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Effects of neutral pH and low-glucose degradation product-containing peritoneal dialysis fluid on systemic markers of inflammation and endothelial dysfunction: a randomized controlled 1-year follow-up study

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Abstract

Background. The local peritoneal effects of low-glucose degradation product (GDP)-containing peritoneal dialysis fluid (PDF) have been extensively described. However, the systemic effects of prolonged prescription of these solutions are unknown. This study aimed to evaluate the effects of neutral pH and low-GDP PDF on systemic inflammation and endothelial dysfunction markers in peritoneal dialysis (PD) patients.

Methods. This is a multicenter, open labeled, randomized controlled trial including one hundred fifty-two patients initiating continuous ambulatory peritoneal dialysis for end-stage renal disease from seven centers in Korea. Participants were randomly allocated to conventional PDF (Stay safe®; Fresenius Medical Care, Bad Homburg, Germany) or low-GDP PDF (Balance®; Fresenius Medical Care) and were followed for 1 year. Primary outcome variable was the inflammation and endothelial dysfunction index (IEDI), a composite score derived from serum levels of soluble intercellular adhesion molecule (sICAM)-1, soluble vascular cellular adhesion molecule (sVCAM)-1 and high-sensitivity C-reactive protein (hs-CRP). sICAM-1, sVCAM-1, residual renal function (RRF), peritoneal membrane transport characteristics, ultrafiltration volume and nutritional parameters were measured as secondary outcome variables.

Results. Of 152 patients randomized, 146 (low-GDP: conventional PDF, 79:67) patients entered the trial (46% male, 53% with diabetes mellitus). At 12-month follow-up, the low-GDP group had significantly lower levels of IEDI, sICAM-1 and sVCAM-1 compared to the conventional group; hs-CRP was not different between groups. Peritoneal transport characteristics, RRF, nutritional parameters, incidence of peritonitis and death-censored technique survival were not different between groups.

Conclusion. Neutral pH and low-GDP PDF likely produce fewer changes in markers of endothelial dysfunction compared to conventional PDF in incident PD patients.

Keywords: endothelial dysfunction; glucose degradation products; inflammation; peritoneal dialysis; soluble adhesion molecules

Introduction

New peritoneal dialysis fluids (PDFs) with neutral pH and low glucose degradation products (GDPs) are used in patients on peritoneal dialysis (PD). Low-GDP fluids are reported to be more biocompatible than conventional PDF. Determination of biocompatibility has mainly focused on local peritoneal effects; recently, there has been interest in evaluating the systemic biocompatibility of these fluids.

In recent analyses of two retrospective cohorts of Korean PD patients, significant survival advantage was shown for patients treated with the biocompatible PDF compared to patients treated with the conventional PDF [1, 2]. However, due to the limitations of an observational study, the mechanisms of survival advantage with low-GPD PDF in these studies are difficult to assess. Additionally, it is not clear that new PDFs favorably impact risk markers of cardiovascular disease (CVD).

Epidemiological studies identified an independent association between inflammation and risk of cardiovascular events and mortality [3]; this association has been confirmed in patients with advanced chronic kidney diseases (CKD) [4, 5]. Other evidence showed that clinically overt vascular events are preceded by endothelial dysfunction and increase in circulating markers of endothelial activation, including vascular cellular adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 [6, 7]. Moreover, there is an association between inflammation and elevated levels of soluble VCAM-1 and ICAM-1 in patients with or at risk of atherosclerosis [8]. Elevated levels of soluble adhesion molecules are found in end-stage renal disease (ESRD patients), especially in patients with CVD and malnutrition [9, 10].

A single exposure to GDPs induces VCAM-1 expression in cultured human peritoneal mesothelial cells [11]. However, it is not clear whether GDPs directly activate endothelial cells and increase circulating levels of adhesion molecules or whether the effect is mediated through the activation of receptor for advanced glycation end products (RAGE). Of interest, advanced glycation end products (AGEs) decreased when patients were converted from standard PDF to low-GDP PDF [12, 13].

Therefore, we hypothesized that conventional PDF as well as uremia itself lead to local peritoneal changes such as peritoneal neoangiogenesis and fibrosis, effects related to ultrafiltration failure and subsequently volume overload. In addition, direct effect of GDPs and/or increased systemic levels of AGEs activate endothelial cells and increase levels of vascular adhesion molecules and inflammation. Both local and systemic effects of PDF are possibly associated with increased cardiovascular risks and mortality in PD patients.

This study aimed to examine the effects of neutral pH and low-GDP-containing PDF on systemic inflammation and endothelial dysfunction markers in incident PD patients in a randomized controlled study.

Materials and methods

Study design and participants

This is a multicenter, open-labeled, randomized controlled trial of incident PD patients. It was registered in ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT01315314). The study population included PD patients who initiated dialysis between October 2005 and April 2007 and were being treated by continuous ambulatory peritoneal dialysis (CAPD). Patients were recruited from seven centers in South Korea. Patients were randomly allocated in a 1:1 ratio to conventional PDF (Stay safe®; Fresenius Medical Care, Bad Homburg, Germany) or low-GDP PDF (Balance®; Fresenius Medical Care) groups and were followed for 1 year. Table 1 reports the composition of each study fluid. Male and female patients aged >18 years and <75 years who were capable of adhering to prescription and provided signed informed consent were included. Patients were excluded if deemed to have <80% likelihood of survival for at least 1 year, any malignancy other than treated skin carcinoma, uncontrolled congestive heart failure, recent (within 60 days) myocardial infarction or cerebrovascular accident, active systemic vasculitic disease including systemic lupus erythematosus, polyarteritis nodosa, Anti-neutrophil cytoplasmic antibody-nephritis, active rheumatoid disease or active venous thrombotic-embolic disease, any acute infection at the time of enrollment, active or actively treated tuberculosis or recent (within 30 days) systemic bacterial infection. The Institutional Review Board at Kyungpook National University Hospital approved this study and all patients gave written informed consent.

