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Effects of low calcium dialysate on the progression of coronary artery calcification in hemodialysis patients: An open-label 12-month randomized clinical trial

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ABSTRACT

Background: The association between the dialysate calcium level and coronary artery calcification (CAC) has not yet been evaluated in hemodialysis patients. The objective of this study was to determine whether lowering the dialysate calcium levels would decrease the progression of coronary artery calcification (CAC) compared to using standard calcium dialysate.
Methods: We conducted an open-label randomized trial with parallel groups. The patients were randomly assigned to either 12-month treatment with low calcium dialysate (LCD; 1.25 mmol/L, $n = 36$) or standard calcium dialysate (SCD; 1.5 mmol/L, $n = 40$). The primary outcome was the change in the CAC scores assessed by 64-slice multidetector computed tomography after 12 months.
Results: During the treatment period, CAC scores increased in both groups, especially significant in LCD group (402.5 ± 776.8, 580.5 ± 1011.9, $P = 0.004$). When we defined progressors as patients at second and third tertiles of CAC changes, progressor group had a higher proportion of LCD-treated patients than SCD-treated patients ($P = 0.0229$). In multivariate analysis, LCD treatment is a significant risk factor for increase in CAC scores (odds ratio = 5.720, 95% CI: 1.219–26.843, $P = 0.027$).
Conclusions: Use of LCD may accelerate the progression of CAC in patients with chronic hemodialysis over a 12-month period.
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1. Introduction

Cardiovascular disease is the leading cause of death in patients with end-stage renal disease (ESRD), and it accounts for almost 50% of deaths in these patients. Vascular calcification (VC), especially coronary artery calcification (CAC), is a significant predictor of future cardiovascular morbidity and mortality in this population [1,2]. In addition, multiple studies have found that worsening renal function is strongly associated with increasing CAC [3] and a high prevalence and increased extent of CAC in patients with ESRD, almost three-fold greater than an age- and sex-matched general population [1,4]. Although the precise mechanism of VC has not been completely elucidated, there are several explanations for the high prevalence of VC observed in patients with chronic kidney disease (CKD). The dysregulation of calcium (Ca) and phosphate (P) metabolism is common in CKD patients, which drives VC [5]. Although an elevated P level is the most significant VC promoter, in some clinical trials, even with the same phosphorus-reducing ability, calcium-based phosphate binder compared to a non-calcium-based phosphate binder was shown to accelerate VC [6–8]. Thus, there are concerns regarding the risk of Ca loading as an inducer of VC.

Total body Ca is accumulated through diet, the use of binders, and dialysate. Currently, the optimal dialysate calcium concentration is not yet determined. A dialysate calcium concentration of 1.5 mmol/L is common in Europe, Japan, and Australia [9]. However, the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [10] propose a dialysate calcium concentration of 1.25 mmol/L in most hemodialysis (HD) patients in order to prevent the excess of Ca and VC. In addition, the guidelines suggest a lower calcium dialysate concentration in patients with an intact parathyroid hormone (PTH) <100 pg/dL. Currently, the use

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of a non-calcium-based phosphate binder and calcimimetics is possible. Kidney Disease: Improving Global Outcomes (KDIGO) [11] suggests using a dialysate calcium concentration of 1.25–1.50 mmol/L, and the dialysate calcium concentration should be individualized to the patient. However, individualization may be not feasible or even safe. In addition, the association between the dialysate calcium level and CAC has not yet been evaluated in HD patients.

Therefore, we designed this prospective randomized clinical trial to test our hypothesis that treatment with a low calcium dialysate (LCD; 1.25 mmol/L) would reduce the progression of CAC compared to treatment with standard calcium dialysate (SCD; 1.5 mmol/L) in patients undergoing conventional HD.

2. Methods

2.1. Patients

We included patients aged >20 years who were receiving maintenance HD (treatment 4 h per session, 3 times per week) with a dialysate calcium concentration of 1.5 mmol/L for ≥3 months at Hallym University Medical Center in Seoul, Korea. The exclusion criteria were patients with severe hypocalcemia (corrected serum Ca <8.0 mg/dL); intact PTH >300 pg/mL; active infections; malignancy; sarcoidosis; previous parathyroidectomy; frequent symptomatic intradialytic hypotension; uncontrolled arrhythmia; and previous coronary stent placement. Seventy-six patients were enrolled from April 2009 to February 2010, and all provided written informed consent. This prospective, randomized, open-label, parallel group study was approved by the local institutional review board, and it was conducted according to the Declaration of Helsinki.

2.2. Study design and interventions

Patients were randomly assigned to one of two treatment groups: (1) they were switched to a low calcium dialysate (LCD; 1.25 mmol/L, Hemo B dex 0.15%; Choongwae Pharma Corporation, Gyeonggi, Korea); or (2) they continued standard calcium dialysate (SCD; 1.5 mmol/L, Hemo B dex 0.1%; Choongwae Pharma). Randomization was conducted by using block randomization with SAS (version 9.2; SAS Institute, Inc., Cary, NC, USA). Patients underwent multidetector computed tomography (MDCT) for the evaluation of CAC at study enrollment and again after the 12-month intervention period.

Blood was drawn at the beginning of the first HD session of the week. The serum Ca and P levels were measured monthly. Intact PTH, total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglyceride levels were measured every 3 months. If the patients' prescription was changed to maintain the target values, the serum Ca and P were rechecked after 2 weeks, and the intact PTH was rechecked after 4 weeks. The Ca, P, LDL and HDL-cholesterols, and triglycerides were measured using the Hitachi model 7600 (Hitachi Electronics Co. Ltd., Tokyo, Japan). Intact PTH was assayed using an electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostics, Mannheim, Germany).

