

SPECIAL ARTICLE

Recent Advances in the Management of End-Stage Renal Disease (ESRD) in Children

by

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I. Dialysis

It has been almost 20 years since the initial report were published detailing the use of the dual treatment modalities of dialysis and renal transplantation to treat children with ESRD. During this time, the outlook for the infant, child and adolescent with ESRD has changed dramatically from abject pessimism to cautious optimism.

Initially, hemodialysis was the principle dialytic technique utilized; however, intermittent peritoneal dialysis was used occasionally in selected centers. The latter required less technical expertise, but necessitated considerably more dialysis time and was significantly less efficient at alleviating the clinical and biochemical consequences of uremia.

During the past decade the significant advance in the area of dialysis has been the development of the techniques of continuous ambulatory peritoneal dialysis (CAPD) and continuous cycling peritoneal dialysis (CCPD). There has been a renaissance of interest in the use of peritoneal dialysis with the description of these two

techniques.

CAPD is based on the principle that continuous long-dwell time peritoneal dialysis facilitates adequate solute and water removal, thereby alleviating the clinical and biochemical consequences of uremia comparable to that achieved with hemodialysis. A major advantage of CAPD is that it requires minimal technical expertise, requires limited amounts of expensive equipment and can be performed by the patient and/or parent (helper) at home. Certainly, CAPD would be an ideal dialytic technique for children in areas of the world with limited financial resources and medical expertise.

The technique of CAPD involves the instillation of dialysate into the peritoneal cavity through a permanent indwelling peritoneal catheter (Tenckhoff) 4 to 5 times daily at 4 to 8 hour intervals, 7 days a week. In general, there are 3 short-term daytime dwells (4 to 5 hours each) and one long (8 hour) nighttime dwell. Infants and young children undergoing CAPD frequently

require an additional daytime dwell to effect adequate solute clearance.

With the above technique, the biochemical consequences of uremia can be reduced to the extent that survival is possible. However, the urea and creatinine clearance with routine CAPD is only 10 to 15 and 5 to 10 ml/min, respectively. The removal of excess fluid is facilitated by the use of hypertonic glucose in the dialysate solution.

The major complications of CAPD involve infections related to the need for a permanent indwelling catheter (exit-site and tunnel infections) and the development of peritonitis. The incidence of peritonitis in our experience is approximately one episode every 12 months. However, a small percentage (20%) of patients in any series has multiple episodes of peritonitis, thereby increasing the overall incidence. In most instances, peritonitis is treated at home by the patient and/or parent with the instillation of antibiotics in the peritoneal cavity.

There are few data detailing the long-term results of CAPD in pediatric patients. Impediments to the long-term success of CAPD as a dialytic modality are the loss of the peritoneum as a viable dialytic membrane because of repetitive episodes of peritonitis and patient and/or parent burn-out related to the technical demands of continuously repeating the procedure. In our experience the latter phenomenon has led to conversion to CCPD, which has sustained the use of peritoneal dialysis in a number of instances.

The technique of CCPD utilizes an automated delivery system to perform the desired exchanges at night while the patient is sleeping. This technique is significantly less labor intensive since it only requires one connection/disconnection procedure

daily in contrast to the 4 or 5 required with CAPD. We have found that five 2 hours exchanges at night followed by a ½ volume daytime dialysate dwell usually provides effective dialysis.

A major indication for CCPD is in infants whose mothers frequently have other young children to care for and are unable to accomplish the number of daytime exchanges required with CAPD and, in addition, undertake their other maternal responsibilities.

Similarly, school aged children prefer CCPD because they do not have to be subjected to peer scrutiny while performing a CAPD exchange at school. Adolescent patients also prefer CCPD because the technique facilitates greater control of their own destiny and life-style.

The complications of CCPD are similar to those described with CAPD. Although it was initially proposed that CCPD would lead to a reduction in the incidence of peritonitis because of the decrease in the number of connections/disconnections required, the data from most pediatric facilities have not substantiated this hypothesis. In our experience the incidence of peritonitis is similar with CAPD and CCPD.