Table 1. Composition of each study fluid[a]

	Low-GDP fluid	Conventional fluid
pH	7	5.5
Sodium (mEq/L)	134	134
Calcium (mEq/L)	3.5	3.5
Magnesium (mEq/L)	1	1
Chloride (mEq/L)	101.5	103.5
Lactate (mg/dL)	315.3	315.3
Bicarbonate (mEq/L)	2	0
Glucose (mg/dL)[b]	1500–4250	1500–4250
3-deoxyglucosone (μmol/L)[b]	42–60	172–324
Methylglyoxal (μmol/L)[b]	<1	6–10
Acetaldehyde (μmol/L)[b]	<2	152–182
Formaldehyde (μmol/L)[b]	<3	7–13

[a]Note: values expressed as mean or ranges. Concentrations of GDPs were derived from reference [14].
[b]Concentrations in 1.5–4.25% glucose dialysis fluid.

Intervention

Patients were selected when they were scheduled for catheter insertion for PD. Serum was collected prior to first exposure to PDF and evaluated for endothelial dysfunction and inflammation including soluble intercellular adhesion molecule (sICAM)-1, soluble vascular cellular adhesion molecule (sVCAM)-1 and high-sensitivity C-reactive protein (hs-CRP) and biochemistry data. Before break-in, patients were randomly allocated to conventional PDF (Stay safe®) or low-GDP PDF (Balance®) group and began exchanges with each allocated PDF. After a 4-week run-in period during which either allocated PDF was used, baseline peritoneal equilibration test (PET) and biochemical analysis were performed, including the serum markers mentioned above and advance oxidation protein products (AOPP) and serum antioxidant capacity. After baseline, PET and biochemical tests were repeated at 6 and 12 months. Primary outcome variable was the inflammation and endothelial dysfunction index (IEDI), a composite score derived from serum levels of sICAM-1, sVCAM-1 and hs-CRP. This score is the mean of summative categorical variables derived from quartiles of each marker at each time point. Secondary outcome variables were the individual component markers of the IEDI including sICAM-1, sVCAM-1 and hs-CRP, residual renal function (RRF) as average of urea and creatinine clearances, peritoneal clearance as weekly Kt/V urea and creatinine clearance, peritoneal ultrafiltration and peritoneal transport status by PET. In addition, nutritional indices including serum albumin, lean body mass (LBM), normalized protein equivalent of nitrogen appearance (nPNA) and subjective global assessment (SGA) were evaluated. Blood pressure (and use of anti-hypertensive medications), peritonitis rates, technique and patient survival were also assessed.

Clinical assessment

PET was performed using 3.86% glucose dialysis solution as previously described [15] and peritoneal membrane transport characteristics were assessed by dialysate-to-plasma creatinine ratio at 4 h of PET. PET was performed after 4 weeks of peritonitis-free interval when patients were diagnosed as peritonitis. Total weekly Kt/V urea (Kt/V_{urea}) and total weekly creatinine clearance (C_{Cr}) were estimated by standard methods.

As nutritional markers, LBM was estimated from creatinine kinetics using the previously proposed formula [16] and nPNA was calculated as previously described [17]. SGA with a four item and seven-point scale was obtained by a trained nurse. RRF was estimated by calculating the average of residual renal clearances of urea and creatinine. Data on duration of survival were not based on actual duration of PD but the duration from baseline visit to the last visit of the study.

Biochemical analysis

sICAM-1 and sVCAM-1 were measured with enzyme-linked immunosorbent assay (R&D systems, Minneapolis, MN) and hs-CRP with high-sensitivity latex-enhanced immunoturbidimetric assay with MODULAR P analyzer (Roche Diagnostics, Indianapolis, IN). AOPP and total antioxidant activity in serum were measured with AOPP assay kit (Cellbiolabs Inc., San Diego, CA) and antioxidant kit (Cayman, Ann Arbor, MI),

respectively. Other biochemical analyses were performed using routine methods at Kyungpook National University Hospital.

Statistical analysis

Sample size was estimated based on the previous report that showed changes of hs-CRP in PD patients [18]. Estimated sample size of 69 per arm archives 80% power at a significance level of 0.025 (two-sided) to detect the differences of −2.6 between the conventional and low-GDP groups. Assuming 10% of dropout rate and 3% of screening failures, the study required 79 patients in each group.

Statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL) and Sigma Plot version 11 (Systat software Inc., San Jose, CA). The results are expressed as means and SD. Statistical comparisons between the groups in baseline characteristics were performed using *t*-test or chi-square test. Changes between the groups were tested by analysis of covariance with baseline values as covariates. Serial data were also analyzed using a linear mixed model. Survival analysis was done by Kaplan–Meier survival analysis with log-rank test.

Results

Figure 1 diagrams the study flow. Among the 152 patients who signed informed consent, 79 were assigned to low-GDP PDF and 73 to conventional PDF. After allocation, 6 patients from the conventional group were dropped and 146 patients entered baseline PET. Among the 146 patients, 79 in the low-GDP PDF group and 67 in the conventional group met the specific requirements at the baseline visit. In total, 122 patients passed Visit 1 at 6 months and 111 patients passed Visit 2 at 12 months. Reasons for dropout are as follows: in the low-GDP PDF group, one patient transferred to kidney transplantation, five patients transferred to hemodialysis, two withdrew consent, two were withdrawn by an investigator and three died. In the conventional PDF group, three transferred to kidney transplantation, four transferred to hemodialysis, nine transferred to non-trial solution, one was withdrawn by an investigator and two died.

