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The Effects of Low Calcium Dialysate on Arterial Compliance and Vasoactive Substances in Patients with Hemodialysis

Soo-Jeong Yoo, M.D., Dong-Jin Oh, M.D. and Suk-Hee Yu, M.D.

Department of Internal Medicine, College of Medicine, Chung-Ang University, Seoul, Korea

Background : Considering that dialysate calcium concentration is potentially a main determinant of the serum ionized calcium level and vasoconstriction is associated with the blood calcium concentration, we conducted a study to evaluate the interdialytic effects of treatment with a low calcium dialysate (LdCa, 1.25 mmol/L) on the changes in arterial compliance (AC), blood pressure (BP), biochemical parameters and vasoactive substances.

Methods : Eight hemodialysis (HD) patients (mean age: 46.8±13.7 years, 4 men and 4 women) were included in the study. AC, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), mean arterial pressure (MAP), serum ionized Ca, intact-PTH, serum nitric oxide and aldosterone were compared after 10 sessions of treatment with LdCa. Right carotid artery diameter was measured 3 times using a real time B-mode ultrasound imager (Hewlett-Packard Sonos 2000®) and AC was calculated using the Hayoz method.

Results : 1) AC was recorded as 0.140 (0.080-0.170) mm^2/kPa at the baseline (1.75 mmol/L calcium dialysate), 0.170 (0.050-0.290) mm^2/kPa after LdCa treatment (p<0.05 versus baseline), and 0.140 (0.070-0.250) mm^2/kPa following the HdCa treatment (p<0.05 versus LdCa data).

2) MAP and PP were calculated at 114.12±10.56 mmHg and 63.50±10.87 mmHg at the baseline; 98.37±15.14 mmHg and 56.50±5.95 mmHg after LdCa treatment (p<0.05 versus baseline); and 115.75±9.64 mmHg and 62.00±15.71 mmHg following HdCa treatment (p<0.05 versus LdCa data).

3) Serum ionized Ca and intact-PTH were measured at 4.66±0.40 mg/dL and 25.08±16.44 pg/mL at the baseline; 4.45±0.28 mg/dL and 90.71±27.03 pg/mL after LdCa treatment (p<0.05 versus baseline); and 4.65±0.43 mg/dL and 24.08±15.44 pg/mL following HdCa treatment (p<0.05 versus LdCa data).

4) Serum aldosterone concentration was 300.8 (65.5-836.1) pg/mL at the baseline, and 220.2 (42.8-527.9) pg/mL after LdCa treatment (p<0.05).

Conclusion : There were favorable changes in AC, BP, biochemical parameters after treatment with LdCa. These changes may be associated with the reduction in serum ionized calcium and decreased serum aldosterone concentration.

Key Words : Calcium, Hemodialysis, Artery, Compliance, Aldosterone, Blood pressure

INTRODUCTION

Despite renal replacement treatment, cardiovascular disease is the prime cause of morbidity and mortality among hemodialysis (HD) patients, leading to more than 50% of the deaths of patients[1]. Arterial compliance (AC), an important vessel wall property, reflects the buffering function of a vessel. A low AC caused by arterial stiffening widens pulse pressure (PP) amplitude by increasing SBP and decreasing DBP[2]. An increased SBP induces left ventricular hypertrophy, whereas a

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• Correspondence to : Dong-Jin Oh, M.D., Department of Internal Medicine, Phildong Hospital, College of Medicine, Chung-Ang University, 82-1, Phildong-2ga, Chung-gu, Seoul, 100-272, Korea Tel : 82-2-2260-2259, Fax : 82-2-2272-8351, E-mail : intmdoh@hanmail.net
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decreased DBP impairs coronary blood flow. A wide PP could be a major predictor of cardiac risk, especially coronary mortality[3-6]. Although wide PP caused by decreased AC are common in patients with end-stage renal disease[2], the underlying pathophysiological process of reduced AC in end-stage renal disease is not yet known. However, research has found that increased serum ionized calcium level augments vascular tone[7]. Although overzealous use of calcium containing agent, vitamin D, acidosis and dialysate calcium concentration all are suggested to influence the serum calcium concentration, the dialysate calcium concentration is potentially a main determinant of the serum ionized calcium level in HD patients[8].

A study reported that HD with low calcium dialysate concentration (LdCa) may have a beneficial role in preventing the ongoing reduction of AC in HD patients[9]. However, this report focused on intradialytic effects and showed relatively short-term results. Moreover, it is currently unknown what specific kinds of vasoactive substances may be related to improving AC in patients with LdCa. Therefore, we decided to evaluate long-term LdCa treatment on AC, BP, biochemical parameters and vasoactive substances.

