INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Effects of Dialysis Solution on the Cardiovascular Function in Peritoneal Dialysis Patients

Ismail Kocyigit[1], Aydin Unal[1], Ozkan Gungor[2], Ozcan Orscelik[3], Eray Eroglu[4], Ender Dogan[4], Ahmet Sen[5], Mustafa Yasan[3], Murat Hayri Sipahioglu[1], Bulent Tokgoz[1], Ali Dogan[3] and Oktay Oymak[1]

Abstract

Objective Peritoneal dialysis (PD) patients have an increased cardiovascular burden. In this study, we aimed to compare certain PD solutions (Physioneal® and Dianeal®) in terms of the ambulatory blood pressure, echocardiographic parameters (ECHO), carotid atherosclerosis, endothelial function and serum asymmetric dimethylarginine (ADMA) level.

Methods A total of 45 PD patients were enrolled in this prospective randomized controlled study: 23 patients in the Dianeal® group and 22 patients in the Physioneal® group. Ambulatory blood pressure measurements, echocardiography, carotid artery intima-media thickness measurements and flow mediated dilatation (FMD) and ADMA values were obtained at baseline and 12 months.

Results The baseline parameters were similar between the groups with respect to the echocardiographic parameters, 24-hour ambulatory blood monitoring measurements and ADMA and FMD levels. All 24-hour blood pressure monitoring measurements, except for the average daytime systolic blood pressure, were significantly decreased in both groups at the first year. In the Physioneal® group, a significant decrease was observed with regard to the ADMA levels. Considering the FMD values, significant augmentation was seen at the end of the first year in both groups. Improvements in the FMD measurements were prominent in the Physioneal® group; however, this finding was not statistically significant.

Conclusion The use of solutions with a neutral pH in PD patients results in decreased ADMA levels, which may be an important contributor to reductions in the incidence of cardiovascular events and deaths in this population.

Key words: peritoneal dialysis, endothelial dysfunction, dialysis solution, ADMA

(Intern Med 54: 3-10, 2015)
(DOI: 10.2169/internalmedicine.54.2763)

Introduction

Until renal transplantation, currently the best renal replacement method, becomes widespread, hemodialysis (HD) and peritoneal dialysis (PD) remain the most common methods for treating patients with end-stage renal disease (ESRD). PD has many advantages over HD, and a recent study demonstrated that if ESRD patients were fully informed about this very important issue, the proportion of those who would prefer PD treatment would rise to 30% (1).

PD patients have an increased cardiovascular (CV) burden, and CV disease is, in fact, the most frequent cause of death. Problems, such as insufficient volume control, dyslipidemia and increased oxidative stress, caused by glucose-based PD solutions are factors specific to PD therapy and have been suggested to affect the incidence of ad-

[1]Department of Nephrology, Erciyes University Medical Faculty, Turkey, [2]Department of Nephrology, KahramanMaras Training and Research Hospital, Turkey, [3]Department of Cardiology, Erciyes University Medical Faculty, Turkey, [4]Department of Internal Medicine, Erciyes University Medical Faculty, Turkey and [5]Department of Biochemistry, Erciyes University Medical Faculty, Turkey
Received for publication February 23, 2014; Accepted for publication May 1, 2014
Correspondence to Dr. Ismail Kocyigit, iikocyigit@gmail.com

verse outcomes in this patient population (2). On the other hand, the significantly higher CV morbidity and mortality rates observed in these patients have been largely attributed to endothelial dysfunction and atherosclerosis. Oxidative stress (OS) plays an important role in the pathogenesis of atherosclerosis and endothelial dysfunction (3). Asymmetric dimethylarginine (ADMA) is an inhibitor of endogenous nitric oxide (NO) synthase derived from the proteolysis of proteins that contain methylated arginine residues (4). Studies have shown higher ADMA levels in patients with carotid atherosclerosis (5) and a strong positive correlation between the ADMA level and endothelial dysfunction (6).

Solutions with different compositions are used in PD. These solutions can be acidic or basic. The use of a bicarbonate-based fluid is considered to be the best option for PD, as it provides a more physiological body buffer. Two studies from the early 1990's indicated that solutions based on a mixture of bicarbonate and lactate (Bic/Lac) may be more biocompatible than those developed using bicarbonate alone. However, there is no clear evidence regarding the superiority of acidic versus basic solutions and/or combinations of these agents. Recently, studies conducted on the effects of Bic/Lac solutions and standard lactate solutions on the characteristics of peritoneal membrane transport, rate of ultrafiltration, clearance of solid materials and incidence of peritonitis have failed to report any definitive outcomes with regards to superiority (7-9). Furthermore, there are no previous studies in the literature comparing Bic/Lac solution and standard lactate solutions with respect to atherosclerosis and the cardiac and endothelial functions.

