New Technologies in Peritoneal Dialysis

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In recent years, there have been some interesting advances in the science and practice of peritoneal dialysis (PD). This review focuses on selected technological advances and the impact that these changes may have on this modality. New, so-called “biocompatible” fluids have more physiologic pH and reduced glucose degradation products. These new fluids may reduce the deleterious effects of chronic exposure to the peritoneal membrane. However, enthusiasm for these new fluids is outstripping rigorous evidence that they change patient outcome. Continuous-flow PD offers a way to increase dramatically small solute clearance. However, there are significant technological barriers to the implementation of this kind of dialysis. Furthermore, there is little evidence that augmented small solute clearance will improve survival in PD patients. Finally, new catheter insertion techniques provide perhaps the most practical advances in allowing successful commencement of this excellent home dialysis modality.


Biocompatible Solutions

Standard peritoneal solutions must be manufactured in a way that the product will remain stable with a practicable shelf life. Because the solution is very high in glucose, a major byproduct of this solution is the formation of glucose degradation products (GDP). These comprise a family of compounds with known or suspected adverse consequences, both at the level of the peritoneal membrane and also systemically, via absorption from the peritoneal cavity (4). The GDP can also link with proteins, leading to the formation of advanced glycosylation end products. An ambient acidic pH will reduce the formation of GDP in the bag of dialysate, and for this reason, the pH of unused peritoneal dialysate is approximately 5.2. Another challenge with formulating peritoneal dialysate for storage is that bicarbonate cannot be used as the buffer, because it has the potential to react with calcium in the dialysate and form calcium-carbonate precipitates. Therefore, lactate is used in lieu of bicarbonate and is rapidly and successfully converted into bicarbonate in vivo. Given the acid pH (but not sufficiently acidic to halt completely the formation of GDP), high lactate, and absent bicarbonate, peritoneal dialysate is not completely physiologic, or “biocompatible.” A number of studies using both in vivo and in vitro methods have suggested that the standard dialysate is associated with depletion of mesothelial cells that line the peritoneal cavity, thickening of the membrane itself, and the development of a unique vasculopathy of the vessels in the peritoneal interface (5–7). It has been postulated that nonphysiologic components of the dialysate, in inducing these anatomic changes, may ultimately lead to the development of rapid-transport status and ultrafiltration failure that is seen in a subset of long-term PD patients.

This observation has prompted the ingenious development of PD solutions that have been labeled as “biocompatible.” The dialysate is divided into at least two subcompartments. One compartment contains the glucose and the electrolytes. This subcompartment has a very low pH, which slows the formation of GDP in the bag of dialysate, and for this reason, the pH of unused peritoneal dialysate is approximately 5.2. Another challenge with formulating peritoneal dialysate for storage is that bicarbonate cannot be used as the buffer, because it has the potential to react with calcium in the dialysate and form calcium-carbonate precipitates. Therefore, lactate is used in lieu of bicarbonate and is rapidly and successfully converted into bicarbonate in vivo. Given the acid pH (but not sufficiently acidic to halt completely the formation of GDP), high lactate, and absent bicarbonate, peritoneal dialysate is not completely physiologic, or “biocompatible.” A number of studies using both in vivo and in vitro methods have suggested that the standard dialysate is associated with depletion of mesothelial cells that line the peritoneal cavity, thickening of the membrane itself, and the development of a unique vasculopathy of the vessels in the peritoneal interface (5–7). It has been postulated that nonphysiologic components of the dialysate, in inducing these anatomic changes, may ultimately lead to the development of rapid-transport status and ultrafiltration failure that is seen in a subset of long-term PD patients.

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of GDP. The other compartment contains bicarbonate or a bicarbonate-lactate mixture. Because the calcium is stored in the glucose-containing compartment, separated from the buffer, there is no risk for calcium-bicarbonate interaction during storage. Before the dialysis exchange, the patient breaks a frangible connection that separates the two compartments, and when the components are mixed, the final pH is close to physiologic. The patient now infuses a normal-pH, low-GDP, bicarbonate-containing solution.

Although it seems reasonable to presume that infusion of dialysate with a more physiologic composition should be a good thing, results have been variable and driven at times more by enthusiasm than by science. Initial reports suggested that these solutions were associated with less infusion pain (8,9). A major, well-conducted, randomized, controlled, crossover trial found, in a secondary end point, that urine volume and residual renal function increased in patients who underwent dialysis with the biocompatible dialysate fluid and decreased with the standard dialysate (10). Indeed, in this crossover format, the patient now infuses a normal-pH, low-GDP, bicarbonate-containing solution.