The drop-out rate with CCPD is substantially less than that of CAPD. The CCPD technique survival in our experience is over 75% at 3 years. Certainly, the rehabilitative potential for infants, children and adolescents undergoing CAPD and/or CCPD does not approach that obtained with a successful renal transplant; however, the ability to undertake either procedure at home without medical assistance enhances self-esteem and permits patients and their families a greater determination of their own destiny.

II. Transplantation

The major advance over the past decade in the area of renal transplantation in children has been the availability of the new immunosuppressive agent, cyclosporine A (Cy A). Although the precise mechanism of action of Cy A is unknown, it has been demonstrated that mediators of "T" cell activation and differentiation are suppressed by Cy A.

Initially significant toxicity was associated with the high dosage of Cy A administered, especially if intravenous Cy A was given in an anuric patient. Recently, protocols have evolved which defer the introduction of Cy A until adequate graft function (serum creatinine level < 2.0 mg/dl) is obtained as well as utilize concomitant azathioprine therapy along with prednisone and Cy A (triple drug regimen) in order to minimize the dose of Cy A prescribed while obtaining adequate immunosuppression. In our experience such a regimen has led to a >80% one year graft survival rate with primary cadaver donor grafts.

As with most immunosuppression drugs, there are a myriad of potential complications with the use of Cy A. Initially, there was an inordinately high incidence of lymphoma reported in recipients treated with Cy A. However, subsequent reports have fortunately not substantiated this finding. In retrospect, the use of Cy A in extremely high dosage (25 mg/kg/day) in conjunction with other immunosuppressive agents probably contributed to the initial high incidence of lymphoma.

Currently the primary clinical complication of Cy A is nephrotoxicity which to some extent is dose related and acute reductions in the glomerular filtration rate (GFR) usually respond to a decrease in the dosage of Cy A. Unfortunately, chronic

nephrotoxicity is probably a uniform finding in recipients treated with Cy A. In all controlled studies performed to date the serum creatinine level of recipients given Cy A has been significantly higher to that of recipients given azathioprine. Fortunately, the chronic toxicity does not appear to be progressive and an unrelentless decline in graft function has not been shown in renal graft recipients receiving Cy A.

The incidence of hypertension in recipients receiving Cy A is higher than that in recipients receiving other immunosuppressive drugs regimens. The etiology of the hypertension is probably related to intrarenal hemodynamic changes produced by Cy A. Antihypertensive drug therapy is usually effective and rarely does unremitting hypertension necessitate the discontinuation of Cy A. Hirsutism is a particularly onerous complication for the pediatric recipient. Fortunately, there is a relationship between Cy A dosage and the magnitude of hirsutism; therefore, as the dosage of Cy A is decreased the degree of hirsutism abates.

There are limited data regarding the outcome of renal transplantation in pediatric recipients receiving Cy A. These data are somewhat discipient in that superb results (>80% one year graft survival rates) have been reported from some centers, whereas other centers have been unable to obtain results better than those achieved with other immunosuppressive regimens (\pm 50% one year graft survival rate). One potential reason for the variability in outcome is the dosage schedule of Cy A utilized. It has been shown that pediatric patients hypercatalolize Cy A and that, in addition to a twice daily dosing schedule, it is imperative to keep a constant surveillance of the Cy A blood level in order to assure ade-

quate immunosuppression. In general, pediatric patients require a higher Cy A dose per kg of body weight than do adult

recipients. Failure to adjust the Cy A dose appropriately may have contributed to the variation in results reported to date.

III. Management of the Infant with End-Stage Renal Disease (ESRD)

The management of the infant with ESRD requires consideration of factors not present when confronted with the child or adolescent with a similar clinical situation. Specifically, the infant with ESRD has the potential for developmental retardation, severe neurologic dysfunction and significant growth impairment. Consequently, treatment of the infant with ESRD is directed at avoiding the development of these clinical consequences as much as possible.