Table 2 reports the baseline characteristics of patients entering the study. There was no difference between groups in terms of sex, age and causes of ESRD. Comorbidity index and body mass index were comparable between the two groups. Blood pressure at baseline was similar in both groups. Among the biochemical parameter, all were similar except serum carbon dioxide (tCO2), which was significantly higher in the low-GDP PDF group. Regarding PET and adequacy data, dialysate-to-plasma ratio of creatinine at 4 h of PET (D4P4cr), at baseline after exposure to the different solutions during the run-in period, was higher in the low-GDP PDF group. Total weekly urea clearance was not different, but peritoneal creatinine clearance was higher in the low-GDP PDF group. RRF or urine volume was not different between the two groups. Peritoneal ultrafiltration volume was lower in the low-GDP PDF group at baseline in keeping with higher peritoneal transport characteristics in this group. Nutritional markers including serum albumin, LBM, nPNA and SGA and blood pressure and number of anti-hypertensive medications were not different between the two groups.

Inflammation and endothelial dysfunction markers

After 12 months of PD, IEDI was significantly lower in the low-GDP PDF group after adjusting for baseline IEDI (Figure 2). However, we are unable to find any significant time

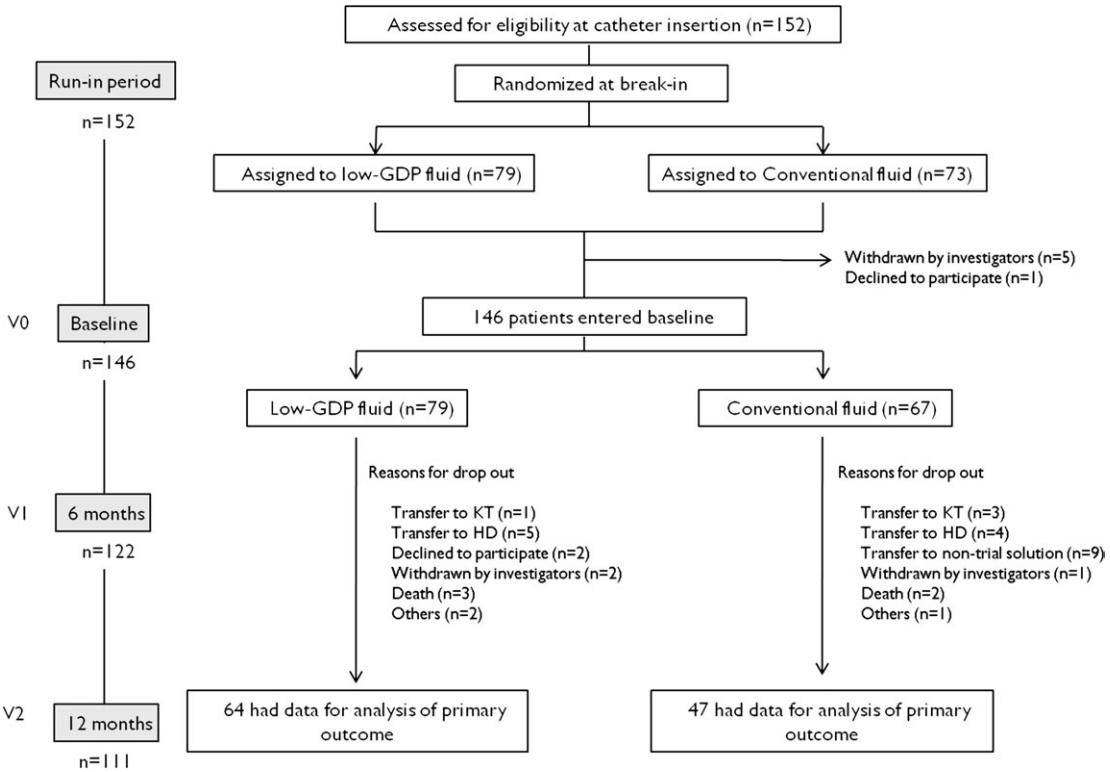

Fig. 1. Study flow. KT, kidney transplantation; HD, hemodialysis.

Table 2. Baseline patient characteristics ($n = 146$)[a]

	Low-GDP fluid ($n = 79$)	Conventional fluid ($n = 67$)
Sex (male, %)	37 (46.8%)	30 (44.8%)
Age (years)	52.2 ± 11.4	52.6 ± 11.1
Cause of ESRD (*n*, %)		
DM	40 (50.6%)	27 (40.3%)
HTN	23 (29.1%)	28 (41.8%)
CGN	10 (12.7%)	4 (6.0%)
Others/unknown	6 (7.6%)	8 (11.9%)
Comorbidities		
DM (*n*, %)	41 (51.9%)	37 (55.2%)
CAD (*n*, %)	6 (7.6%)	1 (1.5%)
Modified Charlson's comorbidity index	4.06 ± 1.56	3.99 ± 1.58
Weight (kg)	59.1 ± 9.2	57.9 ± 9.2
BMI (kg/m^2)	22.9 ± 3.2	22.6 ± 2.6
Blood pressure (mmHg)		
SBP	131.6 ± 19.3	131.4 ± 20.8
DBP	82.2 ± 11.9	81.3 ± 12.1
Use of ACEi or ARB (%)	65.8%	78.1%
Biochemistry		
Hb (g/dL)	11.1 ± 1.5	10.8 ± 1.7
Serum creatinine (mg/dL)	7.3 ± 2.8	7.2 ± 2.6
Cholesterol (mg/dL)	189.6 ± 47.1	191.4 ± 50.1
Triglyceride (mg/dL)	131.1 ± 73.8	169.3 ± 189.9
Ca (mg/dL)	8.7 ± 0.7	8.8 ± 0.9
P (mg/dL)	4.6 ± 1.3	4.7 ± 1.3
tCO2 (mEq/L)	**25.0 ± 3.7***	**23.7 ± 3.4**
Urinary protein (mg/day)	1700 ± 2000	2000 ± 2100
PET and adequacy		
D4/P4 creatinine	**0.74 ± 0.12***	**0.69 ± 0.12**
Kt/V_{urea}	2.4 ± 0.6	2.3 ± 0.6
Kpt/V_{urea}	1.7 ± 0.4	1.7 ± 0.5
Krt/V_{urea}	0.8 ± 0.5	0.7 ± 0.5
CrCl (L/week/1.73m^2)	84.1 ± 30.9	77.5 ± 27.9
Kpcr	**41.4 ± 7.3***	**37.9 ± 6.9**
Ccr	38.9 ± 31.3	36.0 ± 26.2
RRF (mL/min)	3.9 ± 3.1	3.7 ± 2.6
Ultrafiltration volume (mL)		
Total fluid removal (mL/day)	1479 ± 762	1636 ± 586
Peritoneal fluid removal (mL/day)	**621 ± 520***	**962 ± 527**
Urine volume (mL/day)	880 ± 732	717 ± 536
Peritoneal ultrafiltration per glucose load (mL/g glucose)	**5.69 ± 5.04***	**9.54 ± 4.73**
Nutritional markers		
Serum albumin (g/dL)	3.6 ± 0.6	3.6 ± 0.5
LBM (kg)	37.5 ± 9.7	35.1 ± 8.6
nPNA (g/kg/day)	0.91 ± 0.18	0.90 ± 0.25
SGA	5.9 ± 1.2	5.7 ± 1.1

