37 *CAPD—Emerging Front Runner in Renal Replacement Therapy*

RK Sharma

Abstract: Peritoneal Dialysis (PD) has come a long way since the introduction of continuous ambulatory peritoneal dialysis (CAPD) as a form of renal replacement therapy (RRT) for end stage renal failure (ESRF) over a quarter of century it has been in existence. There have been dramatic improvements in outcome in patients treated by PD, such that it is now accepted as an equivalent therapy to hemodialysis (HD). In the last decade, CAPD has proved to be as effective treatment as HD. In some instances it may offer advantages over HD. Currently there are more than 130,000 patients on PD worldwide, representing approximately 15% of the total world population requiring dialysis. The population in India exceeds one billion and is projected to become the reservoir of chronic diseases like diabetes, hypertension and chronic renal failure (CKD). However, in the absence of any renal registry, data on incidence of ESRD in India or other countries of South Asia does not exist. Based on the estimates from rest of the world, tertiary care centre data and collective experience of experienced nephrologists, the incidence rates probably vary between 150 to 225 per million. As per the published literature, Diabetic Nephropathy is the leading cause of ESRD. Further it has been estimated that less than 10% of all Indian ESRD patients receive any meaningful RRT.

PD has grown rapidly in the last five years from 1800 patients to more than 5000 till date. CAPD Penetration in India is about 17%. Majority of patients are on twin bag system from Baxter India Pvt.Ltd. Majority of patients are on three bags per day. Most of the patients are within the age group of 40-70 years.

The average survival of PD patients has improved over the past decade and so is the reduction in incidence of peritonitis rates among Indian PD patients. Data from an unpublished source suggests that one and two year survival is around 82% and 66% respectively. Total number of peritonitis episodes have gone down by more than 150% in the last three years (since the data available is for the last three years) from 1 episode in 19 patients per month to 1 episode in 36 patient per month on therapy.

Results of well practiced PD, including training support by the pharmaceutical industry and proper education to the patients has changed the survival outcomes to a great extent. Majority of patients are now able to contiue their routine work while on the PD, quality of life has improved for such patients. With the introduction of new solutions Extraneal (An icodextrin based PD solution) recently in the country, the technique and patient survival on Peritoneal dialysis is expected to improve further and will help patients on the PD to achieve their ultrafiltration and improve their fluid balance.

INTRODUCTION

One major development in the field of kidney diseases in the 21st century will be in prevention of end-stage renal disease (ESRD). Basic research has made inroads into the understanding of the mechanisms of progression of chronic renal failure, including the understanding of the functions of genes activated by renal damage. All this may well result in a major reduction in the incidence of ESRD. The second important development will be in transplantation, which will constitute the mainstay of ESRD treatment in the next century. The clinical introduction of xenotransplantation and the cloning of one's own organs via one's stem cells may well represent the major areas of replacement therapy. This will reduce need of dialysis as a method to support the main treatment. These predictions will take some time to come to fruition. The first few decades in this century will face a tremendous increase, rather than a decrease, in the number of ESRD patients needing dialysis. Peritoneal dialysis (PD) will feature strongly in meeting this need in at least the first two decades of this century.

PD has come a long way since the introduction of continuous ambulatory PD (CAPD) as a form of renal replacement therapy (RRT) over the quarter of a century it has been in existence. There have been some dramatic improvements in outcomes in patients treated by PD, such that it is now accepted as an equivalent therapy to hemodialysis (HD). In the last 5 year, CAPD has proven to be as effective a treatment as HD, and in some instances may offer advantages over HD. As we move into the new millennium, it is clear that PD will feature strongly in the care and management of patients in ESRD as advances in the understanding of the pathophysiologic mechanisms and means to combat the adverse effects of PD are put into practice. Currently, there are more than 130,000 patients on PD worldwide, representing approximately 15% of the total world population requiring dialysis. It is anticipated that this number will increase during the next decade, especially in developing countries.