MATERIALS AND METHODS

1. Clinical details

Eight HD patients, 4 men and 4 women, with a mean age of 46.8±13.7 years and a mean time undergoing HD of 3±2 years (range, 1 to 7 yrs) were studied.

Exclusion criteria were patients with compromised left ventricular function (ejection fraction<40%), predialytic systolic BP<120 mmHg, frequently symptomatic intradialytic hypotension, intact-PTH level>72 pg/mL, or serum total calcium level<9 mg/dL. Primary kidney disease was hypertension (n=4), and undetermined (n=4). Patients underwent 4 hours of dialysis treatment three times weekly. Hemophane (Gambro, Stockholm, Sweden) hollow fiber dialyzers were used. Dialysate temperature, blood flow, and dialysate flow were 37℃, 250 mL/min, and 500 mL/min respectively. Dialysate composition was sodium, 140 mmol/L; potassium, 2 mmol/L; magnesium, 0.5 mmol/L; bicarbonate, 35 mmol/L; acetate , 3 mmol/L and calcium, 1.75 or 1.25 mmol/L. Before starting the study: 1) all patients were dialysed with an HdCa concentration of 1.75 mmol/L. 2) 4 of 8 patients were administered antihypertensive drugs (calcium channel blocker, ACE inhibitor, beta-blocker, alpha-blocker). None of the dialysis patients changed antihypertensives or other vasoactive drugs during the study period. 3) 1 of 8 patients were administered oral (0.125 μgm/day) alphacalcidol and all patients were administered calcium carbonate (1 to 3 gm/day) during the study period. No patients changed alpha-calcidol or calcium carbonate. 4) No patients was administered aluminum as a phosphate binder during the study period.

2. Study design

We conducted a crossover, prospective clinical trial in this study. At the start of the study, all patients underwent HD with 1.75 mmol/L of dialysate calcium (Baseline). Each patient was assigned to a 1.25 mmol/L of dialysate calcium (LdCa). After ten sessions of LdCa hemodialysis, dialysis fluid was changed to 1.75 mmol/L of dialysate calcium (HdCa) And then, ten sessions of HdCa hemodialysis were performed. At the beginning (Baseline data) and end of each (HdCa or LdCa) session, the biochemical and hemodynamic parameters and vasoactive substances were measured. Above studies were performed simultaneously during the interdialytic period for all patients. The shunt arm was not used for measurement.

3. Biochemical parameters

Arterial blood samples, drawn anaerobically during the interdialytic period, were assessed for ionized calcium, total calcium concentration, phosphorus, total-CO_2, and intact-PTH.

Serum ionized calcium was measured in fresh serum, directly started at 4℃ and measured within two hours using an ion-selective analyzer (Rapidlab 855, Bayer, Germany). Normal values were 4.5-5.3 mg/dL. Phosphorus, total calcium concentration and total-CO_2 were determined on a Hitachi 747 automatic analyzer. Normal values were 1.9-4.4 mg/dL, 8.2-10.4 mg/dL, and 22-28 mol/L, respectively. Intact-PTH was measured by commercial immunoradiometric assay (Diagnostic products corporation, Los Angeles, CA, USA). The normal range in our laboratory was 12-72 pg/mL.

4. Hemodynamic parameters.

Before the start and after the end of LdCa and HdCa treatments, predialytic SBP, DBP were measured with an automatic blood pressure monitor. MAP and PP were calculated by (SBP+2xDBP) / 3, SBP - DBP, respectively. The mean value of three consecutive measurements was calculated.

AC is defined by the arterial volume change per unit of pressure. Systolic and end-diastolic arterial diameters were measured three times at the level of the proximal right common carotid artery using a real time B-mode ultrasound imager (Hewlett-Packard Sonos 2000®). The mean value of the three consecutive measurements was used; AC was calculated using Hayoz formula[10].

Arterial Compliance (mm^2/kPa) = (πD×△D) / 2△P

(arterial diameter (D) mm, △D changes of systolic and diastolic arterial diameter, △P pulse pressure)

SV was measured using 2D-echocardiography.

SV = left ventricular outflow tract (LVOT) area x systolic velocity integral (SVI)

LVOT area = $\pi(D/2)^2$ (D = LV diameter)

5. Vasoactive substances

Nitric oxide (NO) concentration was determined using the method set forth by Green et al[11]. Serum aldosterone concentration was sampled and measured using the Coat-A-Count aldosterone measurement kit (Diagnostic products corporation, Los Angeles, CA, USA) after 90 minutes in a supine position. The normal range in our laboratory was 10-160 pg/mL (supine).

