Biocompatible Peritoneal Dialysis Solutions: Do We Have One?

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Clinical experience and literature evidence suggest that peritoneal dialysis (PD) is a safe and effective treatment in short term (3 to 5 years) for stage 5 chronic kidney disease patients. A major limitation to long-term PD has been peritoneal membrane structural and functional alterations over time, resulting in significant technique failure. Much evidence implicates glucose contained in conventional PD solutions as the major cause of membrane changes. Other harmful characteristics of glucose or its degradation products are thought to cause systemic undesirable metabolic and cardiovascular effects. This led to the search for more "biocompatible" PD solutions to ameliorate complications associated with conventional glucose solutions. Studies in animals and humans show that newer biocompatible solutions may preserve membrane functions better, lead to less therapy failure, and avoid the undesirable metabolic and cardiovascular effects of systemic glucose exposure. There is evidence in specific, clinical, short-term situations of biochemical and metabolic benefits of biocompatible solutions. However, are these solutions superior to glucose in preserving peritoneal membrane long term? Are they truly more biocompatible? Clinical and experimental data suggest that newer solutions, albeit most of them glucose based, are less toxic compared with the current PD solution; however, there is currently no osmotic agent that can safely replace glucose. The future appears to be in using combinations of different osmotic agents in a more biocompatible solution, whether they are mixtures in a single bag or daily exchanges of different osmotic agents. This review discusses the current status of these biocompatible solutions in PD patients.

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Peritoneal dialysis (PD) has been an accepted form of renal replacement therapy (RRT) for end-stage renal disease patients (1). Conventional PD solutions contain dextrose as the osmotic agent. Absorbed glucose is metabolized and is used as a source of energy. However, long-term systemic exposure of glucose has been well recognized to cause metabolic and cardiovascular abnormalities, which contribute to some of the morbidities seen in PD patients. PD solutions have a shelf life, and the glucose over time degrades to form glucose degradation products (GDPs), which have been implicated in a variety of adverse effects on the peritoneal membrane, in addition to the well known other systemic effects. Several studies both *in vivo* and *in vitro* have shown that conventional solutions damage the mesothelial cells lining the peritoneum, cause peritoneal membrane thickening, and lead to changes of the peritoneal blood vessels (2,3). The dextrose-based solutions have been shown to cause structural as well as functional changes in the peritoneal membrane, which in long-term patients ultimately leads to ultrafiltration failure and discontinuation of PD (4,5). The glucose-based solutions do not contain bicarbonate, which is substituted with the buffer lactate to prevent precipitation of calcium with bicarbonate. Absorbed lactate gets converted to bicarbonate in the liver. Thus, the conventional solution has high levels of dextrose, is acidic, and has lactate as a buffer. These characteristics of conventional solution are believed to make it nonphysiologic and nonbiocompatible. These adverse effects have led to a search for more biocompatible PD solutions in the hope of ameliorating the complications of conventional dextrose solutions. The newer solutions are designed to be more biocompatible by either being less acidic, containing physiologic buffer bicarbonate, or having lower GDP concentration, and/or substituting glucose with alternative osmotic agents, like amino acids (AAs) or polyglucose (Table 1). Studies have shown that use of these biocompatible solutions may lead to lower therapy failure and improved patient and technique survival (6,7).

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Is Conventional Glucose-Containing Solution Harmful?: Evidence

Membrane Effects

In 1985, Gotloib *et al.* (8) for the first time reported that the peritoneal postcapillary venules showed basement membrane changes in nondiabetic chronic uremic patients on maintenance intermittent PD. These changes were not observed in nonuremic, nondiabetic controls. This and subsequent similar observations have raised the questions: Do conventional glucose-

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Table 1. Comparison of different PD solutions