[a]Note: data are shown as mean ± SD. Bold indicates the parameters have significant differences between the two groups and asterisk indicates $p < 0.05$ versus conventional fluid group. DM, diabetes mellitus; HTN, hypertension; CGN, chronic glomerulonephritis; CAD, coronary artery disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; tCO2, total carbon dioxide in serum; PET, peritoneal equilibration test; D4/P4 creatinine, dialyzate-to-plasma creatinine ratio at 4 h of PET; Kt/V_{urea}, total weekly urea clearance; Kpt/V_{urea}, peritoneal urea clearance; Krt/V_{urea}, renal urea clearance; CrCl, total creatinine clearance; Kpcr, peritoneal creatinine clearance; Ccr, renal creatinine clearance; RRF [mean of creatinine clearance (Ccr) and urea clearance (C_{urea})].

and group effect with linear mixed model analysis. As an individual endothelial dysfunction marker, sICAM-1 at 12 months was also significantly lower in the low-GDP PDF group. By linear mixed analysis, it was also significantly different between the two groups, although we could not find

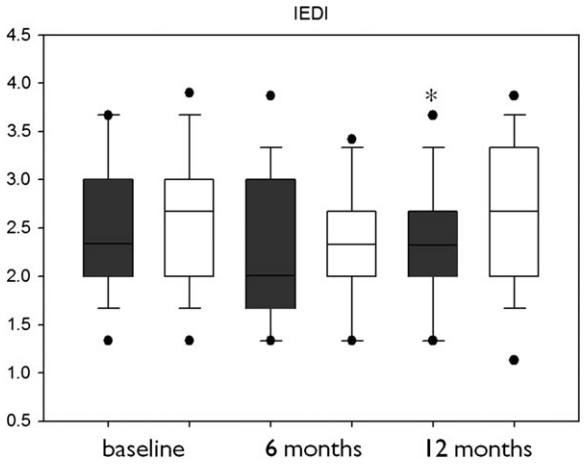

Fig. 2. Changes of IEDI. Gray bar denotes low-GDP group and white bar conventional group. In box plots, horizontal lines at the top, middle and bottom of the boxes show the 75th, 50th and 25th percentiles, respectively, and vertical lines above and below the boxes show the 90th and 10th percentiles, respectively. The lower and upper circles show the 95th and 5th percentiles, respectively. *$P < 0.05$ versus conventional group by analysis of covariance. In linear mixed model analysis, $P = 0.156$ for time effect and $P = 0.147$ for group effect.

any significant time effect (Figure 3A). sVCAM-1 was also significantly lower at 6 and 12 months in the low-GDP PDF group. The difference was also significant by linear mixed analysis, but we could not find any significant time effect (Figure 3B). In contrast to the endothelial dysfunction markers, level of log-transformed hs-CRP was not different between the two groups at 12 months. Log-transformed hs-CRP level at 6 months was slightly higher in the low GDP PDF group (Figure 3C). AOPP and total antioxidant capacity were not significantly different between the two groups (data not shown). In a separate analysis, level of IEDI and individual component, such as sICAM-1, sVCAM-1 and log-transformed hs-CRP, were slightly higher in diabetic patients, but we could not find statistical significance in the levels of these variables (data not shown).

To evaluate whether conventional PD solution would be more harmful in patients with active inflammation, we analyzed the interaction between inflammation and solution group on sICAM-1 and sVCAM-1 at 12 months. In two-way analysis of variance, there was no interaction effect between solution group and hs-CRP. Main effect of solution group controlling for the effect of hs-CRP was significant for sICAM-1 ($P = 0.012$) and sVCAM-1 ($P = 0.024$), respectively. Therefore, reduced sICAM-1 and sVCAM-l levels in the low-GDP PDF group were independent of baseline hs-CRP (Figure 4A and B).