As is well known, the use of Physioneal® (Baxter Healthcare, McGaw Park, USA) and Dianeal® (Baxter Healthcare) solutions can induce oxidative stress to different degrees. The degree of acidification of peritoneal dialysis solutions influence the level of oxidative stress. Currently, there are inadequate data regarding the effects of PD solutions on cardiovascular disease in PD patients. Therefore, we proposed that different PD solutions affect the incidence of cardiovascular events via different oxidative stress profiles and compared two groups (treated with Physioneal® and Dianeal®) at both baseline and 12 months after treatment with respect to cardiovascular and endothelial function parameters, such as the carotid artery intima-media thickness (CA-IMT), flow-mediated vasodilation (FMD), ADMA and echocardiographic variables.

Materials and Methods

Study population

This single-center, prospective, randomized controlled study was performed in patients undergoing PD at the Nephrology Department of the Medical Faculty of Erciyes University, Turkey for a period of 20 months between May 2011 and January 2013. The study was approved by the University Ethics Committee and Local Hospital Review Committee. All participants provided their written informed consent.

In our center, the majority (-90%) of dialysis patients are treated with PD. One hundred and ninety-four PD patients are currently being followed. The inclusion criteria for this study were as follows: PD as the first renal replacement therapy, an age between 18 and 70 years. After considering these criteria, 69 patients were found to be eligible. However, 14 patients refused to participate in the study and another six were excluded due to major cardiovascular disease (history of acute coronary syndrome or coronary artery bypass surgery, cardiomyopathy and cardiac arrhythmia, peripheral artery disease) as assessed based on the patient's history and results of transthoracic echocardiography obtained during this period. Ultimately, a total of 49 PD patients were enrolled in this study. During the study period, four patients died due to cardiovascular events (three of acute coronary syndrome and one of complete A-V block). Forty-five patients completed the one-year follow-up.

In this prospective study, after baseline testing (measurement of the carotid artery intima-media thickness, endothelial function tests, ambulatory blood pressure measurement, echocardiography and biochemical tests), the measurements were obtained 24 hours before the PD catheter insertion procedure. The patients were randomly assigned to one of the two treatment groups.

We compared the effects of a 25-mmol/L bicarbonate/15-mmol/L lactate-buffered, physiologic pH, low-glucose degradation product (GDP) solution (Physioneal®) with those of a standard lactate-buffered, acidic pH, conventional solution (Dianeal®). After each patient was informed and provided their consent for enrollment in the study, he/she was requested to choose a sealed envelope in which "Physioneal® Group" or "Dianeal® Group" was written. There were 23 patients in the Dianeal® group and 22 patients in the Physioneal® group (Fig. 1). No medications known to affect cardiovascular and metabolic risk factors were initiated during the study period.

Biochemical measurements

Blood samples were obtained from the vein of the antecubital fossa, with the subject in a seated position after 20 minutes of rest following 12 hours of fasting. The glucose, creatinine and lipid levels were determined using standard methods. A complete blood count was obtained on a Sysmex K-1000 (Block Scientific, Bohemia, USA) auto analyzer within 30 minutes of sampling. The high-sensitivity C-reactive protein (hs-CRP) level was measured using a BN2 model nephelometer (Dade-Behring, Marburg, Germany). The expected values for hs-CRP in our laboratory range from 0 to 3 mg/L.

ADMA

All specimens were stored at -80℃ until use, and all measurements were performed at the same time after being collected. Measurement of the ADMA values was accom-