Solution	Buffer	pH	Advantages	Disadvantages	Chambers
Balance	Lactate	7.0	• Near physiologic pH • Lower GDP	Local and systemic glucose exposure	Double
Gambrosol Trio	Lactate	6.3	• Lower GDP • Flexibility of solutions with different tonicity	• Not neutral • Local and systemic glucose exposure	Three
Physioneal	Lactate/bicarbonate	7.4	• Physiologic pH • Reduced infusion pain	Local and systemic glucose exposure	Double
Bicavera	Bicarbonate	7.4	• Physiologic pH • Lower GDP levels • Lactate free • Correction of acidosis	Local and systemic glucose exposure	Double
Nutrineal	Lactate	6.7	• Improves nutrition • No GDP	• Low pH • Use restricted to one bag to avoid rise in urea levels	Single

containing PD solutions cause peritoneal membrane changes? The conventional glucose dialysis solutions have been implicated in causing and maintaining mesothelial cell injury concurrent with sustained regeneration (9). The alterations observed after long-term exposure of the mesothelium to PD fluid are mainly caused by the high concentration of glucose *per se*. Subsequent observations (10–13) indicated that *in vivo* exposure of the mesothelium to a high-glucose concentration (hypertonicity) induced a decreased density and viability of the cell population. The main effect of the high-glucose concentration appears to result in a substantial change in the life cycle of the exposed cell population, leading to the cells' premature senescence and apoptosis. This outcome may well be mediated by sustained oxidative stress derived from both a reduced production of scavengers and the increased generation of oxygen-reactive species. Later studies (14) observed that in long-term continuous ambulatory PD (CAPD) patients, high-glucose PD solutions may promote oxidative mitochondrial DNA damage of peritoneal mesothelial cells. Several studies (13,15,16) have incriminated not only glucose but also glucose degradation products in causing mesothelial cell life acceleration and in reducing mesothelial cell regeneration. Advanced glycation end products (AGEs) have been shown to accumulate in the peritoneal tissue of CAPD patients (16). AGE formation in the peritoneum correlates with the development of severe interstitial fibrosis and microvascular sclerosis. These changes are presumed to lead to ultrafiltration failure. Later, bicarbonate was included in the formulation of PD solutions, replacing the lactate to change the acidic nature of fluid. This was intended to avoid the *in vitro* impairment of certain cell functions seen with acidic hypertonic lactate-based fluids (17,18). No significant differences in apoptosis or necrosis rates were found between the solutions adjusted to normal pH. However, bicarbonate solutions were superior to corresponding lactate solutions at an identical pH of 7.4 ($P < 0.01$) (19). The critical lowering of [pH] in PMN, caused by the combination of high lactate concentration and low pH of the dialysis fluids, is responsible for the observed inhibition of respiratory burst activation (20). Some believe acidity *per se* does not contribute substantially to peritoneal worsening in their *in vivo* model for PD (21).

In conclusion, both animal and human observations indicate that glucose *per se* or in hypertonic concentrations along with its degradation product in an acidic pH are detrimental to mesothelial cell function, viability, and life cycle.

Glucose and Long Dwell and Long-Term PD

Glucose, being a small molecular solute and having nearly complete absorption over 8 to 10 hours, is not a good osmotic agent for overnight dwell. Frequently, patients tend to use solutions with high glucose concentration to maintain fluid balance. Use of icodextrin solution during overnight dwell has virtually eliminated this problem of negative ultrafiltration during long dwell exchanges. In patients on long-term PD, low ultrafiltration (so-called ultrafiltration failure), similar to long-dwell exchanges, may occur. In long-term PD patients, low ultrafiltration volume is seen either because of development of fast transport rates due to an increase in vascular surface area as a consequence of neoangiogenesis (2,22,23) or reduction in osmotic conductance of the membrane (24) and, rarely, enhanced lymphatic absorption from the peritoneal cavity (24–26). The observation of diabetiform alterations in microvasculature and tissue accumulation of AGEs (27) has been attributed to long-term exposure of membrane to hypertonic glucose. However, enhanced fluid absorption from the peritoneal cavity via the lymphatics is pressure related and is independent of the glucose or other solute effects. The existence of this mechanism for ultrafiltration failure has not been clearly established. The undesirable effects of glucose are mainly due to dose and time (28,29). It has been shown that with time there is less ultrafiltration due to increased small solute transport and increased lymphatic absorption (30), and the growth capabilities of the exposed mesothelial layer are depleted (31). Davies *et al.* (30,31) have shown that early exposure to higher intraperitoneal glucose concentrations precedes changes in peritoneal membrane

structure and is associated with faster deterioration in membrane function as well.

