Benefits of biocompatible PD fluid for preservation of residual renal function in incident CAPD patients: a 1-year study

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Abstract

Background. In vitro studies of peritoneal dialysis (PD) solutions demonstrated that a biocompatible fluid with neutral-pH and low glucose degradation products (LF) has better biocompatibility than a conventional acidic lactate-buffered fluid (CF). However, few clinical trials have investigated the effects of the biocompatible solution on residual renal function (RRF). We performed a prospective, randomized trial with patients starting continuous ambulatory peritoneal dialysis (CAPD).

Methods. Ninety-one incident patients started CAPD for 12-month treatment with either LF (Balance®, Fresenius, n = 48) or CF (CAPD/DPCA®, Fresenius, n = 43). RRF, peritoneal solute transport rate and solute clearance were measured every 6 months.

Results. LF had a significant effect on the change of glomerular filtration rate (GFR) (P = 0.048 by the mixed model). In per-protocol analysis, GFR in the LF group did not decrease over a 12-month period, while GFR in the control group significantly decreased (0.13 ± 33.4 L/week/1.73 m² for LF versus −13.6 ± 19.4 L/week/1.73 m² for CF, P = 0.049). Subgroup analysis for patients with initial GFR of 2 mL/min/1.73 m² or above showed a significantly higher GFR for the LF group over the 12-month period. At Month 13, serum total CO₂ levels were higher and serum albumin levels were lower in the LF group. No differences between the two groups were observed for the C-reactive protein. Over the 12-month period, effluent cancer antigen-125 levels significantly increased in the LF group, compared with those of the CF group, while effluent interleukin-6 levels were not different between the two groups.

Conclusion. Our study suggests that LF may better preserve RRF over the 12-month treatment period in incident CAPD patients.

Keywords: end-stage renal disease; glucose degradation products; peritoneal dialysis; randomized controlled trials; residual renal function

Introduction

Several studies have reported that a higher residual renal function (RRF) in patients with end-stage renal disease (ESRD) is associated with a more favourable patient survival and that RRF is the major determinant of patient survival in patients on peritoneal dialysis (PD) [1–3]. A retrospective study suggested that the use of biocompatible solutions conferred a survival advantage on PD patients [4].

A cross-over study indicated that patients using biocompatible PD solutions may preserve their RRF [5]. Glucose degradation products (GDPs), which are produced during heat sterilization and storage of the PD solution, can lead to peritoneal membrane damage by promoting the formation of advanced glycation end-products (AGEs) in the peritoneum [6], and by impairing peritoneal mesothelial cell function [7]. GDPs also may be absorbed through the peritoneal membrane into the systemic circulation during PD, and promote apoptosis in renal tubular epithelial cells [8]. This suggests that GDPs can modulate RRF in patients on PD.

Recently, however, two prospective randomized clinical trials from incident patients with biocompatible fluid showed no advantage in RRF [9,10]. One from Hong Kong failed to detect any benefit on RRF due to insufficient statistical power [10], and the other by Fan et al. from the United Kingdom included a heterogeneous patient group with admixture of continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) patients using either Physioneal® (Baxter, Healthcare, Compton, UK) or Balance® (Fresenius Medical Care, Bad Homburg, Germany) [9]. In addition, they observed the RRF changes over only 9 months, which is not regarded as long enough to detect any differences in RRF changes. These might have contributed to the negative results of the study.

We hypothesized that the use of a low-GDP PD solution favourably affects preservation of RRF. We performed a
prospective, multicentre, randomized, controlled trial using single formulation of low GDP PD fluid in incident patients on CAPD over 12 months.

Subjects and methods

Study design

This was a multicentre, open-labelled, randomized, prospective study with parallel arms: patients with a low-GDP solution (LF) and patients with a conventional PD solution (CF). All enrolled patients were randomly allocated to either LF or CF group. After 4-week run-in phase on CF, each group started CAPD with either LF (Balance®) or CF (CAPD/DPCA®; Fresenius Medical Care, Bad Homburg, Germany).

The primary end point was glomerular filtration rate (GFR) defined by the mean of renal urea and creatinine clearance (Ccr). Secondary end points were (1) the urine volume, (2) survival: patient survival, technique survival and peritonitis-free survival, and (3) clinical laboratory data: peritoneal solute transport rate (PSTR) represented by dialysate-to-plasma ratio for creatinine at 4 h (D/Pcr) and blood chemistry.