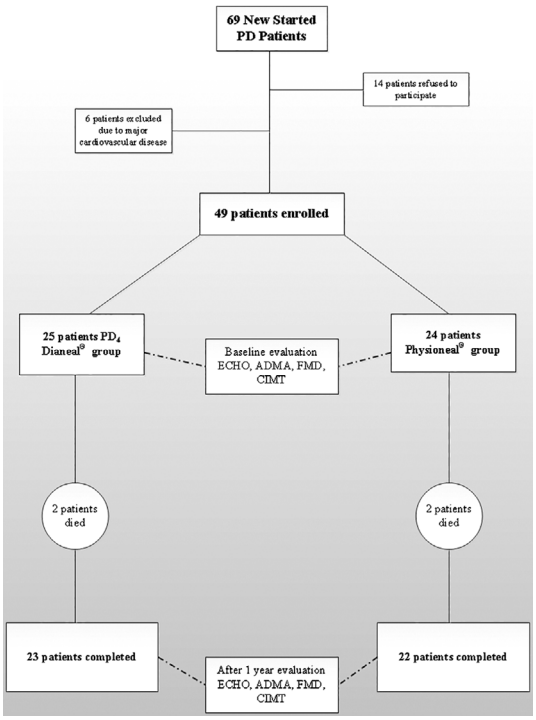


Figure 1. **Diagram showing the flow of the study**

plished with high-performance liquid chromatography using the method described by Chen et al. (10). In brief, 20 mg of 5-sulfosalisilic acid was added to 1 mL of serum, and the mixture was left in an ice-bath for 10 minutes. The precipitated proteins were removed via centrifugation at 2,000 g for 10 minutes. Ten microliters of the supernatant, which was filtered through a 0.2-μm filter, was mixed with 100 μL of derivatization reagent [prepared by dissolving 10 mg o-phtaldialdehyde in 0.5 mL of methanol, 2 mL of 0.4 M borate buffer (pH 10.0) and 30 μL of 2-mercaptoethanol] and injected into the chromatographic system. Separation of ADMA was performed on a 150×4-mm internal diameter Nova-Pak C18 column with a particle size of 5 μm (Waters, Millipore, Milford, USA) using 50 mM of sodium acetate (pH 6.8), methanol and tetrahydrofurane as the mobile phase (A, 82:17:1; B, 22:77:1) at a flow rate of 1.0 mL/min. The peak areas, as detected using the fluorescent detector (Ex: 338 nm; Em: 425 nm), were used for quantification of the ADMA levels. The variability of the method was less than 7%, and the detection limit of the assay was 0.01 μM.

Measurement of the carotid artery intima-media thickness

Ultrasonographic studies of the common carotid arteries were carried out using gray-scale high-resolution color Doppler ultrasound (ATL HDI 5000 scanner Philips, ATL ultrasound, Bothell, USA) equipped with a 5-12 MHz linear transducer. A single blinded operator performed all procedures on both sides of two longitudinal images of each common carotid artery in the morning. The average of two CA-IMT values from each side was used to calculate the mean CA-IMT.

Endothelial function test

Endothelial dysfunction was assessed according to the method described by Celermajer et al. (11). The measurements were obtained by a single blinded observer using an ATL 5000 ultrasound system (Advanced Technology Laboratories Inc., Bothell, USA) with a 12-Mhz probe. The subject remained at rest in the supine position for at least 15 minutes before the examination was started. The right arm was comfortably immobilized in an extended position to allow for consistent recording of the brachial artery 2-4 cm above the antecubital fossa. Three adjacent measurements of the end-diastolic brachial artery diameter were obtained from single 2D frames. All ultrasound images were recorded on Super Video Home System (S-VHS) videotape for the subsequent blinded analysis. The maximum FMD diameter was calculated as the average of the three consecutive maximum diameter measurements after hyperemia and nitroglycerin administration, respectively. The FMD was then calculated as the percentage change in diameter compared with the baseline resting diameter.

Echocardiography

All participants were examined at inclusion using a Vivid 7 instrument (GE Medical Systems, Milwaukee, USA) with a 2.5-MHz transducer and harmonic imaging. The echocardiography procedures were performed in the echocardiography laboratory at baseline by a single blinded operator according to the recommendations of the American Society of Echocardiography. The echocardiographic examinations were conducted in the left lateral decubitus position using the parasternal long-short axis and apical views. At least three consecutive beats in sinus rhythm were recorded, and the average value was determined. The left ventricular (LV) end-diastolic and end-systolic dimensions (LVEDD and LVESD) and interventricular septal and posterior wall thicknesses (IVSd and LPWd) were measured using M-mode images of the left ventricle generated in the long-axis view with the cursor at the tip of the mitral valve leaflet. The LV ejection fraction was calculated using the following formula, LVEF % = (LVEDV-LVESV)/LVEDV ×100, and the left ventricular mass (LVM) was calculated using the following formula, LVM (in g) =0.8 [1.04 ((LVDD+PWD+IVSD)^3-IVSD^3)]+0.6.

