A Comparison of Biocompatible Balance Solution and Standard Peritoneal Dialysis Solution in a Single Center of Central Taiwan: A Pilot Study

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Abstract

BACKGROUND: The possibility that the bioincompatible nature of standard peritoneal dialysis (PD) fluid (SPDF) might interfere with peritoneal integrity remains a concern. We conducted this study to compare Balance, a neutral pH dialysate containing low concentration of glucose degradation products (GDPs), with SPDF in patients starting on PD.

METHODS: In this prospective pilot clinical study with a crossover design, seven patients starting on PD were treated with SPDF for 4 weeks and then switched to Balance for the following 12 weeks. Overnight effluent was collected and assayed for cancer antigen 125 (CA-125) and hyaluronic acid (HA). Serum samples were assayed for interleukin-6 (IL-6) and β-2 microglobulin (β2M).

RESULTS: In patients treated with Balance solution, there were higher effluent levels of CA-125 (P < 0.0001) and lower levels of HA (P < 0.0001) under the generalized estimating equation model, while the proinflammatory cytokine IL-6 (P = 0.022) and β2M (P = 0.018) levels declined significantly. Balance had better biomarkers in PD effluent and serum than SPDF did.

CONCLUSION: We have demonstrated that the neutral pH solution Balance with low concentration of GDPs reduced significantly the proinflammatory cytokines in serum and improved the effluent markers of peritoneal membrane integrity, thus it may be able to improve the homeostasis of the peritoneal cavity. Further long-term, multicenter, randomized controlled studies are needed to elucidate the superiority of the biocompatible Balance solution compared with conventional PD solutions.

KEY WORDS: advanced glycation end products (AGEs), biocompatibility, glucose degradation products (GDPs), peritoneal dialysis solution

Introduction

For patients with end-stage renal disease (ESRD), peritoneal dialysis (PD) is one form of renal replacement therapy that has been established during the past 30 years. Chronic exposure of the peritoneum to PD fluids is associated with structural membrane changes that are believed to contribute to alterations in solute transport and loss of ultrafiltration, leading to peritoneal dysfunction and membrane failure (1-3). Although the factors responsible for these alterations remain to be determined, it is widely accepted that the bioincom-
The compatible nature of conventional PD solutions (low pH, lactate concentration, and the long-term exposure to high concentrations of glucose) contributes to changes in membrane structure and function (4). From measurements of both inflammatory cell functions during PD and markers of mesothelial cell function in peritoneal effluent, the published data suggest that peritoneal homeostasis is adversely affected by the administration of conventional PD solutions (5-8). Long-term exposure to clinically relevant concentrations of glucose degradation products (GDPs) of conventional PD solutions might cause peritoneal fibrosis, and neoangiogenesis, which may contribute to the pathogenesis of peritoneal membrane dysfunction and ultrafiltration failure in PD patients (7-10).

Several studies showed that Balance® solution (Fresenius Medical Care) with neutral pH and low concentration of GDPs preserved better the viability and functions of peritoneal leukocytes, mesothelial cells, and fibroblasts compared with conventional solutions (9-14). Its reduced concentration of GDPs, precursors of advanced glycation end products (AGEs), presumably had less toxic effect on mesothelial cells, thus contributing to peritoneal preservation. The aim of this pilot study was to investigate the effect of neutral-pH, low-GDP Balance solution, compared with conventional solutions, on important biochemical and clinical parameters.

### Materials and Methods

#### Study Design

The current research was an open-labeled, prospective pilot study with a crossover design, which comprised two phases. During phase I, all patients received SPDF (Stay-safe; Fresenius Medical Care, Bad Homburg, Germany) with 1.5%, 2.3%, or 4.25% glucose as appropriate for 4 weeks. During phase II, they were treated with Balance® (Fresenius Medical Care) for 12 weeks. The major differences between Balance and SPDF are shown in Table 1. The concentrations of cancer antigen 125 (CA-125) and hyaluronic acid (HA) in the dialysis effluents and the biochemical markers of serum interleukin-6 (IL-6) and β-2 microglobulin (β2M) recorded during phases I and II were compared. In addition, the adequacy of dialysis (creatinine clearance and Kt/V), ultrafiltration, urine volume, peritoneal membrane function (D/P creatinine at 4 hours), routine blood chemistry, abdominal pain, and tolerability of the two phases were also compared.

#### Study Population

This study was conducted in Taichung Veterans General Hospital (VGHTC) from April 1, 2009 to December 31, 2009. Eight patients were enrolled and...
Chen, Cheng, Wu, Yu, Chuang, Huang and Shu all gave written informed consent (S08087) for participation, but one was excluded due to persistent peritonitis after Tenckhoff catheter insertion, which was removed 2 months later. Complete clinical data were available for the remaining 7 patients. Approval for the study was obtained from the Institutional Review Board of VGHTC. All patients included in the study had started on PD (Table 2).