These results were interpreted as showing that the biocompatible fluid “preserved” residual renal function. What is not appreciated in this study, however, is that there was a change in the peritoneal transport characteristics associated with the new solutions. Indeed, the so-called biocompatible solution was associated with a change to a more rapid transporter phenotype, with consequent reduction in ultrafiltration of 350 ml/d. (It is relevant to remember that one explanation for the higher incidence of congestive heart failure in the control group in the Adequacy of Peritoneal Dialysis in Mexico [ADEMEX] trial was a reduction in ultrafiltration of approximately 100 ml/d.) The contribution of this reduced ultrafiltration and change in volume status to the increase in residual renal function is unclear.

Two recent reports from Korea examined survival in PD patients who underwent dialysis with conventional versus newer neutral-pH solutions. Importantly, these were not randomized studies, and what determined which patients received which solution is not stated. Nevertheless, patients who underwent dialysis with the biocompatible dialysate lived longer compared with those who did not (11,12). There were differences in center characteristics between the two groups, and the younger age of the group that received the biocompatible dialysate alone accounted for half of the mortality difference. Furthermore, a very long-living subset of patients who started therapy on standard solutions and were switched to the newer solutions were correctly included as part of the standard group in the intention-to-treat analysis in the first publication (11) but removed from the analysis altogether in the second report (12). This can lead to a major problem of confounding by indication, in that the physicians may decide to “invest” in the healthier patients and switch them over to the newer, expensive PD solutions.

It is still relatively early for the biocompatible solutions. Although these solutions could lead to less damage by GDP and a small relative reduction in circulating levels of advanced glycosylation end products, extrapolating this to preservation of residual renal function and prolongation of life still remains a big leap. Early findings of reduction in peritonitis have not been reproduced (10,12). It is still too early to know whether the new solutions will delay the development of late ultrafiltration failure in long-term PD patients. Finally, because a rapid-transport state is associated with inflammation and vasodilation of vascular beds in the peritoneum, the increase, rather than decrease, in transperitoneal solute flux with these new solutions remains a concern. However, there is still a sound physiologic underpinning to the design of the newer solutions. What is needed, however, are rigorous controlled trials to prove that biocompatibility translates into better patient outcomes.

**CFPD**

Patients who are on conventional hemodialysis can have their solute clearance augmented via multiple mechanisms, including increasing the blood flow, dialysate flow, ultrafiltration, or time on dialysis. Conversely, patients who are on PD are more limited with respect to maneuvers to increase solute clearance. For patients who are already undergoing dialysis 24 h/d, there is obviously no room to increase time on dialysis. Increasing the volume of dialysate will augment small solute clearance but is limited by the concomitant increase in intra-abdominal pressure. Blood flow to the peritoneum cannot be significantly manipulated. There remains only the variable of dialysate flow. Small solute clearance will increase with increasing dialysate flow. This observation is the rationale for the development of CFPD. Originally described by Shinaberger et al. (13), there is a continuous flow-through of dialysate into and out of the peritoneal cavity. This technique requires either two PD catheters or a double-lumen catheter. Dialysate is infused through one port and is simultaneously drained from the second. Theoretical advantages of CFPD include continuous contact of the dialysate with the dialyzing membrane so that there is no lost time for inflow and outflow. In addition, the concentration gradient for solute diffusion into the dialysate fluid will be maintained over time, because the dialysate-to-plasma ratio will no longer approach unity for small solutes such as urea, as it does with the typical “dwell” on conventional PD. Another advantage with the continuous-flow system is that glucose will be continuously replenished in the dialysate. Therefore, the glucose concentration gradient and, hence, the osmotic gradient will remain intact, leading to enhanced ultrafiltration.

Another advantage is that the dialysate could be generated by an on-line apparatus, which would allow for the production of more biocompatible fluids. Using this on-line process, less modification of the PD fluid would be needed for storage and shelf life (discussed in the previous section). Therefore, the real-time generation of dialysate would allow for bicarbonate-based dialysate with physiologic pH. Another putative advantage is that if blood purification could be achieved in a shorter period of time, then the abdomen could be left dry for several hours a day, allowing for repair and replenishment of the normal intraperitoneal structures (14).