Ambulatory blood pressure measurements

24-hour blood pressure monitoring was performed with a Del Mar Medical Pressurometer Model P6 (Del Mar Reynolds, Irvine, USA), and the results were assessed using the manufacturer's computer software program. Ambulatory measurements were obtained once every 15 minutes from 7 am to 11 pm and once every 30 minutes from 11 pm to 7 am. The evaluation was performed taking the mean values of the day and night blood pressures into account. Hypertension was considered to be present if the systolic pressure was >140 mmHg and/or the diastolic pressure was >90

Table 1. Baseline Demographic and Biochemical Characteristics of the Study Population

Parameters	Overall (n=45)	Dianeal® group (n=23)	Physioneal® group (n=22)	p
Age (years)	45.7 ± 14	44.4 ± 12	46.9 ± 16	0.57
Gender (F/M)	19/26	11/12	8/14	0.43
Presence of DM (n)	17/45	9	8	0.55
Daily urine volume (mL/day)	995±330	1,080±330	906±294	0.08
Uric acid	7.2±2.4	6.9±2.2	7.4±2.5	0.12
Smoking (n)	7/45	4	3	0.52
Intact parathyroid hormone (pg/mL)	284(10-1,217)	262(25-1,217)	296 (10-1,008)	0.91
Body mass index (kg/m^2)	26.6±4.23	26.2±3.82	27.1±4.01	0.34
Usage of Extraneal®(n)	13/45	6	7	0.46
Hemoglobin (g/dL)	10.5 ± 1.1	10.6 ± 1.1	10.4 ± 1.3	0.62
Platelet count (×1,000/mm^3)	300 ± 70	283 ± 48	317 ± 85	0.11
White blood cell count (10^3/uL)	7.2 ± 1.7	6.8 ± 1.7	7.3 ± 1.4	0.21
D/P Creatinine	0.78 ± 0.1	0.80 ± 0.1	0.76 ± 0.09	0.18
Plasma fasting glucose (mg/dL)	82.8 ± 13	80.5 ± 16	83.5 ± 12	0.35
Phosphorus (mg/dL)	4.2 ± 0.7	4.2 ± 0.6	4.2 ± 0.9	0.85
Calcium (mg/dL)	9.0 ± 0.4	8.9 ± 0.4	8.9 ± 0.5	0.76
Fasting total cholesterol (mg/dL)	186 ± 35	188 ± 35	187 ± 36	0.81
Fasting LDL cholesterol (mg/dL)	121 ± 29	120 ± 31	122 ± 27	0.75
Fasting triglyceride (mg/dL)	150 ± 44	146 ± 45	154 ± 43	0.56
Hs- CRP (mg/L)	9.9 ± 3.1	9.5 ± 2.9	10.2 ± 3.2	0.78
Serum albumin level (g/dL)	3.3 ± 0.7	3.3 ± 0.7	3.2 ± 0.8	0.61

mmHg or if the individual was taking antihypertensive medications.

Statistical analysis

Continuous variables were tested for normality of their distribution according to the Kolmogorov-Smirnov test. Continuous data are reported as the mean and standard deviation or median. We compared continuous variables using Student's *t*-test. Categorical variables are summarized as percentages and were compared with the Chi-square test. Pearson correlation coefficients were used to calculate the degree of association between variables. The Wilcoxon signed-rank test and paired t-test were used to compare variables. An analysis of covariance (ANCOVA) was performed to compare the groups in term of changes from baseline in the FMD, CA-IMT and ADMA values. A p-value of <0.05 was considered to be significant, and the confidence interval (CI) was set to 95%. All statistical analyses were performed using the SPSS version 15 software package (SPSS, Inc., Chicago, USA).

The changes in the variables during the study period (rate of change) were calculated using the following formula: Rate of change = [(values at first year) - (values at the baseline)/(values at the baseline)] ×100. We expressed this formula as a "delta" in the univariate correlation analysis of the ADMA and other parameters.

Results

The mean age of the patients was 44.4±12 years in the Dianeal® group and 46.9±16 years in the Physioneal® group. A total of 11 of 23 patients were men in the Dianeal® group, while eight of 22 patients were men in the Physioneal® group. There were no statistically significant differences between the two groups with respect to the baseline demographic data and biochemical measurements (Table 1).

The baseline parameters were similar between the groups in terms of the echocardiographic parameters, residual urine volume, 24-hour ambulatory blood monitoring measurements and FMD and ADMA levels. In the Physioneal® group, a significant decrease was observed in the ADMA levels, whereas no significant reduction was observed at the first year in the Dianeal® group (Fig. 2) (Table 2). Moreover, regarding the FMD values, a significant increase was noted at the end of the first year in both groups (Fig. 3). In the Physioneal® group, there was a significant change in the ADMA, but not FMD, levels, with respect to the rate of change from baseline to one year, as compared to the Dianeal® group (Fig. 4). In addition, there were no significant changes in the CA-IMT measurements in either group.