**Study Protocol**

Blood and effluent samplings, peritoneal function tests, and adequacy measurements were performed at our center on 6 occasions during the study: one after the 1st and 4th week of dialysis using conventional PDF in phase I, and one after the 5th, 8th, 12th and 16th week of dialysis using Balance® in phase II. The sampling window was ±7 days from the scheduled date.

**Effluent Markers**

As seen in the schedule shown in Fig. 1, timed effluent collections were undertaken. Fifty milliliters of effluent were collected from a timed 2.35% overnight (12-hour) drain, filtered (0.2 μm filter), and aliquoted into 3-mL samples. Samples were stored at -20°C or -70°C before assay in our laboratory. All effluent samples were archived and then analyzed in a blinded manner. CA-125 was measured using a radioimmunoassay. HA was measured by commercial ELISA (Corgenix, Inc., Denver, CO) according to the manufacturer’s instructions.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N = 7</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>43.9 ± 8.9</td>
</tr>
<tr>
<td>Gender (male : female)</td>
<td>3 : 4</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>162.6 ± 9.2</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>60.8 ± 10.9</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>22.9 ± 2.4</td>
</tr>
<tr>
<td>Primary renal disease</td>
<td></td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>4 (57.1%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (28.6%)</td>
</tr>
<tr>
<td>Hypertensive nephropathy</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td>Initial BUN (mg/dL)</td>
<td>119.3 ± 27.6</td>
</tr>
<tr>
<td>Initial Cr (mg/dL)</td>
<td>11.5 ± 2.8</td>
</tr>
<tr>
<td>Initial Albumin (mg/dL)</td>
<td>3.7 ± 0.5</td>
</tr>
<tr>
<td>Daily urine volume (mL/day)</td>
<td>1289.3 ± 400.4</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>2.8 ± 2.0</td>
</tr>
</tbody>
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**Peritoneal Membrane Function, Dialysis Adequacy Measurement, and Residual Renal Function**

Peritoneal membrane function was measured using the standard peritoneal function test (PFT) with the QA (quality assurance) procedure (15). Two liters of 2.3% glucose were infused (SPDF or Balance, depending on the phase of the protocol). Samples of effluent were taken at time points 0, 120, and 240 minutes, and a blood sample was drawn during the dwell of the QA exchange. The ratio of dialysate to plasma creatinine at four hours (D/P creatinine) was
calculated. Dialysis adequacy was expressed as Kt/V urea and creatinine clearance (L/wk/1.73 m$^2$). Solute clearance was measured by collecting all the used dialysate effluents over a 24-hour period and taking a plasma sample during the QA exchange period. The concentrations of urea and creatinine were measured in each single bag and in the plasma sample. By using the 24-hour volume, the 24-hour clearance was obtained, which was then multiplied by 7 to give a weekly clearance. Creatinine clearance was standardized to a body surface area of 1.73 m$^2$, while urea clearance was expressed as Kt/V, where Kt is the weekly clearance of urea, and V is the volume of distribution. Residual renal function was assessed by collecting all the urine output over the same 24-hour period as the dialysate collection, measuring the urea and creatinine concentrations, and recording the urine volume. Renal creatinine clearance was corrected using the formula (C urea + C creatinine)/2. Individuals with daily urine volumes equal to or below 200 mL were regarded as being anuric.

Statistics

The results are expressed as means ± SEM. Statistical analysis was performed using the nonparametric method with the Wilcoxon signed rank test and generalized estimating equation (GEE). The significance level was set at P < 0.05. Statistical analysis was performed using SPSS version 12 (SPSS, Inc., Chicago, IL, USA).

Results

Patients and Baseline Characteristics

Seven patients started on continuous ambulatory PD (CAPD) were included in this study. Demographic and primary renal disease data, baseline values for nutritional status and renal function are shown in Table 2.

Safety Parameters and Side Effects

The body weight was similar in the two trial phases (data not shown). Technique and patient survival were 100%. No differences within the SPDF and Balance groups were recorded for any other parameters (e.g., calcium, phosphate, potassium, albumin, cholesterol, triglyceride and hemoglobin (Table 3)). No unexpected side effects were observed during the study. There was no peritonitis in the Balance group, but one episode of peritonitis occurred in the SPDF group in week 4, and dialysate culture yielded *Viridans Streptococcus*. There were no significant changes in blood pressure (either systolic or diastolic) and heart rate during the study period. Inflow pain was not reported in either group.
Urea, creatinine clearance, and peritoneal transport characteristics were demonstrated in either group (Table 4). There was only a trend disclosing higher creatinine and urea clearance. There were no significant differences in ultrafiltration volume (871.4 ± 574.6 mL) between patients on SPDF and those on Balance (1050.0 ± 213.8; \( P = 0.228 \)); the results for the two groups in urine amount and in the peritoneal equilibrium test were similar.

