

EDITORIAL

Current Status of Continuous Cyclic Peritoneal Dialysis (CCPD)

Continuous cyclic peritoneal dialysis (CCPD) was developed as an alternative to continuous ambulatory peritoneal dialysis (CAPD) for patients who are incapable of performing manual dialysate exchanges or unwilling to interrupt their daily routine for dialysate exchanges (1). The clinical experience accumulated during the past eight years has identified other indications for this dialysis modality. At present there are approximately 1300 patients undergoing CCPD in the USA, accounting for 10% of all patients on chronic peritoneal dialysis (2). In view of the consistently positive clinical results published in the literature and the generally accepted statement that CCPD is comparable to CAPD in the treatment of uremia, it is remarkable that its rate of growth has been so modest. Thus, it is pertinent to analyze the accumulated experience with CCPD from the clinical and economic points of view.

Technically, CCPD is essentially a reversal of CAPD where the shorter exchanges are automatically provided at night while the longer exchange is performed during the day. However, the introduction of cycles lasting less than four hours reduces the efficiency in small solute clearance, often requiring additional compensatory exchanges. The long-dwell diurnal exchange (12-14 h) is also unique to CCPD. Hypertonic dialysate is necessary for the diurnal exchange in order to prevent dialysate absorption. Since maximum net ultrafiltration for the diurnal exchange often coincides with the noon meal, many patients experience symptoms resulting from increased intra-abdominal pressure. Consequently, a 25% reduction in dialysate volume is often necessary for the diurnal cycle. The provision of a diurnal cycle is imperative in order to maintain a relatively steady physiologic state and to achieve high clearances of middle molecules. An increase in dialysate flow during the night can only partially compensate for the solute removal achieved with the diurnal cycle, which provides 15 to 20% of the total creatinine clearance and more than 25% of middle molecule clearance in patients with normal peritoneal transport rates (3). Thus, the total elimination of the diurnal cycle results in a significant sacrifice in solute removal. Nocturnal cycling of dialysate without a diurnal exchange should be referred to as nocturnal peritoneal dialysis (NPD) or nightly intermittent peritoneal dialysis (IPD), and never as CCPD.

CLINICAL EXPERIENCE WITH CCPD

Although there are no specific indications for CCPD, its schedule and technical characteristics offer considerable advantages to certain patients. Individuals with neuromuscular limitations, the blind, and those with learning disabilities can benefit from partner assistance. Setting up the cyclor and connecting the patient line to the peritoneal catheter is a relatively short procedure performed only once daily. Modern disconnection techniques using external occlusion have reduced disconnection time to a few seconds and have made it possible to be performed by even the most limited patients (4). Due to the high incidence of peripheral neuropathy and blindness among diabetics, some centers offering CCPD have treated a disproportionate number of diabetics. In our experience, adequate glycemic control is possible with the use of i.p. insulin infusions, although the appropriate insulin dose is more difficult to determine than with CAPD due to the variable length of the cycles.

Children have perhaps benefited more than any other group from CCPD. Nonmedical reasons for conversion of children to CCPD include the need for parental assistance and self-dialysis by children (5,6). Single, working parents benefit from the infrequent procedures required by the CCPD technique. Older children often are capable of mastering the CAPD technique, but either express their reluctance to perform exchanges in the presence of their peers or become noncompliant with the prescribed number of exchanges. CCPD can improve their self-image and esteem. Medical reasons include the frequent need for more than four exchanges per day required for control of hyperkalemia and excessive weight gain (5). Other advantages are the possibility of using reduced dialysate volumes during the day for prevention of hydrothorax, recurrent hernias, and dialysate leaks in children.

The growth rate of children undergoing CCPD has been maintained (7). Most uremic children present with growth retardation (less than 5th percentile) at the initiation of dialysis but are capable of maintaining their same growth velocity during the period of treatment with CCPD (8). The overall growth velocity

index observed in children treated with CAPD and CCPD has not differed significantly.

In our experience, patient preference has been the most common reason for adopting CCPD over other dialytic modalities. One hundred consecutive patients were introduced to peritoneal dialysis by means of audiovisual material and interviews with the home training instructor who answered questions related to both CAPD and CCPD. The educational material emphasized that the effectiveness of both modalities of therapy was similar and that the choice of therapy was entirely up to the individual patient and his family. Cost considerations were not covered, but in the event that the patient inquired about cost, they were assured that there was no cost differential for the patient and no cost incentive to the physician. Sixty percent of the patients elected CCPD and 40% selected CAPD. There has been no difference in the drop-out rate between CAPD and CCPD in our experience and very few patients have transferred from one modality to the other.