Study population

This study was undertaken in four major centres (Kang Dong Sacred Heart Hospital, Hallym University Sacred Heart Hospital, Gachon Gill Hospital and Seoul National University Hospital). Approval for the study was obtained from the local ethics committee in each hospital, and all patients gave written informed consent before study entry. During a 2-year recruitment period between June 2004 and May 2006, 166 patients started CAPD in the four PD centres. All patients were ethnic Koreans and older than 18 years. Among them, 33 patients were excluded: 9 patients had problems with PD catheter, 12 patients expected kidney transplantation within 1 year, life expectancy of 6 patients was less than 6 months, 5 patients had plans to transfer to other hospitals and 1 patient started PD with acute renal failure. As 36 patients refused to participate in the study, 97 patients were finally enrolled and randomized after having given their informed consent, and started CAPD with CF during the run-in period. However, 6 patients (3 in the LF group and 3 in the CF group) discontinued the enrolment due to transfer to other hospitals or death during this period. At Month 1, 91 patients performed a baseline PET test with either LF or CF fluid, depending on their group allocation to which they were randomly assigned. Measurements for GFR, PET, Kt/V and other laboratory parameters at Month 1 were regarded as baseline. Information collected at initiation of the study included age, gender, weight, height, underlying renal disease and comorbidity. Degree of comorbidity was assessed on the basis of the Davies comorbidity score [11]. The Davies comorbidity score comprises seven comorbid conditions, leading to three risk groups, i.e. low (no comorbid disease), intermediate (one or two comorbid diseases) and high (three or more comorbid diseases). The GFR at Month 0 was estimated from serum creatinine using the abbreviated Modification of Diet in Renal Disease Study formula: GFR = 186.3 × (serum creatinine)^−1.154 × age−0.203 × (0.742 for women). This estimated GFR (eGFR) was not used for the analysis of change in residual kidney function, but only for demonstrating the effectiveness of randomization. RRF during the treatment period was assessed by collecting all the urine output over a 24-h period; GFR was calculated as the mean of the values for renal creatinine and urea clearances normalized to 1.73 m² of body surface area (BSA). Patients’ BSA was calculated by the Du Bois and Du Bois equation [12].

Dialysis adequacy and nutritional status were expressed as Kt/V urea, creatinine clearance (Ccr) (L/week/1.73 m²) and normalized protein equivalent of nitrogen appearance (NPN, g/kg/day). Residual renal (Kt/V) urea was calculated using data from 24-h collection of urine. Urea distribution volume was calculated using Watson equation [13]. Peritoneal Kt/V urea and Ccr were calculated by the performance of 24-h collection of dialysate effluent. Total Kt/V urea was calculated by the sum of renal and peritoneal Kt/V urea.

Modified PET using 3.86% glucose solutions was performed, and the peritoneal transport type of each patient was classified as described elsewhere [14]. In short, after overnight dwell with 1.36% glucose PD fluid, patients were subjected to 4-h dwell with 3.86% glucose dialysate fluid. Blood samples were taken at 2 h. D/Pcr were calculated as the dialysate concentration at 4 h divided by the plasma concentration for creatinine. The dialysate creatinine concentration was determined after correction for glucose interference at each laboratory. The determination of creatinine concentration was validated three times for both dialysate and serum samples in each participating centers. Inter-assay coefficient of variance was 8.3%. Daily glucose exposure (g/day) was calculated as the sum of the product of the volume and the glucose concentration for all the daily bags.

Overall survival, technique survival (failure defined as death or transfer to HD; censored for transplantation or transfer to another PD unit) and peritonitis-free survival (censored for death, transfer to HD or other PD unit, and transplantation) were analysed. The diagnosis and treatment of peritonitis were in accordance with the ISPD Guideline [15].

Biochemical tests were performed in each hospital laboratory using Roche modular units analyser (Toshiba 200FR, Toshiba Medical Systems Co., Ltd, Tokyo, Japan). Serum CRP levels were analysed by the non-competitive turbidimetric method (Denka Seiken, Tokyo, Japan). Indirect ion-selective electrode methods were used for electrolyte levels, and the enzyme method was used for measuring bicarbonate levels. Each assay was performed at the local laboratory. There were no differences between the four site laboratories in the baseline parameters including GFR, serum levels of CRP, tCO₂ and albumin. Samples of spent dialysate from the overnight bag were taken and centrifuged. The supernatants were collected and immediately frozen at −70°C for later analysis. Analysis for the dialysate CA-125 and interleukin-6 (IL-6) was performed in a central laboratory. CA-125 was determined by using the electrochemiluminescence immunoassay with Elecsys CA-125 H (Roche Diagnostics, Mannheim, Germany) according to the manufacturer’s instruction. The lower detection limit was 0.6 IU/mL. The dialysate IL-6 concentration was determined using the photometric enzyme-linked immunosorbent assay (ELISA) (Boehringer Mannheim, Mannheim, Germany) with intra- and interassay coefficients of variation (CV) of 2.6% and 7.1%, respectively. The sensitivity was 7.5 pg/mL.

Statistical analysis

The sample size in our study was estimated on the basis of the study reported by Williams et al., because it was the only prospective clinical trial on the benefit of biocompatible PD fluid on RRF when we designed the present study. We predicted that GFR in the CF group would decrease
Results

Baseline characteristics

Table 1 lists the baseline demographics of the two groups. There were no differences in age, gender, comorbidity score, prior requirement for HD, aetiology of ESRD and eGFR at Month 0. Over half of patients in both groups were prescribed angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), and approximately one-third of patients in both groups were prescribed diuretics; there were no significant differences in the prescription of the above medications between the two groups.