Dialysis adequacy, peritoneal membrane transport characteristics, RRF and nutritional status

Table 3 reports the changes in secondary variables. Adequacy data including total Kt/V_{urea} and creatinine clearance were not different except peritoneal creatinine clearance at baseline. Peritoneal creatinine clearance was significantly higher in the low-GDP PDF group only at baseline, but changes of adequacy were not different between the two groups. The change of D4P4cr and peritoneal ultrafiltration

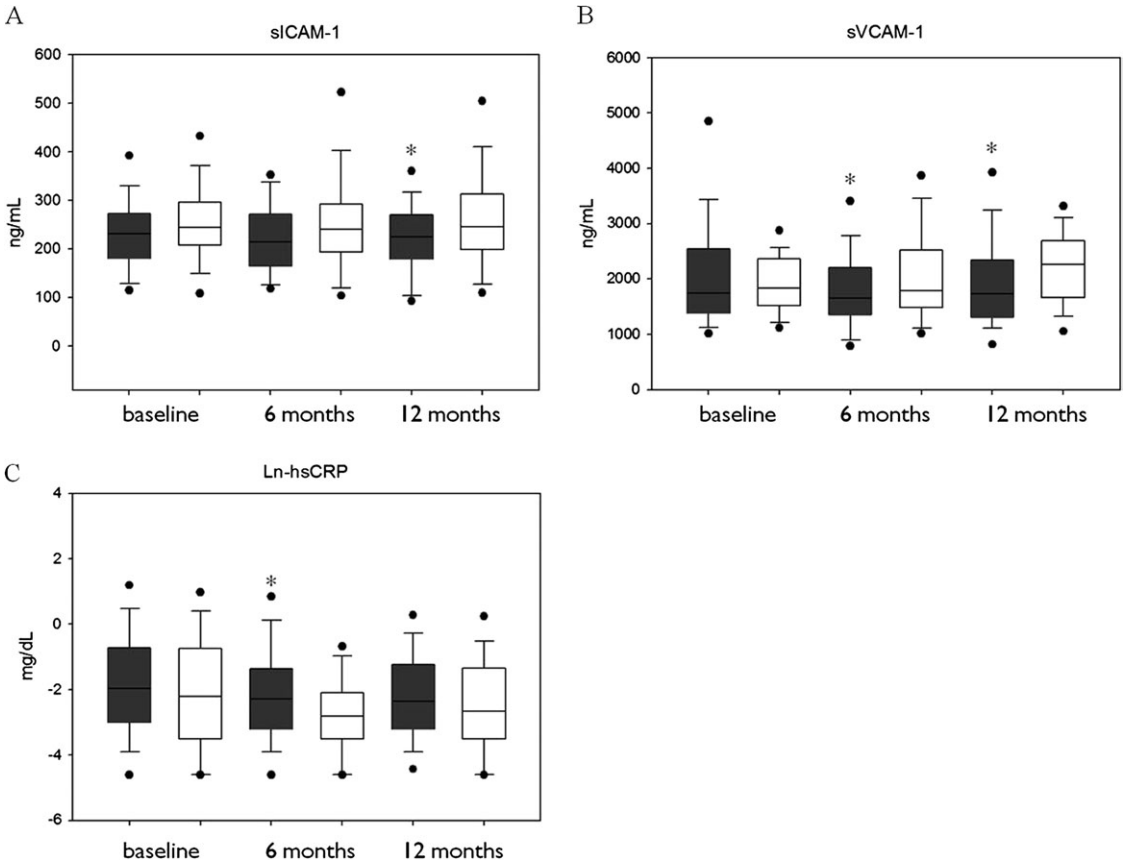

Fig. 3. Changes of sICAM-1 (**A**), sVCAM-1 (**B**) and log-transformed hs-CRP (**C**). Gray bar denotes low-GDP group and white bar conventional group. *$P < 0.05$ versus conventional group by analysis of covariance. In linear mixed model analysis, $P = 0.928$ (time), $P = 0.003$ (group) for sICAM-1 (A), $P = 0.117$ (time), $P = 0.006$ (group) for sVCAM-1 (B) and $P = 0.504$ (time), $P = 0.007$ (group) for log-transformed hs-CRP (C).

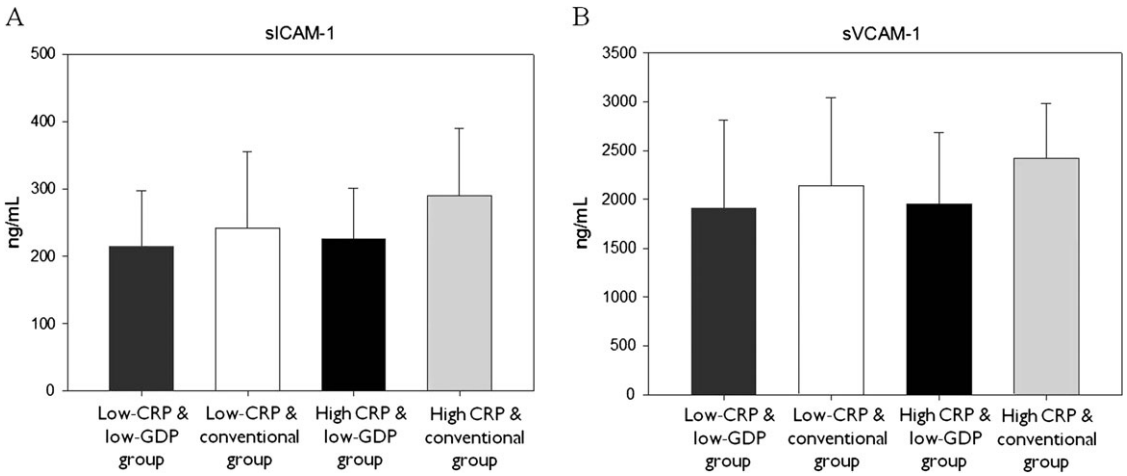

Fig. 4. Effect of inflammation and solution group on sICAM-1 (**A**) and sVCAM-1 (**B**) at 12 months of PD. hs-CRP group was divided by median value of hs-CRP level before PD start. Main effect of solution group controlling for the effect of hs-CRP was significant. $P = 0.012$ (sICAM-1, A) and $P = 0.024$ (sVCAM-1, B), respectively.

volume per glucose loading was significantly different between the two groups by linear mixed model analysis (Figure 5A and B). However, the change of RRF (Figure 5C) or urine volume was not different between the two groups. The change of nutritional markers including serum albumin, LBM, nPNA and SGA was not different between the two groups. In addition, changes in blood pressure and number of anti-hypertensive medications were not different between the two groups.