The indications for initiating dialysis in an infant are somewhat broader than those in the child and adolescent. In addition to the usual clinical manifestations of uremia, failure to achieve appropriate development milestones, lack of appropriate increment in head circumference as an indication of incipient neurological dysfunction and reduced growth velocity, are criteria utilized to initiate dialysis in the infant. Changes in these parameters may be subtle and, therefore, assiduous attention must be paid to these factors by an astute observer.

Hemodialysis over an extended period of time is technically difficult in an infant, especially if anuria is present. Maintenance of a viable vascular access for a protracted period of time in an infant is exceedingly difficult. Therefore, during the past decade some form of extended peritoneal dialysis has been used as a chronic dialytic modality for infants. In our experience, CCPD is the optimal dialytic modality for the infant. It can be performed by the parent for periods of 10-12 hours either during the day or night when the infant is sleeping and

requires minimal technical expertise and a limited time commitment on the part of the caretaker.

Transplantation remains the optimal therapeutic for all pediatric patients with ESRD; however, in the infant the timing of transplantation is a crucial issue. Until recently, transplantation of infants < 1 year of age led to a high mortality rate and few long term successful grafts. However, recent data has demonstrated creditable results utilizing live-related donor grafts for infants < 1 year of age. Similarly, the success rate with cadaver donor grafts in young children < 5 years of age has been associated with rather poor outcome, although live-related donor grafts in this age group yields results similar to that obtained in older children and adolescents.

Because of the current data with cadaver donor grafts, we prefer to defer transplantation in infants undergoing dialysis until 2 years of age. Few data are available utilizing Cy A in this age group, and if subsequent reports indicate a significant improvement in outcome with the use of Cy A in this age group, it is likely that earlier transplantation will be recommended.

As indicated previously, statural growth and intellectual development can be severely affected in infants with the onset of ESRD in the first year of life. The earlier initiation of dialysis along with assiduous attention to correction of acidosis, prevention of renal osteodystrophy and optimal nutritional intake may be helpful in optimizing growth in infants with ESRD. Since the etiology of the developmental

delay in infants with chronic renal failure is unknown, it is difficult to recommend any corrective measures. However, it has been our impression that since we have eliminated the use of aluminium containing antacids as phosphate binders and introduced calcium carbonate as the principle

phosphate binder, the incidence of severe developmental delay has decreased markedly.

Further, longitudinal data are required before an assessment of the effect of earlier initiation of dialysis or both growth and developmental can be made.

IV. Growth in Children with Chronic Renal Failure (CRF)

One of the onerous facets of CRF which develops in infancy or childhood is the associated growth retardation. At least one-third of all children who develop CRF in infancy or childhood will ultimately manifest short adult stature. The precise etiology of the growth retardation is unknown; however, all of the following factors have been implicated: (1) age of onset of CRF; (2) primary renal disease; (3) concomitant renal osteodystrophy; (4) inadequate calorie intake; (5) acidosis; and (6) reduced somatomedin activity. It is likely that each of these factors can contribute to the growth retardation and that the etiology is multifactorial. The age at onset of CRF is certainly a primary factor and infants with onset of CRF at < 1 year of age usually manifest severe growth retardation.

It had been anticipated that the introduction of the dual treatment modalities of dialysis and transplantation would correct the growth retardation. At least two-thirds of the children undergoing extended hemodialysis have continued growth retardation. CAPD/CCPD has been associated with improvement in the incidence of growth

retardation; however, the data are rather meagre. Successful renal transplantation can result in the resumption of a normal growth pattern. Unfortunately, most children are growth retarded at the time of transplantation and, although normal growth velocity may occur following a successful transplantation, sustained growth acceleration is rare. In our experience, the factors which significantly effect post-transplant growth are: (1) graft function; (2) age at transplantation; and (3) corticosteroid dosage.

We have observed accelerated growth in children who are transplanted before 10 years of age when graft function is excellent ($GFR > 60 \text{ ml/min/1.73m}^2$) and the daily prednisone dose is < 0.02 mg/kg/day. Certainly, these 3 factors must be considered if posttransplant growth is to be optimized.

Recently, we have initiated a preliminary study on the use of human growth hormone in children with CRF and the preliminary results of the study will be presented at the meeting.