In terms of the echocardiographic parameters, a significant reduction in the posterior wall in diastole (PWD) and increase in the left ventricular ejection fraction (LVEF) values were observed in the Dianeal® group. Other echocardiographic parameters did not change significantly. The left ventricular dimension in diastole (LVDD), PWD and interventricular septum in diastole (IVSD) values significantly decreased in the Physioneal® group, while the LVEF values significantly increased (Table 2). All 24-hour blood pressure monitoring measurements, except for the average daytime systolic blood, significantly decreased in the Dianeal®

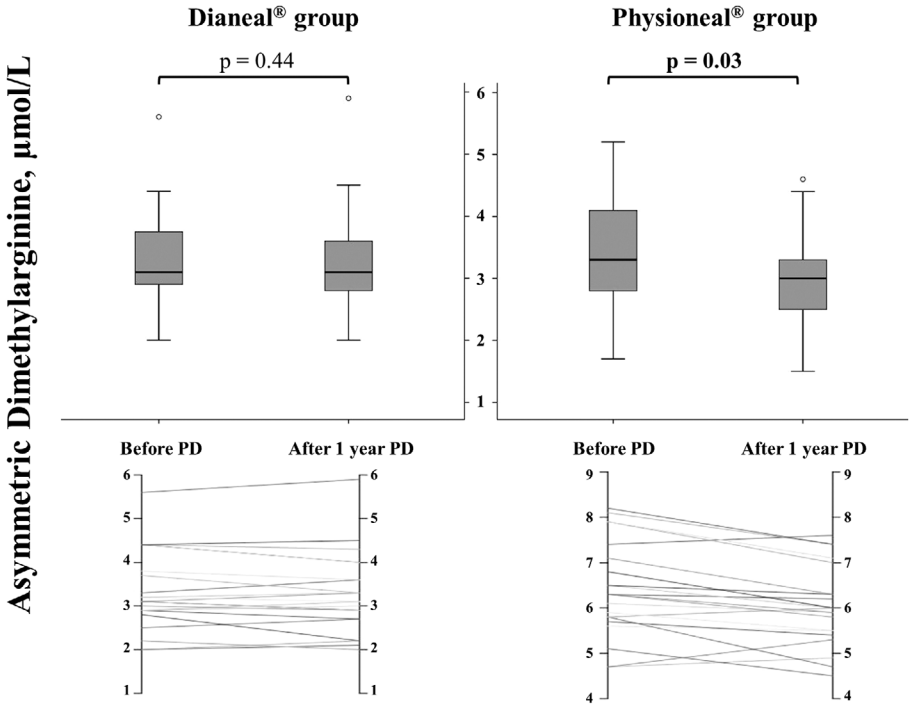


Figure 2. **Differences in the ADMA levels between the Dianeal® and Physioneal® groups at baseline and after one year**

Table 2. **Results of the Study for All Patients**

Parameters	Dianeal® group (n=23)				Physioneal® group (n=22)					
	Baseline	At 1-year	Rate of Change, %	p^1	Baseline	At 1-year	Rate of Change, %	p^1	p^2	p^3
LVSD (mm)	30.6 ± 4.2	30.2 ± 3.9	-0.98	0.87	30.6 ± 2.8	30.3 ± 2.4	-0.77	0.17	0.95	0.18
LVDD (mm)	46.5 ± 3.7	46.4 ± 3.6	-0.32	0.53	47.5 ± 4.0	46.6 ± 2.9	-1.7	**0.004**	0.41	0.25
IVSD (mm)	11.0 ± 1.5	10.8 ± 1.3	-1.3	0.10	11.5 ± 1.8	11.1 ± 1.6	-3.3	**0.01**	0.27	0.10
PWD (mm)	11.0 ± 1.5	10.4 ± 1.1	-3.7	**0.01**	11.3 ± 1.6	10.6 ± 1.6	-6.1	**0.003**	0.32	0.20
LVEF (%)	62.3 ± 7.5	63.5 ± 6.4	2.1	**0.02**	63.1 ± 5.1	65.3 ± 4.5	3.5	**0.001**	0.67	0.19
CIMT (mm)	5.57 ± 0.65	5.52 ± 0.60	-0.68	0.13	5.48 ± 0.97	5.35± 0.96	-2.2	0.06	0.71	0.10
ANCOVA (CIMT)				**<0.001**				**0.001**		0.649
Average 24-h systolic BP (mmHg)	129 ± 9	126 ± 7	-1.8	**0.005**	130 ± 10	126 ± 7	-3.0	**0.002**	0.63	0.71
Average daytime systolic BP (mmHg)	135 ± 12	133 ± 9	-1.3	0.05	139 ± 12	133 ± 7	-3.6	**0.002**	0.30	0.13
Average nighttime systolic BP (mmHg)	122 ± 7	120 ± 6	-2.2	**0.001**	122 ± 9	119 ± 8	-2.3	**0.003**	0.69	0.75
Average 24-h diastolic BP (mmHg)	89 ± 5	84 ± 3	-5.4	**<0.001**	90 ± 4	84 ± 5	-7.0	**<0.001**	0.35	0.13
Average nighttime diastolic BP (mmHg)	81 ± 4	77 ± 3	-5.1	**<0.001**	83 ± 3	77 ± 4	-6.6	**<0.001**	0.32	0.15
Average 24-h mean BP (mmHg)	102 ± 4	98 ± 3	-4.0	**<0.001**	104 ± 4	98 ± 5	-5.4	**<0.001**	0.32	0.11
Average daytime mean BP (mmHg)	109 ± 4	105 ± 4	-4.0	**<0.001**	111 ± 6	105 ± 6	-5.8	**<0.001**	0.18	0.19
Average nighttime mean BP (mmHg)	95 ± 4	91 ± 3	-4.0	**<0.001**	96 ± 4	91 ± 5	-5.4	**<0.001**	0.67	0.13
Residual urine volume (mL/day)	1,080 ± 352	735 ± 247	-29	**<0.001**	906 ± 294	660± 244	-26	**<0.001**	0.09	0.48
ADMA (µmol/L)	3.31 ± 0.8	3.26 ± 0.8	-1.0	0.53	3.38 ± 1.0	3.03 ± 0.8	-8.7	**0.003**	0.78	**0.01**
ANCOVA (ADMA)				0.440				0.03		**0.04**
FMD (%)	6.5 ± 1.2	6.7 ± 1.1	3.4	**0.03**	6.6 ± 0.8	7.2 ± 0.7	9.9	**<0.001**	0.79	**0.01**
ANCOVA (FMD)				**0.021**				**0.006**		0.138

