

# Peritoneal Dialysis Solutions Low in Glucose Degradation Products: Clinical Experience and Outcomes

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*The latest literature describing clinical experiences with peritoneal dialysis solutions low in glucose degradation products (GDPs) is mostly consistent with previous reports suggesting less inflammation, better peritoneal mesothelial mass preservation, a lower rate of decline of residual renal function, and improved patient survival. The data suggest stable peritoneal transport rates, but no definite evidence has yet emerged of superior membrane preservation. Most studies have reported very low peritonitis rates, but without significant differences as compared with rates in patients exposed to conventional solutions. New, appropriately powered randomized clinical trials are needed to confirm the potential benefits of low-GDP solutions and to establish the role of renal function preservation with regard to those benefits.*

## Key words

Peritoneal dialysis solutions, glucose degradation products, biocompatibility, clinical outcomes

## Introduction

The present article updates previous reports on the clinical outcomes obtained with peritoneal dialysis fluids (PDFs) low in glucose degradation products (GDPs) and having a neutral pH (1). Although multiple new biocompatible solutions with a total GDP content lower than that of conventional PDFs are available, total GDP content and the specific GDP concentration vary greatly among manufacturers. This discussion chiefly addresses experiences with ultra-low-GDP PDF (defined as total GDP content  $\leq 80 \mu\text{mol/L}$ ).

The beneficial effects of the combination of neutral pH and low GDP concentration on cell viability

and function for both lactate- and bicarbonate-buffered solutions *in vitro* and in animal studies are abundantly documented in the literature. Two very impressive and consistent effects are peritoneal hemodynamic stability and improved peritoneal host defense. Consequently, long-term evidence of improved clinical outcomes with the use of these novel biocompatible solutions is eagerly awaited.

The first experiences with biocompatible PDF have been, in the main, consistent with the laboratory data generated in animals and tissue cultures, strongly suggesting improved mesothelial cell viability and reduced inflammation (1). Also encouraging are the possibilities of improved patient survival (2,3) and better preservation of residual renal function (RRF) (4). But despite the encouraging experimental data suggesting improved host defenses, none of the clinical reports has substantiated a significant difference in peritonitis rate between biocompatible and conventional PDFs.

## Clinical experiences

Montenegro *et al.* (5) prospectively studied 36 incident peritoneal dialysis (PD) patients treated with conventional ( $n = 18$ ) or low-GDP, neutral-pH, pure bicarbonate ( $n = 18$ ) PDFs and followed for 12 months. The authors observed no significant changes in peritoneal equilibration test parameters [dialysate-to-plasma creatinine (D/P Cr), initial-to-final dialysate glucose concentration (D/D<sub>0</sub> glucose), or net ultrafiltration (UF)] at baseline and at the end of the study, although differences in UF occurred between the groups (UF was higher among patients on conventional PDF). No significant differences occurred between the groups for either venous plasma bicarbonate or change in base excess; however, 4 patients in the lactate group, but none in the bicarbonate group, required oral supplementation. Better urine output, glomerular filtration

rate, and normalized protein catabolic rate ( $p < 0.05$  on linear trend) were observed among patients treated with bicarbonate solution. Overall, however, this study failed to elucidate the role of pH, bicarbonate, or GDP content on promoting the improvements observed.

A recent encouraging, albeit anecdotal, report of a single patient suggests good preservation of peritoneal transport over many years with the use of low-GDP solutions (6). The patient underwent PD with the use of a neutral-pH, low-GDP, lactate-based PDF and was observed for 4 years. Peritoneal membrane histology at the time of initial catheter insertion and 4 years later during catheter removal was normal and essentially unchanged. Both specimens showed normal cellular architecture, with preservation of a single layer of mesothelial cells, thin interstitial tissues, and normal capillary distribution. The patient's 4-hour D/P Cr remained stable in the low-average range (0.60 initially and 0.53 after 4 years) during the period of observation.