6. Results analysis

Statistical analysis was performed using Student's paired *t*-test, or Wilcoxon rank sum test, as appropriate (SPSS Windows version 9.0). Results were expressed as mean±SD, or median (range). Differences were considered significant if the *p* value was less than 0.05.

RESULTS

1. Changes in AC and SV.

AC was 0.140 (0.080-0.170) mm^2/kPa at the baseline (1.75 mmol/L calcium dialysate), 0.170 (0.050-0.290) mm^2/kPa after LdCa treatment (p<0.05 versus baseline data), and 0.140 (0.070-0.250) mm^2/kPa following HdCa treatment (p<0.05 versus LdCa data) (Figure 1).

SV were 66.32±26.85 mL/m^2 at the baseline, 68.88±22.80 mL/m^2 after LdCa treatment (p>0.05), and 66.10±25.75 mL/m^2 following HdCa treatment (p>0.05) (Table 1).

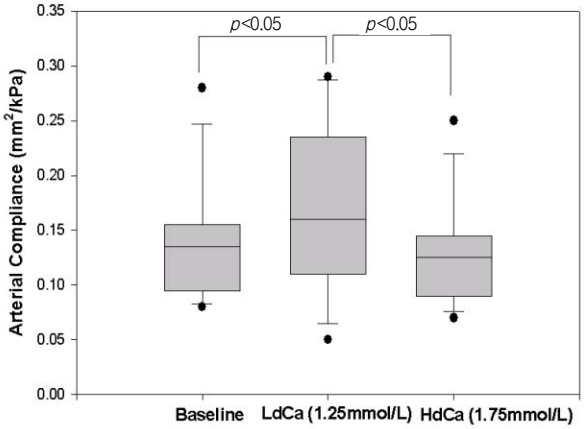

Figure 1. Changes in Arterial Compliance.

2. Changes in SBP, DBP, MAP and PP.

SBP, DBP, MAP and PP were 157.75±15.97 mmHg, 94.25±9.48 mmHg, 114.12±10.56 mmHg, and 63.50±10.87 mmHg at the baseline; 135.25±13.0 mmHg, 78.75±11.24 mmHg, 98.37±15.14 mmHg, and 56.50±5.95 mmHg after LdCa treatment (p<0.05 versus baseline); and 160.50±15.36 mmHg, 94.05±10.34 mmHg, 115.75±9.64 mmHg, and 62.00±15.71 mmHg following HdCa treatment (p<0.05 versus LdCa data) (Table 1).

3. Changes in biochemical parameters.

Serum ionized Ca and intact-PTH were measured at 4.66±0.40 mg/dL and 25.08±16.44 pg/mL at the baseline; 4.45±0.28 mg/dL and 90.71±27.03 pg/mL after LdCa treatment (p<0.05

Table 1. Changes in Hemodynamic parameters

	Baseline	LdCa (1.25 mmol/L)	HdCa (1.75 mmol/L)
SV (mL/m^2)	66.32±26.85	68.88±22.80	66.10±25.75
SBP (mmHg)	157.75±15.97	135.25±13.00*	160.50±15.36**
DBP (mmHg)	94.25±9.48	78.75±11.24*	94.05±10.34**
PP (mmHg)	63.50±10.87	56.50±5.95*	62.00±15.71**
MAP (mmHg)	114.12±10.56	98.37±15.14*	115.75±9.64**

(mean±SD, *p < 0.05 versus baseline, **p < 0.05 versus LdCa)

Table 2. Changes in biochemical parameters

	Baseline	LdCa (1.25 mmol/L)	HdCa (1.75 mmol/L)
Ionized Ca (mg/dL)	4.66±0.40	4.45±0.28*	4.65±0.43**
T-Ca (mg/dL)	9.75±0.65	9.20±0.58	9.56±0.55
T-CO_2 (μmol/L)	21.9±2.78	20.0±3.03	22.16±2.70
Phosphorus (mg/dL)	6.27±1.12	7.38±1.30	6.37±1.02
PTH (pg/mL)	25.08±16.44	90.71±27.03*	24.08±15.44**
Ca×P product	61.76±9.87	67.63±10.99	60.76±9.57

(mean±SD, *p < 0.05 versus baseline, **p < 0.05 versus LdCa)

versus baseline); and 4.65±0.43 mg/dL and 24.08±15.44 pg/mL following HdCa treatment (p<0.05 versus LdCa data). Total-CO_2, phosphorus did not show significant changes (Table 2).