LVSD: Left ventricular end-systolic diameter, LVDD: Left ventricular end-diastolic diameter, IVSD: Interventricular septum diameter, PWD: Posterior wall diameter, LVEF: Left ventricular ejection fraction, CIMT: Carotid intima-media thickness, FMD: Endothelium-dependent vasodilatation, ADMA: Asymmetric dimethylarginine

p^1 = rate of change from baseline to one year in the variables between the study groups

p^2 value = between the Dianeal® group and the Physioneal® group at baseline

p^3 value = between the Dianeal® group and the Physioneal® group at one year

group. In addition, all 24-hour blood pressure monitoring measurements significantly decreased in the Physioneal® group (Table 2). Regarding the rate of change from baseline to one year, there were no significant changes in the blood pressure monitoring measurements in either group.

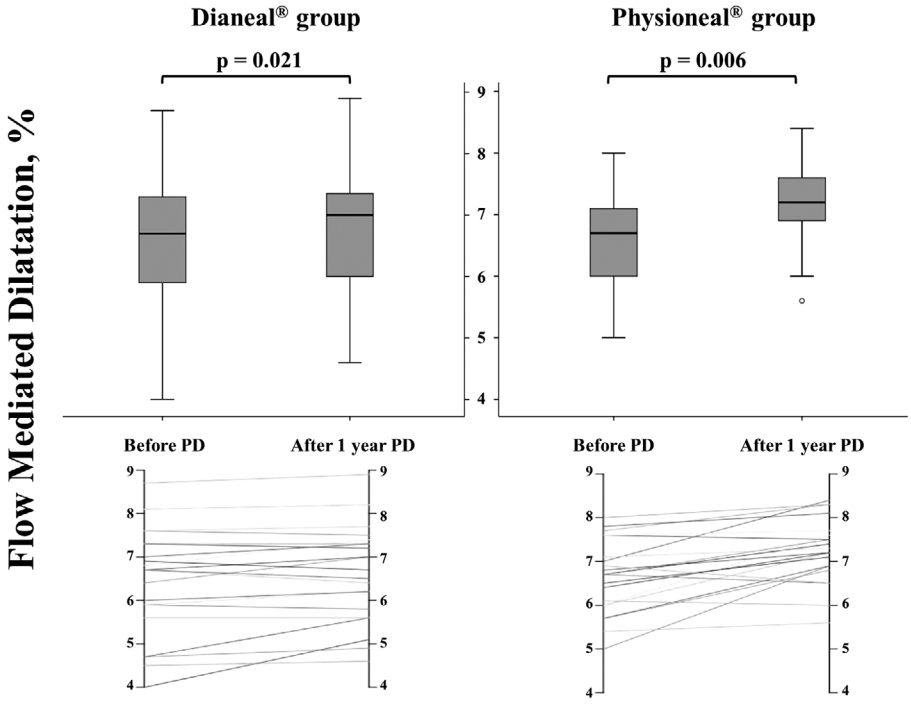


Figure 3. **Comparison of the FMD values between the Dianeal® and Physioneal® groups at baseline and after one year**