The biochemical profiles, hematologic parameters, control of hypertension, and maintenance of adequate hydration with CCPD have been reported to be similar to those achieved with CAPD in children and adults (1, 4, 8-14). The number of hospitalization days, patient survival, and technique survival have been found to be similar to CAPD by the National CAPD Registry (15).

There is significant controversy regarding the incidence of peritonitis among CCPD patients. The largest and most experienced centers providing CCPD to adult patients have consistently reported significantly lower rates of peritonitis, averaging one episode per 20 patient months of observation (1,4, 11-13, 16, 17). In fact, in 1986 the difference in peritonitis rates reported by the National CAPD Registry for CCPD was significantly lower (1.3 episodes per patient year) than that observed for CAPD (1.4 episodes per patient year) (18). Nonetheless, centers with very few patients undergoing CCPD and most pediatric programs have failed to observe a significant difference in the rate of peritonitis.

Several theoretical considerations have been offered to explain a lower rate of peritonitis among CCPD patients. CCPD requires fewer procedural sessions and manual connections between the catheter and the transfer set. The connections also take place at home and other familiar surroundings at elective times, probably leading to better concentration by the patient or partner, and improved aseptic control of the environment. Many patients are assisted by healthy partners capable of performing better connecting procedures. The long diurnal cycle of CCPD may also improve host immunologic defenses by allowing repopulation of the resident peritoneal macrophages (19). During CCPD the initial event after each connection is dialysate outflow. If contamination has occurred, it is likely that the spent dialysate will reduce the magnitude of the bacterial inoculum, particularly when common contaminants such as *S. epidermidis*, with characteristically low adhesiveness, are responsible for infection (20, 21). This last consideration may also explain the low incidence of

peritonitis reported with most modalities of bagless CAPD (22,23).

The higher incidence of peritonitis reported in children is difficult to explain. However, many children depend on multiple partners to effect their connections and several pediatric programs have reported experience with a mixed population receiving both CCPD and nightly IPD. The interpretation of the data on peritonitis is further complicated by the fact that many programs reserve CCPD for patients at high risk of developing peritonitis and those who desire peritoneal dialysis, but have experienced recurrent episodes of peritonitis on CAPD.

MODIFICATIONS TO THE ORIGINAL CCPD TECHNIQUE

Several improvements and modifications of the initial CCPD system have been introduced. These modifications were inspired by the need to make the system simpler and more economical. The first major change was the elimination of the traditional disconnection step and replacement with external occlusion (4, 24). The external occluder consists of a perfectly fitted plastic clamp, placed in the cyclor line immediately distal to its connection with the Tenckhoff catheter. After clamping, the cyclor line is severed with unsterile scissors. This simple procedure can be performed by practically all patients, in a very short period of time, without the need for special sterile precautions. Pressure testing to 20 psi and bacteriological challenges have confirmed the safety of external occluders (24). Furthermore, the clinical experience has confirmed its safety and acceptance by the patients. The use of external occlusion eliminates the cost of masks, gloves, sterile drapings, disinfectants, or mechanical disconnecting devices.

The single item most responsible for the high cost of CCPD over CAPD is the cyclor tubing set. In our attempt to reduce this cost differential we proposed the use of a multiple-use tubing set (MTS) (25). The MTS consists of multiple prongs to accommodate the dialysate containers, connected by a manifold that leads to the cyclor warmer and distribution cabinet and eventually to the patient-cyclor line. The cyclor line has several connectors in-series. The equipment is set up for several day sessions. However, only the bags to be used during that day have their seals broken. At the conclusion of the procedure (or early morning), two external occluders are placed in the connecting segment used for that session and the segment is cut between the two occluders. The system remains closed until the next evening, when a new cyclor-patient connector is opened. This system is convenient to the patient, and especially to partners, by reducing the cyclor preparation time. The cost savings are proportional to the number of sessions accommodated by the particular MTS. At least one manufacturer has adopted this idea (Delmed, New Brunswick, NJ) for three-session use. The preliminary results revealed similar peritonitis rates to those

observed with traditional systems from the same manufacturer (25).

The use of large volume dialysate containers can reduce the cost of CCPD in two ways. First, packaging, labeling, and delivery costs of large containers are lower. Second, smaller containers require more prongs in the cyclor tubing set which add to the complexity and cost of the system. An additional advantage of the large containers is the fewer connections required between the container and the cyclor set, which translates into convenience and safety.