Systemic Effects of Glucose

Besides its effects on the peritoneal membrane, glucose, a significant amount of which is absorbed, causes systemic effects either from glucose itself or GDPs. These metabolic effects of glucose cause lipid changes, and consequently cardiovascular events and endocrine changes (32,33). Rapid absorption of glucose during a dwell, as happens in fast transporters, leads to loss of osmotic gradient and diminished ultrafiltration. The excess glucose absorbed can lead to hyperglycemia and associated hyperinsulinemia in both diabetic as well as nondiabetic patients (34). Studies have shown that higher glucose exposure through PD fluid is associated with an increase in total fat mass and increased fat accumulation (35). Contrary to expectations and despite higher ultrafiltration, use of 3.6% glucose solutions have been shown to cause increased BP along with higher heart rate, stroke volume, and cardiac output when compared with icodextrin (36).

Do Conventional Glucose-Containing Solutions Have Any Benefits?

The glucose in PD solutions has an inherent benefit of an energy source for ESRD patients, who tend to be generally malnourished. In both short- and long-term studies, low glucose loads are not necessarily associated with appreciable consequences; it has been time tested that survival of PD patients using glucose PD solution is similar to hemodialysis patients for up to 5 years (37,38). There are PD patients who have survived long term, some up to and over 20 years.

Icodextrin PD Solution

The polymer icodextrin, because of its larger molecular size, is absorbed less (mainly lymphatic), is not metabolized locally during a dwell, and is retained for a longer period in the peritoneal cavity; thus, inducing relatively high volumes of ultrafiltration compared with glucose solution in both CAPD or automated PD (APD) (39–42).

Studies have shown that icodextrin solution effectively clears small solutes with higher ultrafiltration rates. Its use has resulted in better fluid balance in high-transport patients who have poor ultrafiltration even with 3.86% glucose solutions (43,44). Use of icodextrin during a long dwell can help some anuric patients to be maintained on PD because of better fluid balance (45). A double-blind, randomized study comparing icodextrin to 2.27% glucose solution in high-transport patients showed greater ultrafiltration and higher total fluid loss with the icodextrin group compared with dextrose-receiving controls at 1, 3, and 6 months (46). This study as well as other studies has shown that the use of icodextrin better preserves residual renal function (RRF), despite higher ultrafiltration (47,48). Icodextrin-containing solutions have been shown to improve cardiovascular parameters in patients. In a crossover study of 14 patients on APD (48), use of icodextrin for the daytime dwell resulted in improved fluid balance and BP control compared with 2.27% glucose in these patients. Using multifrequency, bioelectric impedance measurements, the study showed decreases in total body water in the patients while receiving icodextrin, which correlated with the decreases in systolic BP. This study had a small number of patients and lacked a control population. In a randomized, open-label study of 40 patients, with 22 treated with icodextrin *versus* 18 treated with standard glucose solution for long dwell, Konings *et al.* (49) showed a statistically significant decrease in extracellular water as well as left ventricular mass in the icodextrin-treated group. There was also a decline in the renal diuresis in both groups but a greater decline in the icodextrin group, which may be due to a loss of pressor diuresis in the icodextrin group. In this study conducted during 4 months, the controls used 1.36% dextrose solution for long dwell, which is not the practice in many centers, especially in the United States. Icodextrin has also been shown to improve the lipid profile in patients. In a randomized, prospective study, 21 nondiabetic CAPD patients were given icodextrin or standard solution for night dwell (50). The patients randomized to icodextrin showed a significant decrease in total cholesterol and LDL levels, and lower free fatty acids and triglyceride levels, which were independent of blood glucose and insulin levels. In a 12-month observational Japanese study, icodextrin was substituted for glucose-containing solution as a long dwell in 51 diabetic PD patients (51). The study showed improved HbA1C in uncontrolled diabetic patients. The mean total/LDL cholesterol and triglycerides decreased significantly during icodextrin treatment, with greater decreases for patients with baseline total cholesterol equal to or higher than 220 mg/dl, LDL cholesterol equal to or higher than 120 mg/dl, or triglycerides equal to or higher than 150 mg/dl. Two studies using the Homeostatic model (HOMA)-insulin resistance have shown lower insulin levels and improvement in insulin sensitivity in patients using icodextrin compared with glucose-containing solutions (52,53). In a study of 41 nondiabetic patients, 17 were using icodextrin as a long dwell, and the remaining patients were using 2.27% dextrose solution; fasting insulin levels and HOMA scores were significantly lower in the icodextrin group than the dextrose group (52). Another study of 44 nondiabetic CAPD patients treated 17 patients with nighttime icodextrin and 27 with standard glucose solutions. There were significantly lower levels of fasting insulin levels in the icodextrin group compared with the glucose group (20.59 *versus* 10.15; $P = 0.0001$), as well as significantly lower HOMA scores (4.8 *versus* 2.3; $P = 0.025$) (53). In a recent randomized, controlled trial of diabetic PD patients, where 30 patients were randomized to the icodextrin and 29 to the glucose group, the investigators showed better metabolic control in icodextrin group, which required less insulin and had better glycemic control. The icodextrin group also showed a better BP control, especially in the first 6 months as well as a reduction in total body water and ECF volume (54).