Peritonitis and survival

Total peritonitis incidence was 46 episodes of peritonitis per 1550 patient-months. Mean follow-up period of PD

Table 3. Changes in secondary outcome variables[a]

Period	Baseline		6 months		12 months	
Group	Low-GDP	Conventional	Low-GDP	Conventional	Low-GDP	Conventional
Kt/V_{urea}	2.4 ± 0.6	2.3 ± 0.6	2.2 ± 0.5	2.3 ± 0.7	2.2 ± 0.6	2.1 ± 0.7
Kpt/V_{urea}	1.7 ± 0.4	1.7 ± 0.5	1.5 ± 0.4	1.6 ± 0.4	1.6 ± 0.5	1.8 ± 1.1
Krt/V_{urea}	0.8 ± 0.5	0.7 ± 0.5	0.7 ± 0.5	0.6 ± 0.6	0.5 ± 0.5	0.5 ± 0.6
CrCl (L/week/1.73m^2)	84.1 ± 30.9	77.5 ± 27.9	74.8 ± 25.6	74.4 ± 28.1	67.9 ± 24.4	68.6 ± 28.7
Kpcr	**41.4 ± 7.3***	**37.9 ± 6.9**	38.0 ± 7.3	40.4 ± 8.0	38.8 ± 9.3	39.9 ± 8.6
Ccr	38.9 ± 31.3	36.0 ± 26.2	33.1 ± 25.7	29.0 ± 28.0	25.9 ± 23.4	24.3 ± 30.3
RRF (mL/min)	3.9 ± 3.1	3.7 ± 2.6	3.4 ± 2.5	3.1 ± 2.8	2.9 ± 2.3	2.9 ± 3.1
Total fluid removal (mL/day)	1479 ± 762	1636 ± 586	1440 ± 512	1659 ± 665	1469 ± 721	1459 ± 646
Peritoneal fluid removal (mL/day)	**621 ± 520***	**962 ± 527**	**673 ± 522***	**1045 ± 600**	845 ± 633	939 ± 683
Urine volume (mL/day)	880 ± 732	717 ± 536	803 ± 513	677 ± 568	714 ± 537	644 ± 575
Peritoneal UF per glucose load (mL/g glucose)	**5.69 ± 5.04***	**9.54 ± 4.73**	**6.29 ± 5.60***	**9.69 ± 5.47**	7.92 ± 5.86	8.72 ± 6.68
Serum albumin (g/dL)	3.6 ± 0.6	3.6 ± 0.5	3.7 ± 0.6	3.7 ± 0.5	3.7 ± 0.6	3.7 ± 0.4
LBM (kg)	37.5 ± 9.7	35.1 ± 8.6	38.7 ± 10.0	37.5 ± 8.4	39.7 ± 11.1	37.8 ± 9.2
nPNA (g/kg/day)	0.91 ± 0.18	0.90 ± 0.25	0.88 ± 0.18	0.91 ± 0.18	0.88 ± 0.19	0.89 ± 0.21
SGA	5.9 ± 1.2	5.7 ± 1.1	6.0 ± 1.3	5.8 ± 1.1	6.0 ± 1.4	5.9 ± 1.3
Blood pressure (mmHg)						
SBP	131.6 ± 19.3	131.4 ± 20.8	132.0 ± 16.8	132.5 ± 21.7	134.5 ± 20.8	129.6 ± 19.3
DBP	82.2 ± 11.9	81.3 ± 12.1	82.2 ± 9.9	80.9 ± 12.6	82.5 ± 11.3	81.2 ± 11.3
Anti-hypertensive agents (numbers)	2.2 ± 0.8	2.2 ± 0.8	2.1 ± 0.7	2.2 ± 0.9	2.3 ± 0.9	2.4 ± 1.0

[a]Note: data are shown as mean ± SD. Bold indicates the parameters have significant differences between the two groups and asterisk indicates $p < 0.05$ versus conventional fluid group. Kt/V_{urea}, total weekly urea clearance; Kpt/V_{urea}, peritoneal urea clearance; Krt/V_{urea}, renal urea clearance; CrCl, total creatinine clearance; Kpcr, peritoneal creatinine clearance; Ccr, renal creatinine clearance; RRF [mean of creatinine clearance (Ccr) and urea clearance (C_{urea})]; SBP, systolic blood pressure; DBP, diastolic blood pressure.

was 11.0 versus 10.1 months for the low-GDP PDF and conventional PDF groups, respectively. Frequency of peritonitis was not different between the two groups (one episode per 34.8 versus 32.3 patient-months for low-GDP PDF and conventional PDF groups, respectively). During follow-up of 12 months, five deaths were reported. In survival analysis, patient survival and death-censored technique survival were not different between the two groups (Figure 6A and B).

Discussion

This is the first prospective, randomized controlled study investigating inflammation and endothelial dysfunction markers as primary outcomes in incident PD patients exposed to different levels of GDP-containing PDF. Our study demonstrates that endothelial dysfunction markers were significantly lowered in PD patients exposed to low-GDP PDF compared to standard PDF after 12 months of PD.