**RRF of total 91 patients**

At baseline, there were no statistical differences in GFR between the LF and CF groups (GFR at Month 1, 47.9 ± 46.8 L/week/1.73 m² in LF versus 40.0 ± 26.3 L/week/1.73 m² in CF, \( P = 0.336 \)). At Month 13, the value of GFR was 39.6 ± 50.2 L/week/1.73 m² in the LF group and 22.4 ± 18.6 L/week/1.73 m² in the CF group (\( P = 0.065 \) by Student’s \( t \)-test) (Figure 2A). When analysed by the mixed model with adjustments for age, gender, Davies score and GFR at Month 1, GFR at Month 13 for the LF group was significantly higher (\( P = 0.048 \)). After the baseline D/PCR was additionally adjusted, the effects of LF on RRF remained significant.

Per-protocol analysis included 69 patients who completed the three assessment points. The clinical profiles of the 69 patients were not different from those of the total 91 patients (data not shown). The LF group showed that GFRs at Months 1, 7 and 13 were not changed (\( P = 0.982 \)), while the CF group showed that the GFR decreased significantly from Month 1 to Month 13 (\( P < 0.001 \)) (Figure 2B). The change in GFR (the GFR at Month 13 minus the GFR at Month 1 in each patient, \( \Delta \text{GFR} \)) in the LF group was significantly different from \( \Delta \text{GFR} \) in the CF group (\( LF, 0.13 ± 33.2 \) L/week/1.73 m²; \( CF, -13.6 ± 19.4 \) L/week/1.73 m², \( P = 0.049 \)) (Figure 3A). Repeated measures ANOVA showed that there was no significant effect of LF treatment on the change in GFR (\( P = 0.057 \)). Urine volume at Month 13 was not different between the two groups (Table 2).

### Table 1. Demographic data, aetiology of end-stage renal disease (ESRD) and eGFR at Month 0

<table>
<thead>
<tr>
<th></th>
<th>Intention-to-treat analysis</th>
<th>Per-protocol analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LF (( n = 48 ))</td>
<td>CF (( n = 43 ))</td>
</tr>
<tr>
<td>Male, ( n ) (%)</td>
<td>31 (64.6%)</td>
<td>24 (55.8%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.3 ± 13.2</td>
<td>52.8 ± 13.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60.2 ± 10.4</td>
<td>60.8 ± 10.2</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.63 ± 8.84</td>
<td>1.61 ± 8.23</td>
</tr>
<tr>
<td>Davies comorbidity score</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Low (% )</td>
<td>14 (29.2%)</td>
<td>19 (44.2%)</td>
</tr>
<tr>
<td>Intermediate/high</td>
<td>34 (70.8%)</td>
<td>24 (55.8%)</td>
</tr>
<tr>
<td>Use of ACEI/ARB, ( n )</td>
<td>30 (64.6)</td>
<td>28 (58.1)</td>
</tr>
<tr>
<td>Use of diuretics, ( n )</td>
<td>25 (52.1)</td>
<td>24 (55.8)</td>
</tr>
<tr>
<td>HD prior to PD (n/days)</td>
<td>22/21.2 ± 9.36</td>
<td>22/20.1 ± 9.96</td>
</tr>
<tr>
<td>Aetiology of ESRD, ( n )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>27 (56.3)</td>
<td>21 (48.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16 (33.3)</td>
<td>12 (27.9)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>0</td>
<td>4 (9.3)</td>
</tr>
<tr>
<td>Others</td>
<td>5 (10.4)</td>
<td>6 (14)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²) at Month 0</td>
<td>8.91 ± 3.14</td>
<td>8.06 ± 5.86</td>
</tr>
</tbody>
</table>

LF, pH-neutral low glucose degradation products lactate-buffered peritoneal dialysis fluid; CF, conventional acidic lactate-buffered peritoneal dialysis fluid; NS, not significant; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; eGFR, glomerular filtration rate that was estimated from serum creatinine using the abbreviated Modification of Diet in Renal Disease study formula. Values are mean ± SD.

by >60%, and that the GFR in the LF group would decrease by <30% over a 12-month treatment period. Using a 1:1 ratio for randomization, we calculated that a total of 41 patients in each group were needed with a type I error of <0.05 and >80% power to demonstrate the statistical difference, using Student’s \( t \)-test.

The primary end point for this study was the GFR at Month 13. For the analysis of primary end point, we included all the patients who entered into the study (intention-to-treat analysis). We compared the mean GFR between the LF versus CF groups at each time point (unpaired Student’s \( t \)-test). To analyse the effect of LF on longitudinal changes in GFR and adjust for the effects of other clinical parameters, we made post hoc analysis for the effect of LF on changes of RRF by using the mixed models [16], with GFR or UV at Month 1, gender and the Davies comorbidity score as covariates.