Icodextrin use has resulted in some nondesirable effects. Subclinical inflammatory response due to icodextrin is also a cause for concern (52,53). The increase in dialysate inflammatory markers may indicate better host defense capacity, but it may be detrimental in the long term. In a study of 22 patients, Martikainen *et al.* (55) showed that there was an increase in

serum C-reactive protein (CRP) levels, as well as dialysate IL-6 and TNF alpha with 8 weeks of icodextrin use. However, in another study comparing 32 PD patients using icodextrin to 10 patients not using icodextrin, the inflammatory marker high-sensitivity CRP decreased significantly only in the icodextrin group ($P = 0.0048$) (56). In a series of eight anuric patients from Japan who were switched from glucose solutions to icodextrin (long-dwell exchange), the effluent leukocyte counts and fibrin degradation products were increased at 12 and 36 weeks after the switch to icodextrin, whereas IL-6 and CA-125 levels stayed the same (57). In a randomized study of 50 PD patients receiving either 2.27% glucose or icodextrin for a long exchange, there was no differences observed in inflammatory markers, with the exception of plasma albumin at baseline on univariate analysis ($r = -0.39$; $P = 0.007$), which disappeared on multivariate analysis (58). One-week use of icodextrin in eight children on nocturnal intermittent PD when switched to APD led to loss of essential and nonessential AAs in the dialysate without affecting serum albumin or AA levels (59). This loss could be due to the extra AA loss caused by adding a daytime exchange, however the serum albumin levels stayed the same.

Icodextrin-based PD solution used as a once daily dwell has shown beneficial effects on several parameters, such as increased ultrafiltration and better volume and BP control. Better blood sugar and lipid control have been noted with icodextrin use. The lower levels of AGEs with the use of icodextrin are thought to better preserve the peritoneal membrane and prolong the use of PD. There is some concern that icodextrin treatment may induce a subclinical inflammatory response, both intraperitoneally and systemically. Icodextrin thus seems to be a better alternative to high-hypertonic glucose PD solutions, especially for long dwell in maintaining volume status, but its long-term implications on peritoneal function and promotion or protection of encapsulated peritoneal sclerosis have not yet been clarified and require further investigation.

