main biochemical indices reached the standards was <9%. Because medication for the treatment of CKD-MBD in China is significantly inferior to some other countries, and the level of evidence-based medicine suggested by K/DOQI [9] or KDIGO [11] is low, this research center sponsored a multi-center, prospective, and parallel control study to investigate the influence of DCa 1.75 on CKD-MBD biochemical index control and occurrence of short-term complications in MHD patients.

Research has shown that DCa 1.75 can effectively reduce blood P and PTH [10, 12, 13], and the results of this study have demonstrated that the blood P and iPTH levels of the high Ca group patients after modification of DCa decreased significantly compared with the previous year and the control group in the same year. Some research has also shown that the high blood P and iPTH levels are independent risk factors for death in MHD patients [5, 14–16]. Therefore, effective control of blood P and iPTH levels are of clinical benefit. In the case of Ca-sensing receptor agonist failure, vitamin D analogues or non-aluminum phosphate binders of non-Ca as a model drug, DCa 1.75 is an effective control measure of blood P and iPTH levels.

The core problem of restricting the DCa 1.75 clinical application is Ca overload and the resulting metastatic calcifications, such as CAC [17, 18], peripheral arterial calcifications...
Table 2. Comparison of clinical indices between two groups

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Kt/V</th>
<th>Hemoglobin (g/L)</th>
<th>Albumin (g/L)</th>
<th>Cr (μmol/L)</th>
<th>Total cholesterol (mmol/L)</th>
<th>Corrected Ca (mmol/L)</th>
<th>Blood P (mg/dL)</th>
<th>iPTH (pg/ml)</th>
<th>Alkaline phosphatase (U/L)</th>
<th>Bone specific alkaline phosphatase (U/L)</th>
<th>AoACS (score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Ca group</td>
<td>2012</td>
<td>1.5±0.3</td>
<td>114.9±13.6</td>
<td>38.3±2.7</td>
<td>817.5±184.3</td>
<td>4.2±0.9</td>
<td>2.3±0.2</td>
<td>1.9±0.4</td>
<td>425.7±365.1</td>
<td>1057±45.4</td>
<td>17.5±4.66</td>
<td>0.24±0.24</td>
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<td></td>
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<td>425.7±365.1</td>
<td>1057±45.4</td>
<td>17.5±4.66</td>
<td>0.24±0.24</td>
</tr>
<tr>
<td>T value</td>
<td>0.116</td>
<td>-0.71</td>
<td>1.05</td>
<td>0.57</td>
<td>-2.91</td>
<td>2.909</td>
<td>8.377</td>
<td>-0.287</td>
<td>1.304</td>
<td>0.124</td>
<td></td>
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</tr>
<tr>
<td>P value</td>
<td>0.908</td>
<td>0.906</td>
<td>0.48</td>
<td>0.295</td>
<td>0.004</td>
<td>0.004</td>
<td>&lt;0.001</td>
<td>0.774</td>
<td>0.195</td>
<td>0.902</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ordinary Ca group</td>
<td>2012</td>
<td>1.5±0.3</td>
<td>114.9±13.6</td>
<td>38.3±2.7</td>
<td>817.5±184.3</td>
<td>4.2±0.9</td>
<td>2.3±0.2</td>
<td>1.9±0.4</td>
<td>425.7±365.1</td>
<td>1057±45.4</td>
<td>17.5±4.66</td>
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<td>425.7±365.1</td>
<td>1057±45.4</td>
<td>17.5±4.66</td>
<td>0.24±0.24</td>
</tr>
<tr>
<td>T value</td>
<td>-0.473</td>
<td>-0.8</td>
<td>1.18</td>
<td>0.481</td>
<td>1.05</td>
<td>0.382</td>
<td>1.376</td>
<td>-0.836</td>
<td>-0.189</td>
<td>-0.988</td>
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<tr>
<td>P value</td>
<td>0.636</td>
<td>0.425</td>
<td>0.24</td>
<td>0.632</td>
<td>0.297</td>
<td>0.703</td>
<td>0.17</td>
<td>0.405</td>
<td>0.856</td>
<td>0.328</td>
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</table>
| AoACS=The score of calcification of aortic arch.

Note: * is the t-test of the comparison between two groups in 2012; Kt/V=Urea clearance index, iPTH=Intact parathyroid hormone, AoACS=The score of calcification of aortic arch.
The study adopted a multi-center, prospective, and cohort study to observe the influence of different concentrations of calcium dialysate on prevention and treatment of CKD-MBD with MHD patients. The study selected hemodialysis centers with large-scale, standardized management, and stable dialysis quality, and included a large sample of dialysis population to conduct a cohort study, and improve the clinical data reference and lay the foundation for future research.

Conflict of interest
The authors declare no conflict of interest.

References

Table 3. Comparison of end-point events between the two groups

<table>
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</thead>
<tbody>
<tr>
<td>Ordinary Ca group</td>
<td>194</td>
<td>0</td>
<td>13</td>
<td>2</td>
<td>13</td>
<td>14.1(28)</td>
<td>166</td>
<td>0</td>
<td>13</td>
<td>2</td>
<td>15</td>
<td>18.1(30)</td>
</tr>
<tr>
<td>High Ca group</td>
<td>284</td>
<td>0</td>
<td>8</td>
<td>3</td>
<td>16</td>
<td>9.5(27)</td>
<td>257</td>
<td>0</td>
<td>8</td>
<td>1</td>
<td>19</td>
<td>10.9(28)</td>
</tr>
<tr>
<td>X² value</td>
<td>4.886</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.747</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>P-value</td>
<td>0.299</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.098</td>
<td></td>
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</tr>
</tbody>
</table>

Notes: * 5 cases from the high Ca group were transferred; ACM=all-cause mortality, CCVD=Non-fatal cardiac or cerebrovascular disease.