Szeto *et al.* (7) studied 50 incident PD patients randomized to a conventional lactate-buffered PDF (control) and a pH-neutral, lactate-buffered, low-GDP PDF (Balance: Fresenius Medical Care, Bad Homburg, Germany) and followed them for 12 months. The main clinical endpoints were RRF and indices of dialysis adequacy. Other parameters included serum C-reactive protein, effluent cancer antigen 125 (CA125), and hyaluronan. No significant difference in any baseline parameter was observed between the groups, except that the Balance group was marginally older and had a higher Charlson comorbidity score. Adequacy indices, daily UF, RRF decline, hospitalizations, peritonitis, and nutrition were not different between the groups. Patients using the biocompatible solution experienced a reduced degree of systemic inflammation, an increase in effluent CA125, and a decrease in effluent hyaluronan and transforming growth factor  $\beta$ , consistent with a high level of biocompatibility.

The most recent report by Lee *et al.* (3) on their extensive experience with neutral-pH, low-GDP, lactate-based PDF shows a significant increase in the use of low-GDP solutions in Korea. Penetration reached 70% – 80% by the year 2003 and has stabilized at that level. The authors' prospective longitudinal observational study documented the patterns of use of low-GDP Balance PDF in 1909

incident PD patients between January 1, 2002, and mid-year 2005. Patients prescribed low-GDP PDF tended to be younger and were more likely to have been treated in centers with larger enrollment in the database. The survival of diabetic patients treated with the new PD solution was identical to that of the nondiabetic patients treated with standard PDF, and treatment with low-GDP PDF independently reduced the relative risk of death (RR: 0.613; 95% confidence interval: 0.50 to 0.74;  $p < 0.00001$ ) in a proportional hazards model that included age, diabetes status, and center experience. Low-GDP PDF was associated with significantly longer technique survival ( $p = 0.049$ ) in the univariate, but not in the multivariate, analysis. In a multivariate Cox model for time to technique failure, the prescription of low-GDP PDF prolonged technique survival by more than 1 year. No significant differences in peritonitis-free interval or peritonitis rate could be attributed to the prescribed PDF. Table I summarizes the study design and the key results from the two studies by Lee *et al.*

## Discussion

The most recent clinical experiences with the use of low-GDP PDF have expanded the number of patients and observation periods, but they mostly confirm previous reports. A need still exists to determine whether the better survival reported by Lee *et al.* (2,3) with Balance is associated with superior RRF, a factor directly linked to better survival (8).

Woodrow (9) has pointed out the potential limitations of interpreting survival data based on observational studies and called for an adequately powered randomized control trial. Brown and Johnson (10) recently initiated a prospective, randomized, controlled multicenter trial, to be performed in Australia/New Zealand (BalANZ Study) with a minimum of 420 patients, to determine the relative ability of Balance and conventional PDF to preserve RRF. Secondary aims include monitoring patient survival, peritonitis, dialysis adequacy, and inflammation. In addition, new, appropriately powered randomized controlled trials should address potential differences in the preservation of peritoneal transport, rates of peritonitis, hospitalizations, survival, and cost of total patient care between patients treated with low-GDP, neutral-pH solutions and those treated with conventional PDFs.

TABLE I Summary of studies by Lee and colleagues

	Lee et al., 2005 (2)	Lee et al., 2006 (3)
<b>Study design</b>		
Duration (years)	2.5	3.5
Patients ( <i>n</i> )	>1100	>1900
Type	Observational/ITT	Observational
Solutions	Balance <sup>a</sup> vs. conventional	Balance <sup>a</sup> vs. conventional
<b>Key results</b>		
Risk of death	Reduced by 25% ( <i>p</i> <0.046)	Reduced by 39% ( <i>p</i> <0.00000)
Peritonitis-free (%)	77	76
Peritonitis rate (ep./pt.–mo.)	1:48	1:46

<sup>a</sup> Fresenius Medical Care, Bad Homburg, Germany.

ITT = intent-to-treat; ep./pt.–mo. = episodes/patient–month.

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