AA PD Solutions

Protein loss in the dialysate remains a concern in PD patients. Theoretical advantages of using AA solutions are many. AA-containing PD solution as a means to replace the protein loss has been proposed since early 1980. Use of AA solution can minimize undesirable effects of glucose solution. There is no Food and Drug Administration-approved AA solution in the United States. Clinical observations and human studies of AA solutions have provided inconsistent results. The available 1.1% AA solution is equivalent in ultrafiltration capacity of 1.36% glucose solution (60,61). Kopple *et al.* (62) used AA solution in malnourished CAPD patients, resulting in improved nitrogen balance, net protein anabolism, and increased serum transferrin and total protein levels. However, no appreciable improvements were seen in well-nourished patients. A randomized study over 3 months using 1.1% AA solution showed an anabolic response with increase in IGF and lower phosphorous and potassium levels (63). In another study of 22 CAPD patients with serum albumin levels of less than 3.5 g/dl, use of AA dialysate improved their nutritional status, as measured by an increase in serum albumin levels and net protein catabolic rate (64). A randomized study of 60 patients from China conducted over 3 years and in which half of the patients received one daily exchange of AA-based solution showed that patients receiving AA solution maintained better nutritional parameters, although the survival was similar in both groups (65). In both studies, the AA-based solutions were well tolerated, without any significant increase in infection or dropout rates (65,66). There have been studies that compared patients using glucose-based solutions to patients with additional AA solution exchange and showed an increased net protein balance in patients using AA solution in both APD and CAPD patients (66,67). In a crossover study (66) of eight APD patients, patients were given 7 days of AA-based solutions; the net protein balance increased in all patients while receiving the AA solution. In this study, the mean net protein nitrogen appearance of the patients was 0.8 g/kg per day, and mean dietary protein intake was 0.9 g/kg per day. A second crossover study (67) had 12 CAPD patients given a mixture of 1.1% AA solution with glucose *versus* glucose only for 2 days each with a 1-week interval and found that protein synthesis rates were higher with AA solution use, and the malnourished patients had a significant increase in net protein balance compared with patients receiving glucose-only solution. Four of the 12 patients in the study were moderately malnourished, with the mean net protein nitrogen appearance being 0.92 g/kg per day and mean protein intake 0.94 g/kg per day. From the available clinical observations and literature data, one can thus infer that AA-based solutions are useful in malnourished PD patients. The AA-based solutions have other metabolic effects as well. In the previously mentioned study from China with 60 patients, the cholesterol levels decreased in the dextrose group but stayed stable in the AA solution group (65). In a study of seven stable PD patients over a period of 2 months there was a reduction in serum triglyceride levels and fat mass in the AA group; however, the total cholesterol and its fraction did not change, whereas homocysteine levels increased (68). In another study of 18 CAPD patients receiving 6 months of 1.1% AA dialysate as a single daily exchange, there were no effects on dyslipidemia (69). Negative effects attributed to AA solutions include a rise in serum urea levels and worsening of metabolic acidosis. Nausea and vomiting were reported with use of AA solution. In a study quoted previously, cancer antigen 125 (CA125), which is considered a marker of mesothelial cell mass, was found to significantly increase in dialysate during the use of AA solution, with a slight increase noticed during the use of icodextrin solution which was nonsignificant (55). In the same study, use of AA solution showed increases of other biomarkers of inflammation, such as IL-6, in the effluent, which might be attributed to a subclinical inflammatory response but was also seen with PD solution, including icodextrin. Another concern is the elevated levels of serum homocysteine levels seen with AA solution (68,70). This is likely related to the methionine load from the dialysate. Chan *et al.* (71) studied the effects on mesothelial cell function after incubation with spent AA dialysate (compared with glucose-based dialysate) and found that mesothelial cells showed improved ultrastructure and morphology, viability, and protein synthesis; reduced mito-

chondrial damage; and increased IL-6 secretion. Other data from animal experiments also suggest that AA PD fluid may be more biocompatible than glucose-based PD solution (72,73). The reported observations are made on the basis of short-term studies in small numbers of patients with inconsistent results. A clear advantage over glucose solution is yet to be defined, and the authors feel that more needs to be known about the clinical benefits and undesirable effects of the AA solution. Nevertheless, a nutritional benefit in malnourished PD patients appears to be a favorable point in using relatively more expensive AA solution.