The local peritoneal effects of low-GDP PDF are well known from previous studies, showing improvement of peritoneal effluent markers of peritoneal integrity, such as CA125 or hyaluronic acid [12, 19]. Consistently, animal models of PD demonstrate fewer structural alterations in the local peritoneum, such as peritoneal inflammation, neoangiogenesis and fibrosis, with low GPD PDF compared to standard PDF [20]. In addition to its local effects, the systemic effects of low-GDP PDF were partly reported in previous studies, showing lower concentration of systemic AGEs and/or C-reactive protein levels in low-GDP PDF-treated patients [12, 13, 18, 19]. AGEs are commonly seen in patients with CKD; their production is promoted by oxidative and carbonyl stress. The levels of systemic AGEs were more markedly elevated after exposure to conventional PDF compared to low-GDP PDF [21]. Interestingly, the levels of selected AGEs decrease when patients are converted from standard PDF to low-GDP PDF [12, 13, 22]. AGEs activate inflammatory cells and directly stimulate endothelial cells to express adhesion molecules [23]. Certain subtypes of AGEs activate monocytes, which have important pathogenic roles in the progression of atherosclerosis, and subsequently increase production of adhesion molecules and cytokines [24]. Vascular adhesion molecules, such as sVCAM-1 or sICAM-1, are known biochemical markers of endothelial dysfunction [25]. Endothelial dysfunction was partly mediated by AGEs-induced inhibition of nitric oxide synthase through receptor for AGE (RAGE) [26]. In addition, elevated levels of soluble adhesion molecules are found in CKD patients, especially in malnourished, inflamed patients and patients with CVD [9, 10]. Clinically overt vascular events are reportedly preceded by endothelial dysfunction [27]. Endothelial dysfunction and inflammation are suggested to be novel risk markers, in addition to other uremia-related factors, and they act synergistically with the highly prevalent traditional risk factors for CVD in the CKD population.

In this study, we observed less elevation of vascular adhesion molecules in patients receiving low-GDP PDF. This might be associated with a reduction in elevation of systemic AGEs in patients treated with low-GDP PDF. In addition, indirect evidence, such as induced VCAM-1 expression in cultured human peritoneal mesothelial cells following a single exposure to GDPs [11], suggests a direct effect of GDP on vascular endothelial cells. However, there is currently a paucity of scientific evidence supporting a direct effect of GDPs on vascular endothelial cell activation.

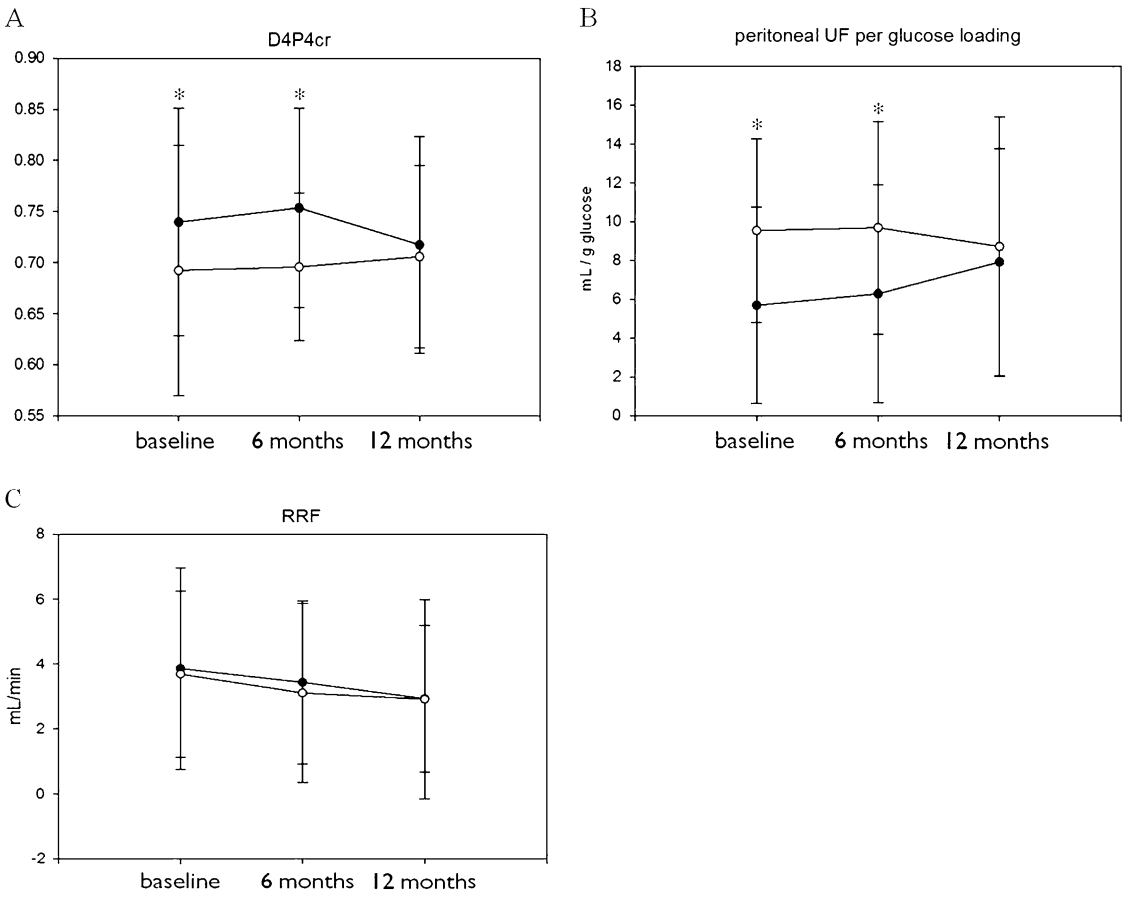

Fig. 5. Changes of dialysate-to-plasma ratio of creatinine (D4/P4cr) (**A**), peritoneal ultrafiltration (UF) volume per glucose load (mL/g glucose) (**B**) and RRF (mL/min) (**C**). Closed circle denotes low-GDP group and open circles conventional group. *P $<$ 0.05 versus, conventional group by analysis of covariance. P = 0.194 (time), P = 0.002 (group) for D4/P4cr (A), P = 0.518 (time), P = 0.003 (group) for UF/glucose (B) and P = 0.309 (time), P = 0.589 (group) for RRF (C).

