

Re: Effects of Low-glucose Degradation Product Solution on Peritoneal Membrane Characteristics in Peritoneal Dialysis Patients: a 3-year Follow-up Study

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Dear Editor,

In the past issue of the *Iranian Journal Kidney Disease*, Park and colleagues compared the standard peritoneal dialysis (PD) solution to the low glucose degradation products (GDP) solution in a 3-year follow-up.¹ Peritoneal dialysis (PD) is an effective and established form of renal replacement therapy in end-stage renal disease over the past 30 years, which is used by approximately 11% of the total global dialysis population. Although PD has improved the quality of life in these patients, several studies have shown inferior PD patients survival compared to hemodialysis patients. Peritonitis and physiologic dysfunction of the peritoneal membrane are major cause of peritoneal failure.² Thus, a major disadvantage of this treatment is PD solution bioincompatibility. Peritoneal dialysis solutions contain elevated concentration of glucose to provide the osmotic drive, lactate buffer to correct metabolic acidosis, and low pH to prevent glucose caramelization during heat sterilization, but heat sterilization of PD solutions can lead to glucose degradation products.

High glucose concentrations in conventional PD solutions have direct cytotoxicity, stimulation of inflammatory cytokine production, and promotion of formation of advanced glycation end products, which provoke peritoneal inflammation and injury in mesothelial cells, resulting in structural changes in the peritoneal membrane and progressive loss of peritoneal function.³ Glucose degradation products-induced mesothelial cell injury and apoptosis lead to intercellular hydrogen peroxide production and free radical formation, which is important for peritoneal membrane inflammation and injury. In particular, experimental and clinical exposure to conventional PD solution leads to significant histopathological changes over time, including loss

of the surface mesothelial cell layer, thickening of the submesothelial, and progressive vasculopathy.⁴ Glucose degradation products directly produce the profibrotic cytokine transforming growth factor- β and stimulate vascular endothelial growth factor synthesis. These two signals have a key role in the progression of peritoneal membrane fibrosis and vascular proliferation in long-term PD patients.

There are several formulations for PD solution, including conventional, physioneal, gambrosol Trio, Balance, and Bicavera. The conventional solution is 1 chamber with lactate buffer and the final pH of 5 to 5.4. The physioneal is associated with 2 chambers, lactate and bicarbonate buffer and the final pH of 7.3. The Gambrosol Trio includes 3 chambers, lactate buffer, and the final pH of 6.5. The Bicavera is similar to the physioneal with 2 chambers, but bicarbonate buffer and the final pH of 7.1, and finally, balance solution is associated with 2 chambers, lactate buffer, and the final pH of 6.8. The use of a multibag system allows for separation into compartments; a low pH glucose compartment, which minimizes the production of GDPs during heat sterilization and storage and a buffer compartment which can be a bicarbonate and lactate mixture or bicarbonate alone.

Several investigations have been done for reducing GDP and improving the biocompatibility of PD solutions. For example, Wieslander and colleagues showed that the separation of the glucose and lactate buffer during storage or heat sterilization reduced GDP formation.⁵ In addition, Erixon and coworkers suggested that sterilization of glucose at a low pH between 2 and 2.6 reduced cytotoxic GDP.⁶ To improve biocompatibility, new PD solutions with neutral pH, low GDP, and low glucose concentration have been generated in recent years. Lee and colleagues, in a large retrospective

cohort study, have shown an association between low GDP, neutral pH, lactate-buffered fluid, and improved survival and outcome.⁷ The recently published baLANZ randomized controlled trial suggests that the use of a neutral-pH lactate-buffered low-GDP fluid (Balance) is associated with a significant delay in the onset of anuria and preserve residual kidney function compared to conventional dialysis solution.^{8,9} In addition, chronic exposure of the peritoneum to peritoneal fluid leads to peritoneal dysfunction and failure. These processes contribute to loss of the mesothelial cell, submesothelial fibrosis, angiogenesis, and hyalinizing vasculopathy. Such alterations are considered to be the major cause of loss of membrane function and ultrafiltration failure. Peritoneal membrane deterioration during peritoneal dialysis is associated with epithelial-to-mesenchymal transition (EMT) of mesothelial cells, which is mainly due to GDP. Thus, peritoneal biopsy is the gold standard for investigation of peritoneal membrane, which shows the EMT. In addition, the measurement of dialysate effluent markers such as dialysate cancer antigen-125, vascular endothelial growth factor, and interleukin-6 may also be considered for the viability of the resident cells of the peritoneum. Bajo and colleagues concluded that mesothelial cell of patients treated with a low-GDP solution had fewer signs of EMT compared to standard solution, indicating a better preservation of the peritoneal membrane structure and favorable outcome in the long-term. It also confirmed the hypothesis that GDP-reduced fluid protected mesothelial cell from the development of EMT.¹⁰ In another study, the effect of Bicavera, a bicarbonate-buffered PD fluid, was investigated in terms of EMT of mesothelial cells in vitro and ex vivo. The findings suggested that patients treated with Bicavera fluid had a trend to acquire an epithelial phenotype, with lower production of proinflammatory cytokines and chemokines (such as interleukin-8) than seen with mesothelial cells from patients treated with a lactate buffer standard solution.¹¹

The first Food and Drug Administration-approved neutral-pH biocompatible PD solution with a low GDP content is Delflex. It is formulated to provide a neutral pH of 7.0 ± 0.4 , which is closer to physiologic pH and it is similar to the Balance, Bicavera, and physioneal peritoneal dialysis fluid.

Extraneal (polyglucose-based solution), although available in the United States with low GDP content, does not feature a neutral pH. The total GDP content was not as low as that of 1.5% or 2.5% glucose solution, but it was less than the 4.25% glucose solution. However, the new Delflex Neutral pH solution contains only a very small GDP concentration, below $100 \mu\text{mol/L}$.¹² Park and colleagues compared the stay-safe solution to the balance for a 3-year follow-up. In this study, the cells in the overnight effluent dialysate were isolated. The cell were cultured and scored according to protocols as follows: (1) cobblestone-shaped human peritoneal mesothelial cells, (2) mixed, and (3) fibroblast-cell dominant. Also, cancer antigen-125 was examined as a marker of peritoneal mesothelial cell mass. This study suggested that the low-GDP solution was associated with a protective effect on the progression to EMT and high effluent cancer antigen-125 and might be associated with the improvement of aquaporin function. Therefore, a low-GDP solution may help improve peritoneal membrane characteristics and preserved mesothelial cells during long-term follow-up.¹ In spite of the fact that this study showed the beneficial effect of low-GDP in long-term period for peritoneal dialysis patients, we need a design multicenter large cohort study on the safety of low-GDP beyond 3 years.

In summary, for PD patients, the development of peritonitis, the loss of residual kidney function, and the loss of peritoneal membrane function are important events that affect both patients and technique survival. The use of conventional PD solution may increase these events. Both in vitro and in vivo evidence suggest that the local and systemic toxicity by the use of glucose solution through the present of GDPs coupled with hyperosmolarity, reduced pH, and the use of lactate as the buffer in conventional PD solution. Although the use of novel solution with the low-GDP may improve patient survival and outcome in peritoneal dialysis, the cost associated with the long-term use of this solution is an important concern before recommending it as a standard care in the management of PD patients.

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