PD Solutions with Neutral pH

ESRD patients are unable to excrete the daily acid load, resulting in metabolic acidosis. The standard PD solutions use lactate as a buffer, which converts to bicarbonate in the liver and helps correct the acidosis. Lactate, by virtue of its acidic pH, causes detrimental effects on the peritoneal cells, causing cell damage and death (3). There is also a concern that systemic lactate flux may cause adverse metabolic effects (74). These potential problems with lactate solutions prompted a search for alternate neutral buffer solutions, and bicarbonate was reconsidered. The two-chambered PD solutions separating bicarbonate and calcium allow the use of bicarbonate near physiologic pH. The separation of glucose, calcium, and bicarbonate allows for solution sterilization at a lower pH without the caramelization and excessive release of GDPs. Pure bicarbonate solutions can raise the pCO2 and have undesirable effects; thus, a combination of bicarbonate/lactate is also available, along with a pure bicarbonate solution. The primary advantages of the bicarbonate-based solution are: (*1*) a physiologic pH; (*2*) a buffer that is physiologic in nature and at a physiologic concentration; (*3*) reduced GDPs; and (*4*) reduced lactate concentration. The bicarbonate buffered PD solutions have been shown to cause less peritoneal damage both *in vitro* and *in vivo* (75). In a crossover study of 12 stable PD patients who were switched to neutral pH, bicarbonate buffered solutions for 6 months, the level of CA125 at baseline was 15.07 ± 5.72 U/ml, which after 6 months of treatment with bicarbonate PD solutions increased to 111.97 ± 66.21 U/ml, whereas the mean values after the patients' return for another 6 months to the conventional solution use dropped again to 22.72 ± 16.06 U/ml (76). In another crossover, randomized trial of 26 stable PD patients, the patients received 3 months of therapy with combined lactate/bicarbonate physiologic pH, low-GDP solution, and 3 months of therapy with conventional glucose-based solutions. The concentration and appearance rate of peritoneal CA125 were significantly higher in patients being treated with neutral pH solution, whereas the concentration and appearance rate of IL-6 were significantly lower in patients being treated with neutral pH solution. No significant difference in serum IL-6 and high-sensitivity CRP concentrations could be found between the two solutions (77). An open-label, randomized, prospective trial looked at effects of conventional peritoneal dialysis fluids (PDFs) and biocompatible PDFs with neutral pH and a very low concentration of GDPs and compared 104 patients who were equally divided between two groups. The effluent CA125 levels were significantly higher in the low-GDP PDF group, and peritoneal Kt/V urea values and total weekly Kt/V urea values at 4 months were significantly higher in the low-GDP PDF group than in the conventional PDF group. RRF was not statistically significant (78). In the Euro-balance trial, the use of neutral solution decreased the markers of peritoneal integrity (79). The study also showed circulating AGE levels decreased, and RRF was better preserved. However, the ultrafiltration volume decreased because of a change in membrane characteristics. In another 12-month randomized study (80), no difference was seen for ultrafiltration volumes, urine output, and RRF in patients that used neutral solution *versus* standard solution. Another study looking at effects of neutral pH and low GDP compared with standard PD solutions in animals over a period of 2 years did not find significant differences in membrane transport characteristics, although the levels of inflammatory markers were lower in the neutral solution arm (81). Additionally, the combined bicarbonate/lactate solutions are observed to be effective in decreasing the infusion pain (82). Clinically, these neutral solutions can influence the RRF and ultrafiltration profile (83). A crossover study that compared 18 patients using Physioneal (25 mmol/L bicarbonate plus 15 mmol/L lactate) with standard lactate-buffered solution found that the net ultrafiltration was significantly lower in the neutral solution (84). Another anecdotal study using a bicarbonate-buffered solution for 1 year showed satisfactory correction of metabolic acidosis but reduced ultrafiltration of approximately 400 ml/d (85), but it observed improvement in RRF. Thus, there seems to be some evidence that neutral pH solutions may improve the integrity of the peritoneal membrane and decrease peritoneal inflammatory response, but whether they improve outcomes is uncertain. Currently, in the United States only lactate-based PD solution is Food and Drug Administration approved. However, in Canada and Europe lactate-bicarbonate and bicarbonate-only neutral solutions are available.

Combination PD Solutions

There are a few clinical studies comparing standard solutions to a combined regimen. One such study by le Poole *et al.* (86) looked at 74 incident patients started on CAPD. Of the 74 enrolled patients 50 completed the study. In a crossover study, control group ($n = 24$) received four exchanges per day of standard PD solution, and the study group ($n = 26$) received the combined regimen of one exchange each of solutions containing icodextrin and AA per day and two exchanges per day of neutral pH, low-GDP solution. After 30 weeks, the groups switched regimens for 24 weeks. Daily ultrafiltration and Kt/V body weight, BP, urine volume, residual creatinine clearance, and laboratory measurements did not differ significantly between the two groups during two phases. Serum bicarbonate level was significantly higher in both groups during combined regimen. A similar combination regimen (a minimally glycemic combination of one AA, one icodextrin, and two 1.36% glucose lactate/bicarbonate-containing exchanges) study by Marshall *et al.* (87) in diabetic CAPD patients showed a tighter glycemic control.