4. Changes in vasoactive substances.

Serum aldosterone concentration was found to be 300.8 (65.5-836.1) pg/mL at the baseline, 220.2 (42.8-527.9) pg/mL after LdCa treatment (p<0.05 versus baseline), and 218.1 (75.1-483.2) pg/mL following HdCa treatment (p>0.05 versus LdCa data) (Figure 2). Serum NO concentration was 286.1 (109.2-764.3) μmol/L at the baseline, 230.4 (94.5-311.3) μmol/L after LdCa treatment (p>0.05 versus baseline), and 222.1 (174.1-394.2) μmol/L following HdCa treatment (p>0.05 versus LdCa data) (Figure 3).

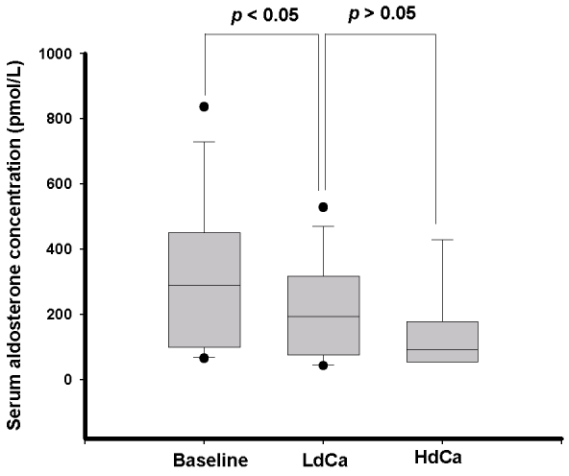

Figure 2. Changes in serum aldosterone concentration.

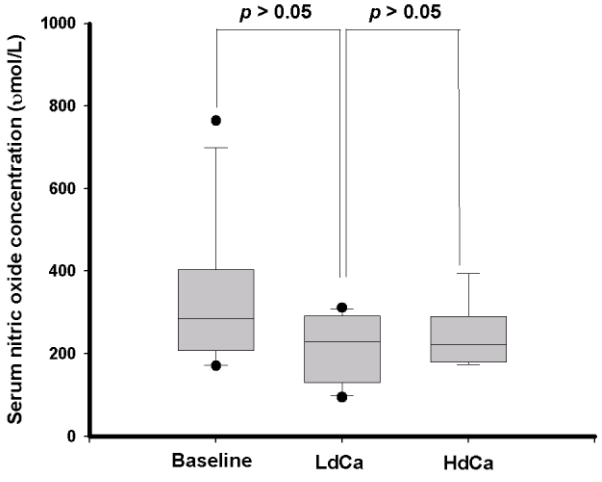

Figure 3. Changes in serum nitric oxide concentration.

DISCUSSION

AC is known to be 13~32% lower in HD patients, compared with age- and BP-matched controls A decreased AC widens PP amplitude and a wide PP can provoke increased cardiovascular mortality in HD patients[12]. Considering that cardiovascular disease is the prime cause of morbidity and mortality among HD patients, it is important to prevent and improve AC reduction after the start of HD. Although the underlying pathophysiological process of reduced AC in the uremic state is not yet known, there are structural changes such as atherosclerosis and hypercalcemia caused by chronic hypervolemia, high calcium dialysate use, and the overzealous use of the calcium-containing agent, vitamin D[13]. It is generally acknowledged that calcium has a major role in the generation of the vascular contractile process. Dialysate calcium concentration is potentially a main determinant of the serum ionized calcium level and the reported vasoconstriction is associated with increments of the calcium concentration[14-16]. Therefore, we conducted a study to answer the question of whether low calcium dialysate treatment is advantageous to AC and BP.

Our results demonstrated that AC was significantly improved and serum ionized calcium level was significantly reduced to within the lower normal limit after 10 sessions of LdCa treatment. Recent study by Kiriazis *et al* demonstrated that AC increased by 32% after 4 sessions of LdCa treatment[13]. Marchais et al showed an increase of 20% in serum ionized calcium level during HD with 1.75 mmol/L of dialysate calcium, and a reduction in both aortic and brachial distensibility by 12% and 22%, respectively[7]. The results of our study are consistent with findings from previous reports, and suggest that changes in serum calcium concentration can have an impact on arterial elastic properties. We can speculate that decreased extracellular calcium levels may have a favorable impact on the structure of the vessel wall, through decreased calcium deposition on medial elastic fibers after-long-term LdCa treatment, and subsequently result in improved AC. Even a minimal change in serum ionized calcium level after LdCa treatment can have an influence on AC.

There was no significant changes in SV in our study. This finding is not consistent with Kyriazis's report that showed a significant decrease in SV that was caused by a reduction of cardiac contractility after treatment with LdCa. We can speculate that the reduction of afterload by low blood pressure after treatment of LdCa compensated for the reduction in cardiac contractility by the low serum ionized calcium level.