Since 22 patients (24.2%) dropped out during the study period, we also conducted paired \( t \)-tests for the analysis of the change of GFR in each group, by including only patients who fulfilled three assessments at Months 1, 7 and 13 (per-protocol analysis). Additionally, repeated measures analysis of variance (ANOVA) was used, with the GFR as the repeated measure, and the treatment group as the between-group factor.

For the patient subpopulation with baseline GFR ≥2 mL/min/1.73 m², a subgroup analysis was made, where the statistical methods mentioned above were employed.

Patient, technique and peritonitis-free survivals for the two groups were analysed using the Kaplan–Meier method and tested by the log-rank test, and were additionally analysed for the adjustment of age, gender and comorbidity index using Cox regression. Statistical analysis was performed using SAS 9.1 version (SAS Institute Inc. Cary, NC, USA). Data that were normally distributed were expressed as mean ± SD. A \( P \)-value of <0.05 was considered significant. All probabilities were two-tailed.
Fig. 2. Effects of LF on residual renal function in the total population. (A) Intention-to-treat analysis and (B) per-protocol analysis. LF, low glucose degradation products peritoneal dialysis fluid; CF, conventional peritoneal dialysis fluid. GFRs during treatment period are calculated using the formula as follows: GFR = (kidney urea clearance + kidney creatinine clearance)/2/1.73 m². ¹P-values between the LF and CF groups are analysed by using the unpaired Student’s t-test, and the *P*-value is analysed by using the mixed models. ²P-values between Months 1, 7 and 13 are analysed by using the paired t-test, and the **P*-value is analysed by using repeated measures ANOVA. Values are mean ± SEM.

Fig. 3. Comparison of changes in glomerular filtration rate (the GFR at each month minus the GFR at Month 1 in each patients, \(\Delta\text{GFR}\)) between the LF and CF groups in the total population (A) and in subgroup \(\text{GFR at Month 1} \geq 2 \text{mL/min/1.73 m}^2\) (B). LF, pH-neutral low glucose degradation products lactate-buffered peritoneal dialysis fluid (grey box); CF, conventional acidic lactate-buffered peritoneal dialysis fluid (white box). P-values between the LF and CF groups are analysed by using Student’s t-test.

Table 2. Urine volume and other parameters related to peritoneal dialysis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group</th>
<th>Month 1</th>
<th>P-value</th>
<th>Month 7</th>
<th>P-value</th>
<th>Month 13</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine volume (mL/day)</td>
<td>LF</td>
<td>783 ± 630</td>
<td>0.459</td>
<td>731 ± 620</td>
<td>0.346</td>
<td>750 ± 679</td>
<td>0.112</td>
</tr>
<tr>
<td></td>
<td>CF</td>
<td>698 ± 430</td>
<td>0.060</td>
<td>614 ± 455</td>
<td>0.060</td>
<td>532 ± 408</td>
<td>0.001</td>
</tr>
<tr>
<td>Peritoneal ultrafiltration (mL/day)</td>
<td>LF</td>
<td>865 ± 338</td>
<td>0.486</td>
<td>926 ± 487</td>
<td>0.060</td>
<td>750 ± 350</td>
<td>0.824</td>
</tr>
<tr>
<td></td>
<td>CF</td>
<td>923 ± 430</td>
<td>0.060</td>
<td>1154 ± 576</td>
<td>0.060</td>
<td>1047 ± 334</td>
<td>0.824</td>
</tr>
<tr>
<td>Total Kt/V</td>
<td>LF</td>
<td>2.41 ± 1.01</td>
<td>0.110</td>
<td>2.29 ± 0.86</td>
<td>0.334</td>
<td>2.16 ± 1.08</td>
<td>0.692</td>
</tr>
<tr>
<td></td>
<td>CF</td>
<td>2.08 ± 0.59</td>
<td>0.060</td>
<td>2.13 ± 0.58</td>
<td>0.060</td>
<td>2.08 ± 0.51</td>
<td>0.692</td>
</tr>
<tr>
<td>nPNA (g/kg/day)</td>
<td>LF</td>
<td>0.92 ± 0.23</td>
<td>0.418</td>
<td>0.89 ± 0.22</td>
<td>0.62</td>
<td>0.82 ± 0.21</td>
<td>0.163</td>
</tr>
<tr>
<td></td>
<td>CF</td>
<td>0.89 ± 0.19</td>
<td>0.060</td>
<td>0.91 ± 0.19</td>
<td>0.060</td>
<td>0.90 ± 0.23</td>
<td>0.163</td>
</tr>
<tr>
<td>Glucose exposure (g/day)</td>
<td>LF</td>
<td>121 ± 21.1</td>
<td>0.928</td>
<td>127 ± 34.1</td>
<td>0.203</td>
<td>118 ± 32.4</td>
<td>0.824</td>
</tr>
<tr>
<td></td>
<td>CF</td>
<td>121 ± 48.7</td>
<td>0.928</td>
<td>116 ± 39.8</td>
<td>0.203</td>
<td>116 ± 31.9</td>
<td>0.824</td>
</tr>
</tbody>
</table>

nPNA, normalized protein equivalent of nitrogen appearance; LF, pH-neutral low glucose degradation products lactate-buffered peritoneal dialysis fluid; CF, conventional acidic lactate-buffered peritoneal dialysis fluid. P-values were analysed by using Student’s t-test. Values are mean ± SD.
**Subgroup analysis**