Is There a Survival Advantage with Newer Solutions?

Two studies from the same Korean center have created controversy in the PD community. The studies claimed survival benefits in a group receiving biocompatible solutions (6,7). In a retrospective observational study of over 2000 PD patients, two groups of patients, one treated with balance ($n = 611$) and the other ($n = 551$) with standard PD solution, were compared. Treatment with a low-GDP solution independently reduced the relative risk of death by 0.75 ($P = 0.0465$) (6). The second prospective study (7), which observed a database of 4000 patients, showed that the survival of diabetic patients treated with the newer PD solution was identical to that of the nondiabetic patients treated with standard PD solutions, and treatment with low-GDP PD solutions independently reduced the RR of death by 0.613 ($P < 0.00001$). However, in the first study (6), the patients who crossed over were included in the intention-to-treat analysis but were excluded in the second study (7). There were more than 300 such patients with very high survival rates, and had these patients been included in the latter study there might not have been a survival advantage or a weaker survival advantage in the group using biocompatible solutions. The biocompatible solution group was younger in age by 2 years and accounted for almost half of the survival advantage. More patients in the biocompatible group were treated at larger centers (66% *versus* 44%), and the effect of this on survival was not determined. Moreover, this was an observational study, which is not the same as a randomized, controlled clinical trial, and thus results should be interpreted with caution.

Is There an Effect on RRF?

Several studies have shown that PD patients retain RRF for longer periods compared with hemodialysis patients (88,89), mainly because of stable volume status in PD patients and newer PD solutions (90,91). It is postulated that newer PD solutions containing lower levels of GDPs are less nephrotoxic, and hence may preserve RRF longer. Additionally, the effect of fluid status on preservation of RRF cannot be ignored and should be included in the equation. This is an area of current controversy, because some of these studies have been criticized for being associated with informative censoring (92). Nevertheless, it is an area that is being looked at more closely to clarify whether newer PD solutions with lower GDPs preserve RRF better or whether this is an incidental finding due to better volume status.

Conclusions

There is evidence in specific, clinical short-term situations of biochemical and metabolic benefits of "biocompatible solutions." However, are these solutions superior to glucose in preserving peritoneal membrane over a long term? Are these solutions truly more biocompatible? Conclusive evidence as yet is not in, but long-term observations and specific studies are needed that look at membrane alterations, particularly the dreaded, encapsulating peritoneal sclerosis. Non-glucose-based solutions are being used as substitutes for one or two exchanges in place of the standard PD solutions in specific situations, with some short-term clinical benefits. Icodextrin, in clinical use for over 15 years, has been useful as a single exchange or two exchanges in patients who have ultrafiltration failure, thus allowing some patients to stay on PD longer. Icodextrin is being increasingly used now for its glucose-sparing effects in both diabetic and nondiabetic PD patients. AA PD solutions at a single exchange a day could be beneficial in improving nutritional status in patients with severe malnutrition. Neutral pH solutions with low GDPs have perceived advantage over glucose solution, but a clear, documented clinical benefit is yet to be documented. Although newer solutions have been implicated in causing higher levels of inflammatory markers in the effluent, it is unclear whether this is an inflammatory response or lessening of impaired peritoneal defense mechanisms, leading to better healing of peritoneal membrane. However, neutral solutions have shown lower levels of inflammatory markers in the effluent but have not translated into better clinical outcomes. There is a perception that some of these solutions may preserve RRF longer and may show survival advantage.

There has been a great enthusiasm for use of newer biocompatible solutions; however, in light of inconclusive experimental and clinical data to suggest their clear advantage over glucose solution, it is premature to conclude that we have a new batch of biocompatible solutions that can replace glucose. Clinicians should use the newer solutions with specific indications while keeping in mind the benefits and the cost differential. Using a combination of different osmotic agents, whether they are mixtures in a single bag or daily exchanges of different osmotic agents (*i.e.*, glucose, AAs, polyglucose *etc.*) seems to be the future for now. It is reassuring to see a flurry of activities in this area. It is hoped that with better understanding of the various factors that cause peritoneal membrane changes, over time a truly "physiologic PD solution" will be introduced. With all of the drawbacks glucose has, it still remains the indispensible standalone osmotic agent for PD.

Disclosures

None.

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