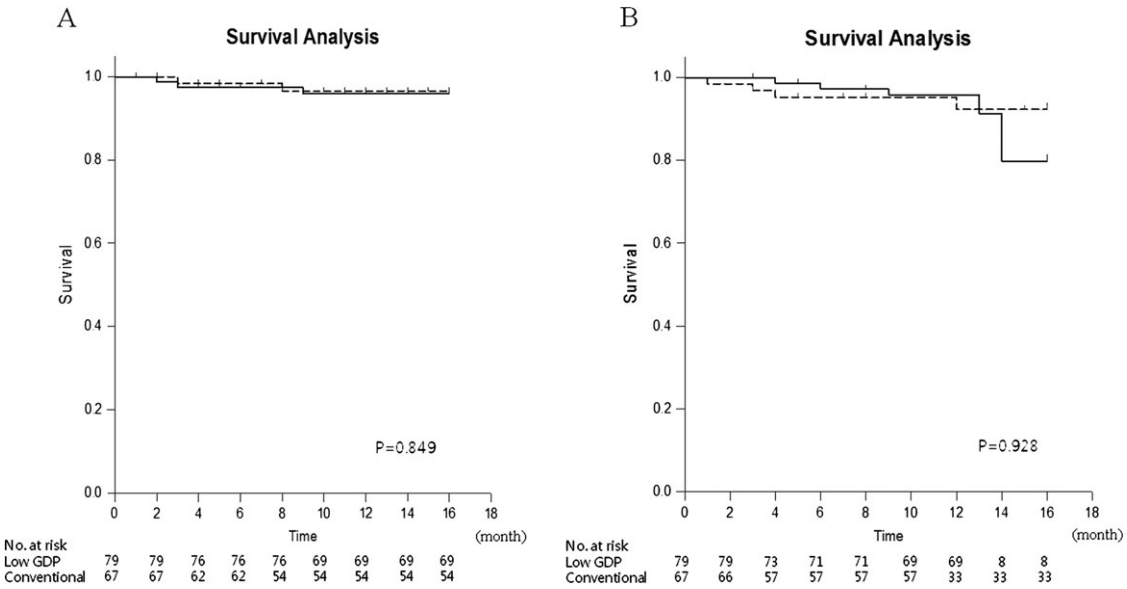

Fig. 6. Survival analyses for patients (**A**) and technique survival (**B**). Solid line denotes low-GDP group and dashed line conventional group. In log-rank test, P = 0.849 and 0.928, respectively.

Besides soluble adhesion molecules, however, we were unable to demonstrate significant differences in inflammation and oxidative stress markers between the two treatment groups. In this study, hs-CRP was not significantly different between the two groups after 12 months of PD. This is in contrast to previous reports, which found lower hs-CRP in the low-GDP groups in prevalent and incident PD patients [18, 19].

We could not explain exactly how this difference in the changes of hs-CRP occurs in our study. However, we assume that a higher level of hs-CRP at baseline, even though it is not statistically significant, may affect the change of hs-CRP, at least, at 6 months. Moreover, from an other point of view, if the low-GDP solution harmfully affects hs-CRP levels beyond 6 months, the difference would be more prominent at 12 months. However, we could not find a significant difference of hs-CRP at 12 months.

In a retrospective analysis of Korean PD patients, use of bicarbonate/lactate, low-GDP PDF is associated with improvement in overall patient survival [2]. However, it is not clear whether the favorable effect of low-GDP PDF is directly linked to the improvement of cardiovascular outcomes in PD patients. Based on our results, changes in vascular adhesion molecules as a marker of endothelial dysfunction, in addition to surrogate markers for cardiovascular outcomes in PD patients, may provide evidence of cardiovascular effects.

Considering secondary outcome variables, we found higher peritoneal membrane transport characteristics in the low-GDP group at baseline. During the run-in period before baseline PET, patients were already exposed to different dialysis solutions for at least 4 weeks; thus, peritoneal membrane transport characteristics might be affected by a different PDF. Similarly, the Eurobalance trial [12] reported higher peritoneal membrane transport in the low-GDP group after 12 weeks of PDF exposure. In addition, in this study, peritoneal ultrafiltration volume was significantly lowered until 6 months of PD without difference in RRF. Change of urine volume was not significantly different between the two treatment groups. Therefore, differences in peritoneal ultrafiltration volume may be associated with peritoneal membrane transport characteristics rather than RRF in our study. The effects of low-GDP fluid on RRF were not consistent in several studies, with some reporting protective effects [12,28] and others finding no influence [19]. Similar to our study, changes of RRF and urine volume were not statistically different between the incident PD patients (including automated PD) treated with biocompatible PDF and standard PDF in a randomized controlled trial of 1-year [29]. However, in an another 1-year of randomized study in incident CAPD patients, low-GDP PDF was beneficial for maintaining RRF, especially in patients with a GFR of $\geq$2 mL/min/1.73m^2 [30]. This may be related to variations in compounding factors affecting RRF as well as population of patients.

Peritonitis incidence, expressed as episodes per patient-months, was not different between the two groups. This is consistent with previous studies with low-GDP PDF. Moreover, the data for survival analysis were also consistent with a previously reported randomized study [19].

Some limitations of this study should be noted. We measured endothelial dysfunction only by biomedical markers not by functional endothelial dysfunction due to the limitation of standard instruments and procedures in different multiple centers. Previous reports show that flow-mediated vasodilatation, a commonly used method for endothelial dysfunction, correlates with levels of vascular adhesion molecules [31,32]. This indicates that vascular adhesion molecules could be a useful biomarker for functional endothelial dysfunction. Secondly, in this multicenter study, center effect was not fully adjusted. We assumed minimal center effect because all centers have similar characteristics regarding the PD program. In addition, allocation of patients was performed randomly at each center. All seven centers participating in this randomized study have experienced PD-oriented doctors with >100 PD patients for five centers and 40 patients for two centers. Lastly, the number of patients in both groups was not completely balanced when entering baseline study period because of higher drop rate during the run-in period for the conventional PDF group. This may lead to a selection bias.

In conclusion, neutral pH and low-GDP PDF likely have a beneficial effect on endothelial dysfunction markers compared to standard PDF in incident PD patients, although the association of these surrogate outcome markers and long-term clinical outcomes of low GDP PDF needs to be evaluated in further studies.

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