At baseline, 67 patients (33 in the LF group, 34 in the CF group) had GFR of 2 mL/min/1.73 m² or above. The analysis of these subpopulation revealed that GFR was 57.5 ± 55.8 L/week/1.73 m² in the LF group and 26.1 ± 18.7 L/week/1.73 m² in the CF group at Month 13 (P = 0.013 by the unpaired t-test) (Figure 4A). When analysed by the mixed model with adjustments for age, gender, Davies score and GFR at Month 1, GFR at Month 13 for the LF group was significantly higher (P = 0.004). After the baseline D/PCr was additionally adjusted, the effects of LF on RRF remained significant.

Per-protocol analysis included 47 patients who completed 12-month treatment. Within-group analysis showed that GFRs decreased significantly from Month 1 to Month 13 in the CF group, while those in the LF group were not changed (Figure 4B). Levels of ΔGFR in the LF group were smaller than those in the CF group, but there was no statistical significance (LF, 0.09 ± 40.9 L/week/1.73 m²; CF, −16.8 ± 19.9 L/week/1.73 m², P = 0.094) (Figure 3B). In contrast, repeated measures ANOVA showed that there was a significant effect of LF treatment on the change in GFR (P = 0.009). Urine volume of the LF group was higher than that of the CF group at Month 13 (LF: 1009 ± 700 versus CF: 613 ± 380 mL/day, P = 0.025).

**Body weight, blood pressure and medications**

Although body weight tended to increase after 12-month treatment, there were no significant differences between the two groups either at baseline or after follow-up (Month 1, LF: 60.8 ± 10.9 versus CF: 62.1 ± 10.4 kg; Month 13, LF: 64.4 ± 11.9 versus CF: 65.1 ± 12.4 kg). There were no differences in mean arterial pressure (MAP) either at Month 1 or at Month 13 (Month 1, LF: 97.9 ± 11.2 mmHg versus CF: 93.3 mmHg; Month 13, LF: 96.7 ± 12.1 mmHg versus CF: 96.9 ± 13.7 mmHg). The proportions of patients prescribed ACEI/ARB or loop diuretics were not different at Month 13 (ACEI/ARB, LF: 41.7% versus CF: 45.5%; loop diuretics, LF: 55.6% versus CF: 54.5%). No patient was taking additional bicarbonate medication during the treatment period.

**Survival data: overall survival, technique failure and peritonitis-free survival**

There were no differences in patient survival, technique survival and peritonitis-free survival between the LF and CF groups (P = 0.303, P = 0.614, and P = 0.069, respectively; Figure 5). There were 14 peritonitis episodes in patients using LF with an at-risk period of 689 patient-months (0.24 episodes per patient-year), while there were 6 episodes in patients using CF with an at-risk period of 789 patient-months (0.09 episodes per patient-year). Patient, technique and peritonitis-free survivals were also analysed for the adjustment of age, gender and comorbidity index using Cox regression. After the adjustment of the age, gender and comorbidity index, the hazard ratio of LF versus CF in patient, technique and peritonitis-free survival analysis was 0.374 [95% confidence interval (CI), 0.092–1.514], 1.063 (95% CI, 0.364–3.106) and 1.912 (95% CI, 0.714–5.119), respectively.

**Peritoneal equilibrium test**

At Months 1, 7 and 13, the PET test was performed using either LF or CF, depending on the group to which the patient was assigned. The D/PCr at Month 1 was higher in the LF group than in the CF group, and these differences persisted until Month 13 (Figure 6A). Repeated measures ANOVA showed that there was significant difference in the D/PCr between the two groups (P = 0.001). However, the within-group changes of the D/PCr were not significant for each group over the 12-month period. Peritoneal ultrafiltration (UF) volume during the PET test was slightly higher at Months 7 and 13 for the CF group, compared to the LF group, but there was no statistical significance (Figure 6B). Repeated measures ANOVA also showed that...
there was no statistical difference in the UF capacity between the two groups ($P = 0.091$).

**Other parameters related to PD**

At Month 13, daily peritoneal UF of the LF group was lower than that of the CF group (Table 2). However, there was no significant difference between the two groups in total fluid removal (daily peritoneal UF plus urine volume). In the analysis of correlation between peritoneal UF and GFR at Month 13 in total patients, peritoneal UF was well correlated with GFR ($r = -0.367$, $P = 0.006$). There were no significant differences in daily glucose exposure, total Kt/V or nPNA between the two groups.