The total serum Ca level was adjusted for the albumin level using the following conversion factor: corrected Ca (mg/dL) = total Ca + 0.8 × (4 – serum albumin [g/dL]). The serum Ca, P, and intact PTH levels were controlled according to the KDOQI guidelines [14], which recommend the following target values: <9.5 mg/dL, <5.5 mg/dL, and 150–300 pg/mL, respectively. The Ca, P, and intact PTH levels were modulated by medication according to routine clinical practice at our dialysis center. To address the Ca, P, and intact PTH control, the P was prioritized and was controlled by calcium carbonate (Calcium Carbonate Nexpharm, 500-mg tablets; Nexpharm Korea Co., Ltd., Seoul, Korea). If the serum P was ≥5.5 mg/dL, despite the use of calcium carbonate, sevelamer hydrochloride (Renagel, 800-mg tablets; Kyowa Hakko Kirin Co., Ltd., Chiyoda-ku, Tokyo) was added. The phosphate binder assignment was not blinded. Intravenous calcitriol (Bonky, 1 mcg/mL ampoules; Yuyu Pharma, Inc., Seoul, Korea) was administered if the intact PTH was ≥300 pg/mL. If the serum Ca was ≥10.2 mg/dL, the calcium carbonate and calcitriol dosage were decreased or discontinued. No patient received calcimimetics. Physicians were blinded to the MDCT results, and no clinical decisions were made based on the results of the scans.

2.3. Multidetector computed tomography

CAC analyses were acquired at baseline and at 12 months using a 64-slice multidetector computed tomography scanner (Somatom Sensation 64, Siemens, Forchheim, Germany) in conjunction with a 187 ms scan time, 3 mm slice thickness, and electrocardiogram triggering and breath holding. The scan was triggered at 60% of the RR interval; thus, all the images were obtained at the same point in diastole during a single breath hold. To determine the quantity of coronary artery calcium, each of the 40 levels was evaluated sequentially.

CAC scoring was performed by a radiologist blinded to the clinical data according to Agaston scoring on the reconstruction image sets with a detection threshold of 130 HU by using semi-automated software (Syngo Calcium Scoring; Siemens Medical Solutions, Erlangen, Germany). The total calcium score was determined by summing individual lesion scores from four anatomic sites (left main, left anterior descending, circumflex, and right coronary arteries).

2.4. Outcomes measures

The primary outcome measure was the change in the coronary artery calcium score (CACS) from baseline to 12 months determined by MDCT. Patients were divided into tertiles according to the severity of the CAC change. We defined progressors as patients at second and third tertiles of the change. The secondary outcomes included changes in the serum biochemical markers of mineral metabolism at 12 months.

2.5. Statistical analysis

We assigned 36 patients or more to each group. The number of 36 would be enough to provide clinically meaningful information in treatment group evaluation. When it is assumed that the minimum CAC change was 10 and its standard deviation was 15, difference between the groups would give 80% power with a two-sided significance level of 5%. Continuous variables, if normally distributed, were expressed as means ± standard deviations, and if non-normally distributed, they were expressed as geometric means (GM) and 95% confidence intervals (CIs). Categorical data were described as numbers and percentages. Logarithmic transformation was used to analyze variables with skewed distributions, (i.e., the triglyceride, intact PTH, C-reactive protein, and CACS). Differences between the groups were analyzed using the Student *t*-test, χ^2 test, or repeated measures analysis of variance. Analysis of the baseline characteristics was based on the intention-to-treat principle, although the primary analyses of change in the CACS were restricted to the

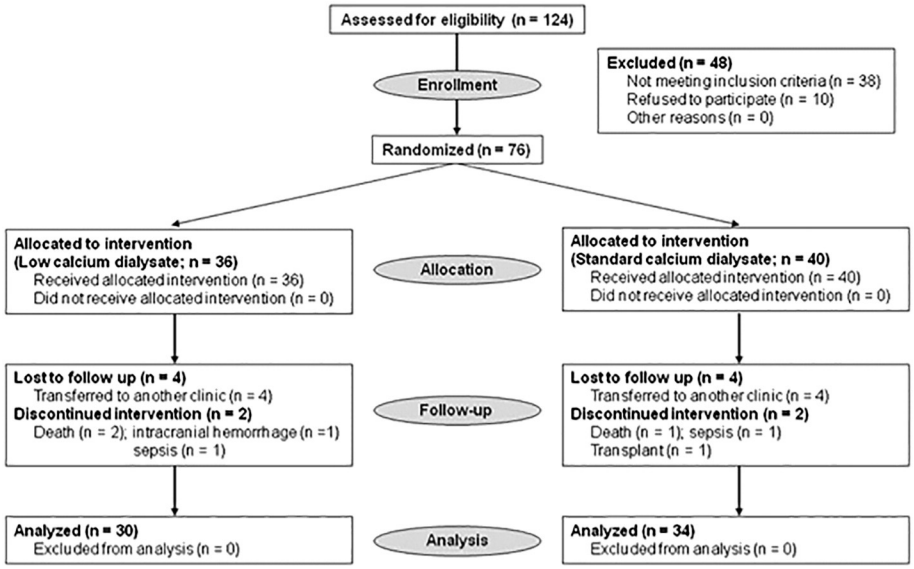

Fig. 1. The patients' disposition.

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