Peritonitis in the Patient on Peritoneal Dialysis: Does the Composition of the Dialysis Fluid Make a Difference?  

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To reduce the chance of peritonitis, patients undertaking training in peritoneal dialysis (PD) are taught the importance of hand-washing, a clean environment, and the donning of a surgical mask when performing a bag exchange. When patients do develop peritonitis, they are often questioned about forgetting to mask, or whether a fan was on in the room, or whether a dog walked by, or other risks that might explain it. Yet, thousands of times every day in germ-laden hospitals, nurses change intravenous bags without masking, gloving, or in any other way ensuring a sterile procedure. Nonetheless, patients do not routinely get bacteremia after each intravenous bag exchange. Clearly there is something about the PD process that renders the peritoneal cavity vulnerable to infection.

Considerable in vitro and in vivo evidence indicates that continuous exposure of the peritoneal membrane to conventional peritoneal dialysis fluid alters not only its structural integrity but also the innate defense of the peritoneal cavity against infection. The effect of the dialysis fluid may be mediated by some or all of the following: dilution and washout of resident peritoneal immunoglobulin and other factors involved in innate defense against microbes, and the acid pH, glucose degradation products (GDPs), and high glucose content of the dialysate itself (1). In vitro studies have linked 3,4-di-deoxyglucosone-3-ene (3,4-DGE), a toxic GDP, to increased apoptosis in neutrophils and PMNs (2). Conventional PD fluid decreases in vivo leukocyte recruitment in a rat model compared with a bicarbonate-buffered, neutral-pH, low-GDP fluid (3).

The propensity for peritoneal infection associated with conventional dialysis fluid underscores the interest in biocompatible PD fluids; there seems to be biologic plausibility to the hypothesis that they might lead to better patient outcomes, whether it be decreased peritonitis rates or improved membrane and technique survival. The evidence for benefit has so far been mixed, however (4). Several observational studies have assessed their association with peritonitis-related outcomes. Randomized controlled trials (RCTs) in this area tend to be small and underpowered, with most reporting on peritonitis rates as a secondary outcome only.

Funkert et al. described a retrospective study of 120 patients undergoing continuous ambulatory PD (CAPD) in a center that switched to a low-GDP solution in 2000 (5). Patients after 2000 tended to be older and were more likely to have diabetes; however, they had lower rates of peritonitis and exit-site infections. The authors conceded that these results could have been mediated by an era effect, however. Montenegro et al. conducted a prospective observational study of 100 incident CAPD patients who were treated with a conventional solution or a neutral-pH, low-GDP solution (6). Peritonitis rates were lower in the biocompatible fluid group, with better-preserved residual renal function at the end of the study period. Survival was also higher in this group, although this perhaps speaks more to how patients were prescribed one fluid over another in this nonrandomized study.

Other observational studies have not found this benefit in peritonitis rates. Lee et al. conducted a larger retrospective observational study of 1162 patients who started CAPD with a conventional solution (stay.safe) or a neutral-pH, low-GDP solution (Balance) (7). Patients treated with Balance were younger in general. Of note, 175 stay.safe patients switched to Balance during the study period. In Kaplan-Meier analysis, the biocompatible fluid group had better survival at 28 months, although this difference disappeared when patients were stratified by age. In their multivariate model, age, diabetes, and use of the conventional fluid increased patients’ risk of death. However, peritonitis rates and peritonitis-free survival did not differ.

More recently, the large, open-label balANZ Trial randomly assigned 185 patients, incident to dialysis within 90 days, to the same biocompatible PD fluid as that used in Lee and colleagues’ study (Balance) versus a conventional fluid (stay.safe) (8). Patients were followed for 2 years. Only patients on CAPD were eligible because the biocompatible fluid was not available for use with a cycler during the study period. Although the primary outcome was the rate of change of residual kidney function, peritonitis-free survival was included as a secondary outcome. Unfortunately, only 55% of the prespecified recruitment target was met.

In the balANZ trial, the decline of residual kidney function did not differ between groups, but the patients assigned to biocompatible fluid had a longer

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time to first peritonitis, with a lower overall rate of peritonitis. This held after adjustment for covariates. Interestingly, the bioincompatible group also had a lower incidence of nonperitonitis infections.