**Biochemical data**

Venous total CO$_2$ levels were higher in the LF group and serum anion gaps were lower in the LF group at Month 13, as shown in Table 3. Serum albumin levels of the LF group were significantly lower than those of the CF group at Month 13. There were significant differences in the change of these parameters between the two groups over 12-month treatment (Table 3). There were no differences between the two groups in the C-reactive protein. In the within-group analysis, venous total CO$_2$ levels at Month 13 were increased compared to those at Month 1 in the LF group ($P = 0.039$), while there was no difference between those at Months 1 and 13 in the CF group ($P = 0.080$). The serum anion gap levels in the LF group did not change from Month 1 to Month 13 ($P = 0.736$). The serum anion gap levels in the CF group increased slightly from Month 1 to Month 13, but there was no statistical significance ($P = 0.059$).

**Mesothelial integrity and inflammation**

In the LF group, effluent CA-125 levels were significantly increased over the 12-month period and were higher than those of the CF group over the treatment period (Month 13, LF: $31.6 \pm 19.5$ versus CF: $12.7 \pm 8.98$ U/mL, $P < 0.001$).
Table 3. Effect of LF on the biochemical parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group</th>
<th>Month 1</th>
<th>P-value</th>
<th>Month 7</th>
<th>P-value</th>
<th>Month 13</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous tCO₂ (mmol/L)</td>
<td>LF</td>
<td>24.1 ± 3.77</td>
<td>0.071</td>
<td>25.3 ± 4.02</td>
<td>0.008</td>
<td>25.6 ± 3.56</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>CF</td>
<td>22.5 ± 3.94</td>
<td></td>
<td>22.9 ± 3.43</td>
<td>0.095</td>
<td>21.4 ± 2.99</td>
<td></td>
</tr>
<tr>
<td>Serum anion gap (mmol/L)</td>
<td>LF</td>
<td>12.5 ± 4.50</td>
<td>0.278</td>
<td>12.2 ± 4.09</td>
<td>0.043</td>
<td>12.5 ± 4.31</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>CF</td>
<td>13.5 ± 4.28</td>
<td></td>
<td>13.7 ± 3.68</td>
<td></td>
<td>15.2 ± 3.34</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>LF</td>
<td>33.9 ± 0.56</td>
<td>0.319</td>
<td>34.5 ± 0.61</td>
<td>0.043</td>
<td>35.0 ± 0.47</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>CF</td>
<td>35.1 ± 0.51</td>
<td></td>
<td>37.5 ± 0.64</td>
<td></td>
<td>38.3 ± 0.40</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>LF</td>
<td>3.94 ± 0.46</td>
<td>0.721</td>
<td>3.38 ± 0.62</td>
<td>0.751</td>
<td>8.24 ± 1.29</td>
<td>0.339</td>
</tr>
<tr>
<td></td>
<td>CF</td>
<td>4.51 ± 0.89</td>
<td></td>
<td>3.96 ± 0.9</td>
<td></td>
<td>5.61 ± 0.87</td>
<td></td>
</tr>
</tbody>
</table>

LF, pH-neutral low glucose degradation products lactate-buffered peritoneal dialysis fluid; CF, conventional acidic lactate-buffered peritoneal dialysis fluid. P-values were analysed by using Student’s t-test. Values are mean ± SD.

Discussion

This study was designed in order to verify the hypothesis that the use of low GDP PD solutions favourably affects preservation of RRF. Inclusion of all the patients into analysis (intention-to-treat) in our study showed that there was a tendency to a higher GFR in the LF group at Month 13, although not statistically significant (Figure 2A, \( P = 0.065 \)). There was a small, although not significant, between-group difference in baseline GFR. Therefore, the mixed model was employed as post hoc analysis in order to adjust for the baseline GFR at Month 1, age, gender and Davies comorbidity score. Here, it was shown that GFR in the LF group after treatment is significantly higher than that in the CF group. To include only those patients who fulfilled all the three assessments, GFR in the LF group did not decrease while GFR in the CF group significantly decreased over the 12-month period (Figure 2B). Besides, in an analysis for the subgroups with GFR ≥2 mL/min/1.73 m² at baseline, the LF group had a significantly higher GFR at Month 13, compared to the CF group (Figure 3A). Over time, there was an obvious tendency to a wider divergence of GFR values between the two groups. The present study suggested a beneficial effect of low GDP fluid on GFR for the first time in a prospective randomized controlled study with parallel arms.