Early trials of CFPD suggested that with dialysate flow rates between 120 and 300 ml/min, urea clearance could be as high as...
as 125 ml/min (15). Other studies have reported that the mean creatinine clearance more than doubled compared with conventional automated PD and was five-fold greater than with CAPD (16).

The Faulty Rationale for CFPD

Although at first glance the dramatic increase in small solute clearance is appealing, it is important to remember that higher peritoneal small solute clearance has not been associated with a survival benefit in PD (17,18). PD treats chronic kidney disease in a manner that is different from that of hemodialysis and is poorly estimated or quantified by small solute kinetics such as Kt/V urea. This is evidenced by the weekly Kt/V urea in PD, which is approximately half as much as that on hemodialysis yet is associated with comparable survival to that on HD (19–21).

Benefits of PD likely relate to preservation of residual kidney function, clearance of middle and larger molecular weight uremic toxins (via both the peritoneal membrane and the residual kidney function), and the “continuousness” of the dialysis. Indeed, with respect to the continuous nature of PD, leaving the CFPD patient dry during part of the day because of “enough” small solute clearance during the procedure may do the patient a disservice. That kind of regimen will turn a continuous dialysis process into an intermittent one, and the benefit of the continuousness will be lost. In addition, removal of middle molecular weight uremic toxins is time dependent and thus proportional to the total number of hours on dialysis. Using CFPD for just part of the day would likely impair removal of these toxins. Indeed, one analysis suggested no major increase in middle molecule clearance, even using CFPD in combination with CAPD dwells for the rest of the 24-h cycle (22). It follows, therefore, that a regimen such as CFPD for 8 h, with no dialysis for the other 16 h, would compromise daily middle molecule clearance.

The use of CFPD to augment small solute clearance seemed rational when it was believed that higher small solute clearance was associated with increased survival in PD patients (23). Some studies, however, have not shown this to be the case (24–26). There may be other advantages to CFPD, such as enhanced ultrafiltration, but it cannot be promoted solely on the basis of achieving a higher Kt/V urea. There are considerable technologic challenges with this process also, including designing double-lumen catheters, avoiding streaming or recirculation with these catheters, and, of course, technology to match inflow to outflow to maintain a constant intraperitoneal pressure. The mechanics of these innovations should be practicable in the future, and certainly on-line generation of the peritoneal dialysate is an attractive alternative to the delivery, storage, and hanging of bags of fluid. What remains to be determined, however, is whether these innovations improve patient outcome.

The benefit of biocompatible dialysate and the technique of CFPD are, as mentioned, unproven. In contrast, more “low-tech” innovations with respect to the placement of the dialysis catheter are now in use in many centers. These techniques can be helpful in addressing important but perhaps underappreciated barriers to the use of PD: Primary catheter dysfunction and the “crash start” patients on hemodialysis.

New PD Catheter Placement Techniques

Insertion under Laparoscopic Visualization

Although it is difficult to document, a nonfunctioning or poorly functioning PD catheter is a major cause of technique failure and a hindrance to the establishment of a successful PD program. Whereas hemodialysis has the tunneled or nontunneled internal jugular line as a default option for the patient who is unable to maintain a fistula or a graft, there is no equivalent for the PD patient, who will then be forced to change dialysis modality.

Options for placement techniques include conventional surgical insertion, insertion under peritoneoscopic or laparoscopic guidance, “blind” insertion, and radiologic insertion with fluoroscopy. It has been considered that the particular method of insertion is not as important for the success of the catheter as much as the experience and the interest of the operator performing the insertion. Because the nephrologist has an interest in the success of the catheter, it is not surprising that good results have been reported with the techniques when the nephrologist performs the procedure (27). However, many nephrologists do not have the time, training, or inclination to insert peritoneal catheters. In that case, the insertion usually falls to a surgeon. Again, results may be predicated on the interest or the experience of the surgeon. In addition, blind surgical placement can be hampered by stool-filled bowel, a lively omentum, and bowel adhesions.

Insertion of the dialysis catheter under direct visualization by laparoscopy affords a number of advantages. The operator can ensure, in real time, that the catheter tip is placed in the deep pelvis. Adhesions can be lysed during the procedure, and a large, redundant omentum can be tacked up into the upper abdomen (“omentopexy”) to prevent it from wrapping around the catheter tip in the pelvis. Furthermore, the part of the catheter that traverses the rectus sheath in the abdominal wall can be tunneled superinferiorly so that the catheter has a “built-in” directionality into the pelvis and decreases the chances of its flipping into the middle or upper abdomen (Figure 1).