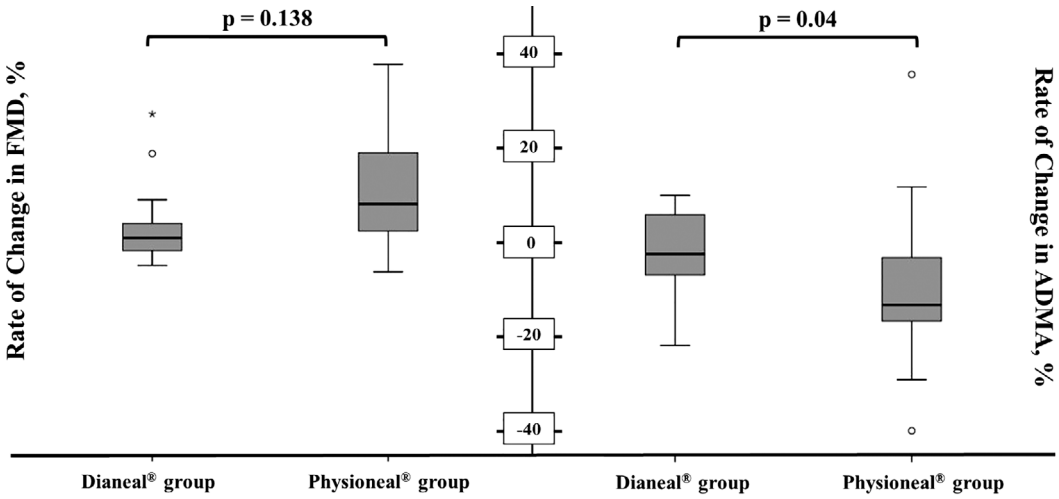


Figure 4. **Comparison of the rate of change in the FMD and ADMA values between the Dianeal® and Physioneal® groups at baseline and after one year**

Discussion

In the current study, we investigated the CV effects of two different PD solutions. Significant improvements were detected in the ambulatory blood pressure values, echocardiography parameters and CA-IMT values in both groups. Meanwhile, a significant decrease was observed in the serum ADMA levels in the Physioneal® group, and the FMD values significantly improved in both groups (the change was more significant in the Physioneal® group), although the rate of change over time was not statistically significant.

We use a strict volume control strategy for our patients in our clinic. Our target is to maintain the patient's blood pressure below 130/80 mmHg and cardiothoracic index below 48 percent. The patients are given minimal salt in their diet (4-5 g), and we increase the dose of diuretic agents and/or use icodextrin solution depending on the clinical data obtained at control visits.

Conventionally produced, lactate (Lac)-buffered, glucose-containing PD solutions usually have a low pH (5.5) in order to reduce the formation of GDPs during heat sterilization (12). A low pH, if combined with Lac, appears to cause vasodilatation, with the recruitment of microvessels (13).

The main physiologic buffer in the extracellular space is bicarbonate, a good solution with a buffering action within a physiologic pH range (5.5-7.5). Recent studies have proposed that a mixture of Bic/Lac may be more biocompatible than a solution comprised of bicarbonate alone, although bicarbonate has been well established to be an ideal buffer for PD (14, 15). In addition, the Bic/Lac solution appears to be more effective than pure bicarbonate solution in correcting infusion pain in PD patients (16). Tranaeus et al. showed that the Bic/Lac solution is safe and effective in correcting uremic acidosis, providing relief of inflow pain/discomfort and improving ultrafiltration and body weight (9). Simonsen et al. showed that a new bicarbonate/lactate-buffered solution with a neutral pH (of 7.2) and low level of GDP appears to promote improved ultrafiltration (UF) compared to a lactate-buffered solution with a pH of 6.3 that is equally low in GDP (13). In contrast, Fang et al. documented that, compared to the standard Lac-based solution, a Bic/Lac-based, pH neutral, low-GDP solution prevents intraperitoneal acidity. The peritoneal mass transport kinetics are similar for small solutes. The net UF is significantly lower with a Bic/Lac solution; the mechanism for this phenomenon is currently unclear (8). Nourse et al. demonstrated that peritoneal fluid kinetics are not significantly altered if pH-neutral dialysis solutions are applied, as compared to acidic solutions (17). In the current study, no significant differences were found between the two groups with respect to peritoneal membrane kinetics and ultrafiltration volumes.