The only disadvantage of large containers is their weight. Some patients require assistance carrying containers over 1 kg. The problem is compounded by having to lift the bags above the patient's shoulders. Several manufacturers have solved this problem by adding a dialysate transfer pump to their cyclors (Travenol, Fresenius) capable of measuring a preprogrammed volume of dialysate and pumping it to the heating cabinet above the patient level. The combination of MTS and large dialysate containers is by far the most effective means of reducing the cost of CCPD.

The greatest menace to the survival of CCPD is the possible elimination of Reimbursement Method II by the Health Care Financing Administration (HCF A) (26). The need to contain costs in the provision of end-stage renal disease (ESRD) therapy is clearly our responsibility. However, the delivery of specialized care to individuals in the best possible manner is often expensive. If indeed CCPD provides a better alternative for certain individuals, then it is our duty to effectively transmit this knowledge to our legislators and those responsible for the distribution of our health budget.

FUTURE DEVELOPMENTS

The value of peritoneal dialysis as chronic renal replacement therapy has been questioned (27). Despite the emotion generated by this criticism, the society of responsible and enthusiastic workers in the peritoneal field have both characterized the flaws and limitations of the existing tools and responded with ingenuity to its potential improvement. We have recognized different and changing peritoneal solute transport patterns in individual patients (28) and have developed tests to characterize these patterns (29-31) as well as alternative therapies for the provision of more adequate dialysis (32,33). Attention has also been given to the factors responsible for malnutrition in peritoneal dialysis, its prevention and treatment. The unphysiologic nature of the solutions used in peritoneal dialysis is evident and possible ways of correcting the problem are being entertained by several investigators. The problems we face with peritoneal dialysis are of similar nature and magnitude as those encountered with hemodialysis 30 years ago. The recognition of these problems brightens the future of automated peritoneal dialysis.

The use of a standard clinical tool to measure peritoneal transport rates has been proposed (peritoneal

equilibration test or PET; 30, 31). This approach, in combination with our knowledge of the patient's metabolic needs and residual renal function, can provide us with the first scientific experience in prescription peritoneal dialysis. While we should avoid the use of CCPD with a dry peritoneum during the day in patients with normal peritoneal solute transport due to a significant sacrifice of clearances, it has been properly used in patients with high peritoneal transport rates. In fact, individuals with high peritoneal permeability can accomplish better clearances with highflow nocturnal peritoneal dialysis (NPD) than with CAPD or CCPD, while enjoying the convenience of a shorter cycling session (8 vs. 10 h) and lower intra-abdominal pressures during the day (34). It is also of interest that many pediatric programs favor NPD in order to accomplish adequate ultrafiltration and potassium removal in small children. Although peritoneal transport has not been fully characterized in children, in view of the satisfactory clinical experience with NPD it is likely that their solute transfer is faster. The shorter cycles of NPD also provide appropriate ultrafiltration in these patients. The routine testing of peritoneal transport at the initiation of therapy, or when ultrafiltration problems arise, has resulted in the use of NPD for 8 to 10% of our patients on peritoneal dialysis (35).

The use of peritoneal equilibration tests (PET) has also identified a few individuals with low peritoneal solute transport rates, which require high volume/ flow peritoneal dialysis in order to attain adequate clearances. Since larger volumes of dialysate are better tolerated in the supine position, automated cycling at night is often a better alternative. However, even the highest flow peritoneal systems in existence today cannot provide adequate solute removal in some patients (*vide infra*).

Our quest for improved dialysis efficiency reflects our concern with inadequate solute removal. In 1979, Blumenkrantz *et al.* described a technique of peritoneal dialysis called "reciprocating dialysis" (36, 37). Varying volumes of dialysate (1-1.5 L) were infused i.p. and allowed to dwell continuously, while 500 mL of dialysate were rapidly cycled in and out to accomplish total exchange rates of up to 9 L/h. This experience revealed that clearances could be significantly augmented from 21.5 mL/min with 4 L/hour exchanges to 31.5 mL/min with 9 L/hour exchanges, confirming Tenckhoff's earlier results (38). However, the authors later concluded that higher urea clearances were the consequence of the high dialysate flow rate, but that the reciprocating technique did not play a significant role in enhancing clearances.