Figure 1. As a result of rectus sheath tunneling, the catheter has a “built-in” directionality toward the pelvis. In contrast, if the catheter is inserted at right angles to the surface, then it will be more prone to migrate into the middle and upper abdominal quadrants. Courtesy of Dr. J. Crabtree (28).
Excellent results have been reported with the insertion techniques using direct visualization. Crabtree et al. (28) noted very high rates of primary and long-term function with laparoscopic placement of peritoneal catheters, compared with their experience with the blind surgical technique. Conversely, others have had very good experience with blind placement or placement with the aid of a peritoneoscope (where placement and visualization can be done only in sequence, not simultaneously). Furthermore, the literature has been contradictory in terms of comparisons between laparoscopic and surgical insertions (29,30). A recent review and meta-analysis of randomized trials that compared laparoscopy with laparotomy reported no significant difference in peritonitis, catheter replacement, or technique failure (31). In the final analysis, the most important predictor of successful catheter implantation is likely having an operator who is committed to and engaged in the procedure.

Furthermore, the literature has been contradictory in terms of comparisons between laparoscopic and surgical insertions (29,30). A recent review and meta-analysis of randomized trials that compared laparoscopy with laparotomy reported no significant difference in peritonitis, catheter replacement, or technique failure (31). In the final analysis, the most important predictor of successful catheter implantation is likely having an operator who is committed to and engaged in the procedure. Nonetheless, the laparoscopic technique affords the surgeon a greater degree of visualization and control over the proper placement of the catheter and the opportunity to deal with impediments such as intraperitoneal adhesions.

**Buried Peritoneal Catheters**

Another relatively new technique is that of “burying” the distal end of the newly implanted PD catheter subcutaneously so that no part of the catheter is extracutaneous. The original intent of this technique, proposed by Moncrief et al. (32), was to allow complete healing of the catheter tunnel in a sterile environment. By avoiding unintended bacterial inoculation of the catheter, exit site, or tunnel, a germ-free seal could be formed during the wound healing. After a period of time, originally proposed as 3 to 5 wk, the distal end of the catheter could be externalized.

A recent analysis of randomized studies that compared this technique with standard implantation showed no difference in exit-site or tunnel infection rate (two trials, 2511 patient-months; relative risk 0.90; 95% confidence interval 0.39 to 2.08) or a significant reduction in peritonitis (relative risk 1.16; 95% confidence interval 0.37 to 3.60) (31).

Although results have perhaps been disappointing with regard to prevention of catheter-associated infections, the Moncrief technique has been revisited as a method to implant a PD catheter preemptively. Because the whole catheter is subcutaneous or deeper, there is no risk for exit-site infection or inoculation at the time of implantation and no need (and indeed no access) for flushing of the catheter. In theory, the catheter could stay unused for months or even years and then quickly mobilized by an externalization procedure that can be done in the office or the bedside and used immediately for PD. In this way, the buried catheter could be, similar to early construction of an arteriovenous fistula for hemodialysis, part of good predialysis planning for patients, enabling them to have ideal access in place at the time of commencement of dialysis, even when dialysis has to be started urgently.

Because the catheter is to be inserted and left without access to flushing, it is crucial that the implantation technique proceed so that the intraluminal portion does not fill with clot or with fibrin and that the omentum is not activated and wraps around the intraperitoneal portion of the catheter. There have been previous reports of these complications with the embedded technique (33). However, with careful attention to these issues during the implantation, the buried technique can be a useful way to secure peritoneal access ahead of time so that the patient can start either electively or urgently with this modality, rather than risking interim insertion of a temporary hemodialysis catheter (34).

**Conclusion**

The past few years have seen a number of advances in the technical aspects of PD. However, there has been little in the way of rigorous studies to prove whether they will have an impact on outcome. There are challenging technological barriers to the implementation of CFPD, in conjunction with questions about the ultimate benefit of this modality. The enthusiasm for new, so-called biocompatible dialysis solutions has, so far, outpaced proof that these solutions are actually beneficial (35). There is an urgent need for well-conducted studies to demonstrate benefit of the new solutions. Perhaps the greatest cause for enthusiasm lies in innovations in methods of catheter implantation, so as to prevent the disheartening experience of primary nonfunction of the peritoneal catheter. The function of the peritoneal catheter remains an important hurdle in the successful implementation of this excellent form of renal replacement therapy.

**Disclosures**

None.

**References**

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