Increased levels of pro-oxidants, defined as oxidative stress, can cause tissue damage. The development of OS in chronic renal failure patients is attributed to the effects of uremic toxins, proinflammatory cytokines, iron overload and underlying metabolic disorders, such as diabetes (18). Increased OS may also be related to uremia, including chronic inflammation and the effects of materials of the extracorporeal circuit and/or dialysis solution (19). Moreover, exposure to high-glucose fluids and/or glucose degradation end products may be responsible for the generation of reactive oxygen species, thus causing membrane hyperpermeability, neoangiogenesis and peritoneal fibrosis (20). The decreased effectiveness of the intracellular and plasma antioxidant protection system contributes to increased oxidative stress, and the degree of acidification of the peritoneal dialysis solution is associated with the level of oxidative stress. Yamaji et al. showed that iron is released from transferrin in conventional low pH PD solutions and subsequently induces oxidative stress. A low-pH PD solution may therefore enhance oxidative stress in peritoneal tissue, as a low-pH environment enhances oxidative stress *in vitro* (21). Potential OS can also be avoided by neutralizing the PD solution. ADMA is principally an endogenous nitric oxide synthase inhibitor, and an increased ADMA level is recognized to be a risk factor for cardiovascular disease. It is also known that the ADMA levels are higher in PD patients than in the normal population (22). Increased oxidative stress raises the ADMA level, and antioxidants accelerate the degradation of ADMA. Although there are insufficient data related to this issue, it is possible that the use of an acidic PD solution leads to increased oxidative stress, resulting in an increased ADMA level, whereas the use of a neutral solution decreases oxidative stress. In the current study, there were no significant changes in the ADMA levels in the Dianeal® group at the first year, while a significant decrease was observed in the ADMA levels in the Physioneal® group at the same time point. This difference can be explained by the fact that Physioneal® solutions are neutral.

The decreased availability of NO, an anti-atherogenic molecule, is closely linked to endothelial dysfunction, a proatherogenic condition. In addition, the serum ADMA level and FMD measurement are indicators of cardiovascular disease in PD patients (23). Kocak et al. demonstrated a relationship between the ADMA and FMD values in PD patients (24), and Mittermayer et al. showed that the ADMA level correlates with the basal FMD in PD patients, although no relationship is observed with the FMD value obtained after stimulation with acetylcholine or nitroglycerin (25). We observed an improvement in the FMD rates in both groups within one year, although the improvement was higher in the Physioneal® group (not significant). It is likely that the improvements in the FMD values observed in both groups were due to the effects of superior volume and uremic control. This difference possibly originates from the fact that the ADMA levels decreased more notably in the Physioneal® group.

Advanced atherosclerosis is a major cause of CVD. CA-IMT measurement using B-mode Doppler ultrasonography is an inexpensive, convenient, reliable and non-invasive method for diagnosing atherosclerosis (26). It can be argued that measurements of the CA-IMT obtained with ultrasonography do not reflect the severity of atherosclerosis (27). There are no data in the literature regarding the impact of CA-IMT on CV outcomes in an isolated PD population. However, our study showed a significant reduction in the CA-IMT measurements over time in both groups. It has been demonstrated that the serum ADMA level is associated with CA-IMT progression in patients with a history of renal transplantation or hypertension. Meanwhile, Cobanoglu et al. reported that the serum ADMA level can be used to predict CA-IMT progression in renal transplant patients (5), and Furuki et al. showed that the ADMA level predicts CA-IMT progression in hypertensive patients (28).

The present study showed decreased CA-IMT levels and improved FMD values in both groups after one year of follow-up. However, the rate of change between the two groups was not statistically significant. It is well established that the ADMA level is associated with both the CA-IMT and FMD. Moreover, the use of Physioneal® solutions with a neutral pH results in a decreased ADMA level. The small sample size and short follow-up duration observed in the present study are possible causes of the lack of significant results in terms of the CA-IMT and FMD. In fact, Cobanoglu et al. followed their patients for 25 months, and Furuki

et al. followed their patients for 72 months. The observed reduction in the Physioneal® group in comparison to that noted in the Dianeal® group may have been different over a longer follow-up period.

There are some limitations associated with this study. The small sample size and short follow-up period are the major limitations, as we performed our study in PD patients treated at a single center. However, that this study is the first designed study to evaluate the effects of two different PD solutions on cardiovascular risk parameters prospectively makes its findings valuable.

In conclusion, the application of solutions with a neutral pH in PD patients leads to decreased ADMA levels. In the light of this finding, the use of Physioneal® may result in a decreased frequency of CV events over the long term, although further studies are required before any definitive conclusions can be made.

The authors state that they have no Conflict of Interest (COI).

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