### Effluent CA-125 and HA Levels

Effluent CA-125 levels were increased in patients treated with Balance (Fig. 2A) under the GEE model (\( P = 0.054 \)). CA-125 levels were 13.3 ± 11.6 U/mL after 4-week treatment with SPDF, rising to 24.3 ± 12.2 U/mL after 12-week treatment with Balance (\( N = 7, P = 0.054 \)).

The HA levels were significantly lower in patients dialyzed with Balance compared with those dialyzed with SPDF (Fig. 2B; \( P < 0.0001 \)). HA levels were 211.0 ± 152.1 ng/mL after 4-week treatment with SPDF, decreasing to 76.7 ± 81.1 ng/mL after 12-week treatment with Balance (\( N = 7, P = 0.030 \)).

### Discussion

In the Euro-Balance Trial, the use of Balance, a neutral pH, low-GDP dialysis solution, achieved a
significant improvement in effluent markers of peritoneal membrane integrity and a marked decrease in circulating AGE levels. Another crossover design study indicated enhancement in residual renal function using Balance, accompanied with a decrease in peritoneal ultrafiltration (16). In the Korean BALNET study, Balance preserved residual renal function (RRF) better than SPDF did with significant residual GFR over a one-year treatment period (17). In a Hong Kong study, Balance had a superior profile of effluent markers of peritoneal mesothelial cells and a lower degree of systemic inflammation, but there was no difference in dialysis adequacy indices, ultrafiltration volume, urine output, residual renal function, peritonitis rate or need of hospitalization in one year as compared with conventional PD solution (18). In this pilot study, we demonstrated that Balance reduced the proinflammatory cytokine IL-6 and β2M levels in serum. This reduction was accompanied by a significant improvement in effluent markers of peritoneal membrane integrity and a decrease HA and CA-125 levels after 12 weeks of Balance treatment.

CA-125 is a high-molecular weight glycoprotein that is present in mesothelial cells (19-21). In a stable patient on CAPD, peritoneal effluent CA-125 can be considered as a marker of viable mesothelial cell mass and cell turnover. In many studies, it has been reported that switching dialysis solution from SPDF to Balance results in a higher concentration of CA-125 in PD effluent, indicating that normal cell function in the peritoneal cavity is restored by the use of Balance as compared with SPDF (7, 16, 22). In the crossover design study of the Euro-Balance Trial, the increase in concentration of CA-125 was associated with the use of Balance (16), not the duration of PD. It is believed that low levels of GDP and a more biocompatible solution to improve mesothelial cell homeostasis by increasing CA-125 levels, which likely reflected synthesis by the resident mesothelial cell population with biocompatible standard fluid (23, 24).

HA is a major component of the glycocalyx that forms a protective barrier around mesothelial cells, and bestows upon the peritoneal membrane a slippery non-adhesive surface preventing abrasion, infection and tumor dissemination (25). The level of HA in PD effluents is often used as an indicator of peritoneal inflammation, which is also associated with mesothelial-to-mesenchymal transdifferentiation, recruitment of leukocytes to sites of inflammation (26, 27), and mediates the reparative process after tissue injury by initiating increased synthesis of growth factors (25). Similar to the results of previous Balance studies, our data disclosed significantly lower HA levels in biocompatible solution than in SPDF (16, 28, 29). Mesothelial cells that line the peritoneal cavity are capable of producing several proinflammatory cytokines such as interleukin-6 and β2M after exposure to bioincompatible PD solution (21, 30). The mesothelial cells exposed to this bioincompatible PD solution might amplify the intraperitoneal inflammation to elicit the systemic response, and the systemic inflammation could then be adjusted by using the biocompatible Balance dialysate.

The major limitations of our study were the small sample size and very short observation period. The sample size may be too small to show the traits that truly exist in the population. The crossover design without simultaneous control and different durations of exposure to SPDF and Balance might cause length bias that exists even under the null hypothesis and loss of efficiency when exposure effects do exist. In view of the above limitations, studies in larger peritoneal dialysis populations are needed to confirm our findings.

**Conclusion**

We have demonstrated that the low-GDP, neutral-pH dialysis solution Balance reduced significantly the proinflammatory cytokines in serum and
improved the effluent markers of peritoneal membrane integrity, thus contributing to enhance the homeostasis of the peritoneal cavity. According to our initial findings, long-term, multicenter, randomized controlled studies are needed to elucidate the superiority of the biocompatible Balance solution compared with conventional PD solutions.

References