Twardowski *et al.* have revived this concept in their trial of tidal peritoneal dialysis (TPD) (39). This method incorporates the use of a reserve volume (RV) of dialysate that remains constant in the peritoneal cavity and a tidal volume (TV) that constantly flows into and out of the peritoneal cavity. TPD requires a cyclor that is volume rather than time controlled. The preliminary clinical experience suggests significant improvement in small solute clearances. This im

provement in clearances is superior to that obtained with the traditional intermittent technique using similar dialysate flows, suggesting that TPD results in better mixing of dialysate and reduction of stagnant dialysate films along the peritoneal membrane. Further clinical experience is necessary to define the importance of this technique in augmenting PD efficiency, but the concept clearly deserves our attention.

Another interesting concept that has remained dormant is peritoneal dialysis with continuous regeneration of dialysate by use of a sorbent cartridge (36). The sorbent system consists of a closed circuit using a small volume of dialysate (2-3 L) which is recirculated through a sorbent cartridge for regeneration. The sorbent cartridge contains layers of: a) activated carbon to remove creatinine, uric acid, and other organic compounds; b) hydrous zirconium oxide to remove phosphate and fluoride; c) zirconium phosphate to remove ammonia, calcium, magnesium, and potassium; d) urease to convert urea to ammonium carbonate; and e) a purification layer to remove heavy metals and oxidants. Calcium and magnesium are added to the regenerated dialysate. The efficiency of the system is greatly enhanced by maintaining a high diffusive gradient made possible by high dialysate flow rates while using a small volume of dialysate. Although this technology is available, two problems halted its development. Protein in the dialysate interferes with function of the cartridge causing release of urease. Also, the cost of manufacturing disposable regenerating cartridges made it noncompetitive with low-cost CAPD. However, we must not dismiss this alternative as a more effective peritoneal dialysis system. It is possible that interest in high-efficiency peritoneal dialysis and newer manufacturing techniques may make this concept a future reality.

High-flow peritoneal systems are limited by the cost of dialysate and by the inconvenience of storing dialysate containers. Both of these problems could be solved by using a reverse osmosis (RO) water system. The extensive experience with IPD using RO proportioning systems taught us that dialysate can be safely produced by mixing RO-treated water with dialysate concentrate. The storage problem is eliminated and the cost of dialysate manufacturing could be competitive when large volumes are required. However, this system was difficult to maintain and it was technically complicated. Recent progress in membrane manufacturing and the fact that smaller volumes of water would be required than for IPD, qualifies low-efficiency RO systems as a possibility in the future of automated peritoneal dialysis.

Nutrition, and especially protein malnutrition, remains a prominent complication of peritoneal dialysis. The factors that lead to malnutrition include: a) the continuous protein losses through the peritoneal effluent; b) the constant glucose loads which lead to anorexia and poor protein intake; c) increased intraabdominal pressure causing dyspepsia; and d) insufficient dialysis which often leads to dyspepsia, dysgeusia, anorexia, nausea, and vomiting. The short-term experiences with peritoneal solutions containing

amino acids have shown that amino acids could be used as a possible alternative osmotic agent to glucose and represent a realistic approach to nutritional supplementation (40-42). The use of amino acid solutions for the diurnal cycle of CCPD could enhance ultrafiltration during the day, provide a significant amino acid load, and thus minimize the problem of malnutrition. This alternative would be particularly attractive for diabetics due to the elimination of the continuous glucose loads during the day and the provision of protein supplementation. Similarly, the long diurnal cycle of CCPD could be utilized for other nutritional supplements such as vitamins and trace minerals.

A major obstacle to the use of amino acid solutions is the generation of hydrogen ions and the resulting metabolic acidosis (40). Progress is being made in the development of bicarbonate containing peritoneal dialysate which could both result in a more physiologic dialysis solution as well as the incorporation of amino acids as osmotic agents and nutritional supplements (43,44).

The recent studies on the contribution of lymphatic absorption to peritoneal ultrafiltration could be applied to the CCPD technique. During the long dwell exchange of CCPD substantial absorption of dialysate takes place through the subdiaphragmatic lymphatics which could account for 40 to 50% of net ultrafiltration. Preliminary studies suggest that the i.p. infusion of agents such as neostigmine and phosphatidylcholine may block lymphatic absorption and increase net ultrafiltration (45-47). If the clinical experience in humans shows that these agents are effective and safe, the volume of the diurnal exchange of CCPD could be reduced, the concentration of glucose could be lowered, and effective net ultrafiltration could be substantially increased.

CCPD is a hybrid modality of therapy which has helped to bridge the manual and automated techniques, the concepts of continuous and intermittent dialysis, and has opened the doors to the evolution of peritoneal dialysis into a more efficient and physiologic mode of therapy.

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