So far, a few prospective randomized clinical trials using low GDP PD fluids have shown a diversity of outcomes. Szeto et al. reported no differences in peritoneal UF volume, GFR and RRF between the LF and CF groups, but their study was not adequately powered to show any differences in RRF \[10\]. Fan et al. reported no benefit of biocompatible solutions for RRF preservation from a larger number of patients \[9\]. However, their negative results may be, in part, due to the lack of homogeneity for each study group; they used two different formulations for each study group, and included both CAPD and APD patients. RRF may decline rapidly in some of the APD patients \[17,18\], and admixture of APD and CAPD patients might render the analysis of the data more complicated and attenuate the statistical power. Moreover, the changes of RRF between Months 3 and 12 were analysed, and the 9-month period is relatively short for observing any reduction of RRF in PD patients. In contrast, in the present study, all participants were uniformly placed on CAPD and each group was assigned to a single formulation of a PD solution. RRFs were tested three times over the 12-month treatment period, which enables us to observe a consistent trend for the...
change in GFR. These characteristics for the present study, which are distinct from the above studies, may have contributed to potentiating the statistical power and resulted in a different outcome.

We had a 1-month run-in period, during which patients were equally prescribed CF. At the end of the run-in period, patients were evaluated for the baseline RRF, Kt/V and D/PCr. In our study, some patients performed HD for a short period prior to PD and the mean duration of HD was ~20 days. The 1-month run-in period could also help stabilize the RRF for such patients, although the decline in GFR while on HD for a short period would be small. Additionally, there was no effect of the prior exposure to HD before PD on the RRF (data not shown).

Approximately one-quarter of our study subjects had GFR of <2 mL/min/1.73 m², after the 1-month run-in period. It could be said that for some ESRD patients with GFR <2 mL/min/1.73 m², few therapeutic managements would be helpful in preserving their RRF. Therefore, we performed a subgroup analysis encompassing only 67 incident PD patients with baseline RRF (GFR ≥2 mL/min/1.73 m²). In the subgroup analysis, the difference of GFR at Month 13 was more distinct between the two groups by unpaired t-test (P = 0.013). LF significantly preserved the absolute value of GFR and urine volume over the 12-month treatment period, compared to CF. The difference in ΔGFR between the two groups did not reach statistical significance. It might be because the number of patients employed in the subgroup analysis was limited and there was a small, although not significant, between-group difference in the baseline GFR. However, other statistical analysis employed in the present study—both intention-to-treat and per-protocol analyses—consistently showed significant differences between LF and CF.

The gender and Davies comorbidity score could also have an effect on RRF. Especially, male gender may be associated with faster decline of residual GFR in CAPD patients [19]. The proportion of drop-out between Months 1 and 13 was approximately one-quarter of the total participants, which was similar to those of other reports [9,20]. This is why we used the mixed models, which could include these censored data and adjust for GFR and UV at Month 1, and gender and Davies comorbidity score, although no statistical differences existed in those parameters.

GDPs are thought to be pivotal mediators of the poor biocompatibility of PD solutions. GDPs such as 3,4-dideoxyglycoson-3-ene that are absorbed through the peritoneum during PD, promote apoptosis in mesangial and renal tubular epithelial cells [8]. GDPs from PD fluid enter the systemic circulation, where they promote an increase in plasma AGE compounds [5,21,22]. In addition, administration of low GDP solutions reduces plasma AGE levels in patients on PD [5,21]. Animal data demonstrated that AGE influences the glomerular structure and function, leading to glomerulosclerosis [23]. AGE formation is increased in the kidney from hypertensive rats, which may cause local vascular and tubular damage [24]. These evidences may provide underlying mechanism by which the low-GDP solution, through reduction of GDP and AGE in the systemic circulation, better preserves RRF from CAPD patients.

Another mechanism underlying the beneficial effect of low GDP fluid on RRF could partly be suggested by reduced peritoneal UF. Excessive peritoneal UF may, by provoking intravascular volume depletion, play a causative role in the decline in RRF [25,26]. It is possible that, in the present study, increased D/PCr and, consequently, lower peritoneal UF volume in the LF group might provide a lower risk of intravascular volume depletion and higher probability of preserving RRF. This possibility is supported by our data showing an inverse correlation between peritoneal UF volume and GFR at Month 13.

There are some debates on the effect of newer biocompatible PD solutions on the PSTR and peritoneal UF. Williams et al. reported in a multicentre randomized prospective trial that the transport of small molecules represented by D/PCr slightly but significantly increased after low GDP fluid use (Balance®) [5]. They explained that vasoactive substances may influence blood flow or permeability of the peritoneal vascular bed [5,27,28]. Single exchange using a bicarbonate/lactate buffered, low GDP product solution (Physioneal®) had lower net UF during PET, compared to CF [29]. Similar results were also reported by Montenegro et al. [30] who evaluated the peritoneal solute transport and UF in a single exchange with the same PD solution as employed by the present study (Balance®). They reported no apparent difference in the peritoneal transport of creatinine and glucose but significantly lower net UF obtained by Balance®. This could be explained by an acute effect of newer biocompatible PD solutions on the peritoneal blood flow. Solutions with acidic pH and a high concentration of GDP induce a marked initial vasodilatation and recruitment of capillaries [31].