In this issue of CJASN, Cho et al. report on the results of the largest observational study to date examining the effect of biocompatible solutions (defined as any multicompartment solution with a neutral pH) on peritonitis-related outcomes (9). Using ANZDATA (Australia and New Zealand Dialysis and Transplant Registry data, they followed 2245 Australian patients incident to dialysis—and specifically PD—between January 1, 2007, and December 31, 2010. In contrast to the balANZ participants, the population was very heterogeneous (e.g., a mix of CAPD and cyclic therapy, and the use of different biocompatible solutions).

In this study, 7.0% of patients used biocompatible solutions at some point, although the prevalent use of biocompatible solutions declined to 4.2% throughout the study period. Variations in use depended on center size, patient age, and comorbid conditions; small to medium-sized units and younger and nondiabetic patients were more likely to use biocompatible solutions. Patients on automated PD were less likely to be on biocompatible solutions.

The results were perhaps unexpected. Overall, patients who had any history of use of biocompatible solutions had higher peritonitis rates with a shorter time to their first peritonitis. This significant effect persisted in multivariate models and sensitivity analyses. There were also some differences in the microbiology of these infections. However, there seemed to be no difference in clinical outcomes, such as PD catheter removal, modality switch to hemodialysis, and hospitalization and death.

Cho et al. acknowledge that it is challenging to postulate a biologic mechanism for their findings, and furthermore note that their results are limited by the usual constraints with observational database studies, such as the lack of granularity in the data (e.g., timing and cumulative exposure to biocompatible fluids for each patient) and allocation bias. Certainly, given the uncommon and declining use of biocompatible solutions during the study period, patients (and centers) who used them may represent a very different group.

Another consideration is that biocompatible fluids are not as healthy for the peritoneal membrane as anticipated. Several studies have measured CA-125 levels in patients treated with biocompatible fluid and found them to increase. In the Euro-Balance Trial, with its randomized crossover design, Williams et al. measured PD effluent CA-125 as their primary outcome (10). CA-125 levels increased three- to four-fold during treatment with Balance. Peritonitis-related variables were not prespecified outcomes in this trial, although the investigators reported no difference between the two groups. Although CA-125 in PD effluent has traditionally been considered a biomarker of mesothelial cell health and mass, it also, interestingly, is markedly elevated during peritonitis. The increase in CA-125, interpreted as a salutary result with biocompatible solutions, may have been misunderstood (11). Perhaps these solutions promote peritoneal inflammation, through mechanisms that have yet to be elucidated, rendering the patient more prone to peritonitis, as reported by Cho et al.

An important caveat is that Cho and colleagues’ study population in fact included participants in the balANZ trial, which showed the opposite effect of the biocompatible solution Balance on peritonitis rates; note that the balANZ trial did not include patients receiving cyclical therapy. Whether this discrepancy in results can be attributed to the heterogeneity of different biocompatible solutions available on the market, or inherent differences in the patients who were prescribed biocompatible versus conventional peritoneal fluids, or something else altogether, is unclear and was not answered by this study.

How, then, do we reconcile the conflicting body of evidence to which this study adds, but does little to resolve? On the one hand, we have a relatively large RCT in a field that needs this kind of study, although the authors were unable to reach their recruitment target. On the other hand, we have an even larger, albeit retrospective observational, study, which appears to be more generalizable but seems to contradict the RCT. Like a research rock-paper-scissors game, does an RCT always trump an observational study?

Although some previous comparisons of observational studies and randomized trials have shown that the nonrandomized studies yielded larger treatment effects, other comparisons have shown that well designed observational studies can yield results similar to those of RCTs (12). In other words, although the traditional hierarchy of evidence is a useful tool, in a field where large randomized trials are challenging to implement, RCTs should not necessarily be considered to have the last word. As tempting as it would be to hail biocompatible solutions as an intervention we can offer our PD patients to reduce peritonitis, Cho and colleagues’ study should give us pause.

Disclosures

J.M.B. is on the speaker’s bureau for DaVita Healthcare Partners.

References


Published online ahead of print. Publication date available at www.cjasn.org.