There were statistically significant decreases in predialysis SBP, DBP, MAP, PP after LdCa treatment. This finding is consistent with the report by Argiles et al[17]. Argiles et al. studied

the long-term hemodynamic effects of reducing the dialysate calcium in seven patients not administered antihypertensive drugs for a 1-year period after changing the dialysate calcium concentration from 1.5 to 1.25 mmol/L. At the end of study, 24-hour ambulatory SBP, DBP, and heart rate had decreased 5.3%, 6.7%, 4.6% from baseline values, respectively[17]. PP was known to be a parameter of AC changes[18]. There was an 11.1% decrease in PP with LdCa treatment. In our study, changes in BP were inversely correlated with dialysate calcium level through parallel changes in serum ionized calcium level.

There were significant changes in serum ionized calcium level and intact-PTH among biochemical parameters. Serum ionized level decreased to within the lower normal limit and intact-PTH increased to about 4 times the baseline value. There were no cases above 100 pg/mL in intact-PTH level. However, long-term prospective study will be needed to assess whether renal osteodystrophy develops after treatment of LdCa. In our study, total CO_2 remained unchanged after LdCa treatment. This result showed that the effect of an acidosis correction on the changes in serum ionized calcium level could be ruled out.

Various cytokines and hormones are known as vasoreactive substances, vasoconstrictors or vasodilators. In its capacity as a mineralocorticoid hormone, aldosterone has receptor-ligand endocrine properties on epithelial cell sodium and potassium exchange in classic target tissues, such as the kidneys, colon, and salivary and sweat glands[19, 20]. Recent reports showed that receptors have also been located on non-epithelial sites in the blood vessels, brain, and heart. Furthermore, sites of aldosterone formation outside the adrenal gland have been discovered, including human endothelial cells and vascular smooth muscle cells, and within myocardial cells in animal studies[21]. Ullian et al demonstrated that aldosterone may promote vascular smooth muscle cell hypertrophy by inducing the upregulation of angiotensin II receptors, thus potentiating the pressor responses of angiotensin II[22]. Fraquiharson and Struthers demonstrated that aldosterone produces endothelial dysfunction, perhaps by inhibiting nitric oxide release[23]. Above adopted reports have shown that mineralocorticoids have led to increased vasoreactivity and peripheral resistance, and could be measured more readily than angiotensin II or endothelin. So, we decided to evaluate changes in serum aldosterone concentration after LdCa treatment in this study. Moreover, hyperaldosteronism and adrenal hypertrophy are common findings in the remnant kidney model, with plasma levels of aldosterone that increased approximately ten-fold[24]. Clinical studies have also demonstrated a relationship between augmented levels of aldosterone and renal deterioration[25, 26]. In HD patients, the changes in the concentration of aldosterone did not have significant correlation with volume reduction[27, 28]. But, there were no data on the changes in serum aldosterone concentration after low calcium dialysate treatment in HD patients. In our present study, we observed that high serum aldosterone concentration in hemodialysis patients was significantly reduced after LdCa treatment. But no significant changes in serum nitric oxide concentration were observed. In these results, we may suggest that improved arterial compliance and blood pressure may be associated with a decreased serum aldosterone level. But, we cannot reveal the direct relationship of the changes of serum ionized calcium, serum aldosterone level and improved vascular properties. Therefore, further studies will be needed whether or not decreased serum ionized level can induce a reduction in aldosterone production in the adrenal gland, endothelial cells and vascular smooth muscle cells.

In order to prevent changes in AC and vasoactive substances, due to the acute blood volume reduction during dialysis, AC, BP, biochemical parameters, and vasoactive substances were measured in the pre-hemodialysis or interdialytic period. There were no significant changes recorded in body weight and ultrafiltration rate. So, we can rule out the effect of reduced body fluid on the changes in AC, BP, and vasoactive substances.

We measured the systolic and diastolic arterial diameter of the right proximal carotid artery by the real-time B-mode ultrasound imager. Because earlier studies found that arterial wall abnormalities were more pronounced in central elastic large-type capacitance arteries than medium-sized muscular arteries[29], we think that this method may be superior to brachial artery measurement.

In conclusion, there were favorable changes in AC, BP, biochemical parameters after treatment with LdCa. These changes may be associated with a reduction in serum ionized calcium and a decreased serum aldosterone concentration partially. So, LdCa treatment may have a beneficial role in the preventing the ongoing reduction of arterial compliance in selected HD patients, and thus improve cardiovascular prognosis.

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