In the present study, study patients conducted a modified 3.86% PET test at Months 1, 7 and 13. On each occasion, the test was performed with either LF or CF, depending on the treatment group. D/PCr was higher in the LF group on all three time points, and within-group change of D/PCr was not significant over time. Peritoneal UF volume was lower for the LF group at Months 7 and 13, albeit not statistically significant (P = 0.051 and P = 0.056, respectively). Although the mechanism is not clarified yet, it is possible that the acute, as well as chronic, effect of the neutral-pH, low-GDP PD solution (Balance®) on the peritoneal microcirculation could have contributed to the difference of PSTR and UF volume in our study. Mechanistic researches are warranted to elucidate the effect of neutral-pH, low GDP fluid on the peritoneal solute transport and water removal.

Decreased serum albumin levels for the LF group in our results could partly be explained by increased loss of albumin into the peritoneal fluid resulting from higher PSTR in the LF group than in the CF group. It was shown in our previous study that the serum albumin level correlated inversely with D/PCr and peritoneal albumin clearance [32]. Low level of serum albumin and high level of D/PCr correlated with poor survival [33,34]. In our data, there were no differences in the patient or technique survivals between the two groups, although the LF group had lower albumin levels and higher D/PCr levels at Month 13, which could be potentially harmful. However, the present study was not sufficiently powered to demonstrate any effect of LF on
the survival. Besides, there is a lack of data on whether the use of LF beyond the 1-year treatment period will continuously increase D/PCr and decrease the serum albumin concentration.

In the present study, peritonitis rates were uniformly low for both groups. However, the LF group tended to have a higher rate of peritonitis, although not to a significant level. Such tendency was also shown in a previous study [9]. A larger scale study might be warranted in order to demonstrate any effect of low GDP fluid on the peritonitis rate.

Feriani et al. reported that the bicarbonate-buffered CAPD solution significantly improved metabolic acidosis [35]. We also found that the venous bicarbonate levels were higher and the serum anion gap levels were lower in the LF group at Month 13. Dietary protein intake assessed by nPNA was not different between the two groups. The differences of the venous bicarbonate and the serum anion gap may have resulted from better correction of metabolic acidosis by preservation of RRF, decrease of endogenous bicarbonate loss, or increased absorption of bicarbonate from neutral-pH PD fluid. Although this mechanism has not been clearly investigated, it is possible that a biocompatible solution may be effective in countering the daily acid production.

CA-125 has been suggested as a measure of mesothelial cell mass and membrane integrity [36]. In the LF group, the dialysate CA-125 levels increased over time, and were higher than those of the CF group, which indicated better recovery of the mesothelial cell mass [5,37]. During the peritoneal inflammatory response, the intraperitoneal actions of IL-6 are particularly regulated by mesothelial cells [38]. Pecoits-Filho et al. reported that the intraperitoneal levels of IL-6 were several-fold higher than the plasma concentrations, indicating local production of IL-6 during the course of PD treatment using conventional PD solutions [38]. Other clinical studies using a bicarbonate/lactate solution have shown that the intraperitoneal cellular response to the more biocompatible solution leads to lower dialysate levels of IL-6 in comparison to the standard solutions, suggesting a reduced inflammatory response [39]. In our study, there were no differences in the effluent IL-6 levels between the two groups. Systemic inflammation was correlated with loss of RRF in chronic renal failure patients [40]. Szeto et al. reported that use of LF results in a lower degree of systemic inflammation [10]. Our data showed that there was no difference in CRP between the two groups over time, which was similar to the result by Fan et al. [9]. Our data do not conclude whether the use of LF may reduce systemic or peritoneal inflammation.

The present study is partly limited by the lack of sufficient patient numbers for a concrete statistical power and by a small between-group difference in baseline GFR. Not all the statistics employed in our study provided a significant difference. However, authors employed supplementary statistical analyses to adjust for the baseline GFR and other covariates. Besides, regardless of statistical methods used, the results have shown a consistent trend of difference in GFR at all the follow-ups over the study period, whether in an intention-to-treat or per-protocol analysis and from entire population or subgroup analysis.

In summary, our prospective, randomized, multicentre, controlled study suggests that low GDP PD fluid may better preserve RRF in incident PD patients over the 1-year treatment period, especially in PD patients with baseline RRF (GFR of 2 mL/min/1.73 m² or above), compared with CF. More trials on a larger scale with sufficient patient numbers should follow to robustly demonstrate the benefit of a low-GDP solution in RRF.

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Conflict of interest statement. This study was partly supported by Fresenius Korea. One of the authors, K.H.O., is currently an external member of the advisory board of Fresenius Medical Care, Korea since May 2008. However, the authors declare that they have no financial connections, either direct or indirect with Fresenius Medical Care, Korea. Authors have no involvements that might raise the question of bias in the work reported or in the conclusions, implications or opinions stated.

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