CURRENT OUTCOMES

Several analyses have been undertaken in comparing the outcomes on PD and HD. Nolph[1] analyzed the relative risk of death on PD as compared with HD and by and large found that mortality risk was equal for HD and PD in the various studies reported. Analysis from the Canadian Organ Replacement Registry on patients starting RRT between 1990 and 1994 showed that for incident patients, the survival with PD was better in the first 2 year of treatment compared with HD with subsequently no difference up to 4 year.[2,3] In addition, it showed that there was a significantly lower risk of death in PD patients across all ages, regardless of whether or not the patient had diabetes; for ages 0 to 64 year, the relative risk of death was 0.54 for PD patients without diabetes (for HD, the relative risk was 1) and 0.73 for patients with diabetes. A further comparative analysis from 11 Canadian centers showed that the apparent survival advantage of PD patients was due to lower comorbidity and a lower burden of acute onset end-stage disease at the inception of dialysis; survival was otherwise equal.[4]

More recent analysis of the USRDS data shows similar results: 5 year survival of the 1993 cohort of dialysis patients is identical for PD and HD patients.[5] The analysis on Medicare patients in the United States by Collins et al[6] on the cohort of patients 1994 to 1997 concluded that in the first 2 year of therapy, short-term PD is associated with superior outcomes compared with HD at all ages except in elderly women with diabetes. A further analysis of 17,000 PD patients from the Canadian Organ Replacement Registry database (1981 to 1997) has shown significant decrease in mortality rates during this period.[7] Long-term survival from single center analysis shows no difference at 15 yr between PD and HD patients.[8]

A reasonable conclusion from all this information is that mortality is the same for HD and PD when comparing identical types of patients, at least for the first 3 to 4 yr of RRT. Patient survival

statistics from long-term studies in PD patients during the 1990s show a 50 to 70% 5-year survival.[5,8] It is likely that the results will continue to improve as the various developments outlined below are incorporated into routine practice.

PD to date has proven its utility and has become established in certain areas of care of patients with ESRD. These aspects, which have to be maintained or even further improved in the future, are outlined in Table 37.1.

CURRENT PROBLEMS REQUIRING IMPROVEMENT

Technique Failure and Long-Term PD

If PD is going to achieve wider acceptance, then several outstanding problems that currently detract from greater acceptance need to be overcome. Two major issues are the higher technique failure in PD compared with HD (still related in a third of dropouts to HD to peritoneal infections) and the low rate of achieving long-term PD. The latter is to a large extent related to long-term changes in peritoneal membrane structure and function. In the analysis by Davies, et al[9] technique survival in the seven studies in the 1990s was 30 to 50% at 5 year. The major causes of dropout derived from these analysis are shown in Figure 37.1. The nonachievement of long-term PD is to a large extent related to long-term changes in peritoneal membrane structure and function. Long-term (more than 10 yr) PD is limited to a small percentage of those who start PD,[10] and single-center analysis shows that survival for those who use PD is 20% at 10 year.[8] The major cause of failure in long-term studies is ultrafiltration failure, inadequate solute clearance, and peritonitis.[11] In data from Japan[12] long-term survival from a cohort of 242 patients was for a median of 5.8 year, with patient's failure to respond to this technique related to membrane problems.

Peritoneal Infections

Peritonitis remains a problem and a major source of transfer to HD,[13,14] even though rates have improved dramatically with the advent of technologic improvements related to the disconnect systems.[15] The problem lies in persistent unresolving peritonitis due to *Pseudomonas*, fungal, and to a lesser extent *Staphylococcus aureus* infection.[16,17] At present, there appears no obvious means to prevent gram-negative and fungal infections, and the only option is to develop better therapeutic regimens to improve the outcome of these infections.

For *S. aureus* infection, there is greater reason for optimism. Several studies have shown nasal carriage of *S. aureus* is related to increased exit site infection and peritonitis.[18,19] Prophylaxis with intranasal mupirocin, exit-site mupirocin, or cyclical rifampicin can dramatically reduce not only *S. aureus* exit-site infection and peritonitis, but also infections from other organisms.[20,21] Mupirocin routinely administered to exit sites is now advocated in published guidelines[22] and is likely to favorably affect infection rates and survival.

Patient dropout after persistent peritonitis remains a problem, and those who require catheter removal for cure do not return to PD. More research needs to be done into techniques for safer catheter removal and reimplantation in the presence of persistent peritonitis to avoid interruption of PD. Prevention of adhesions, which are extensive in some patients with persistent peritonitis, is also important.

Peritoneal Access

Transfer of patients to HD for peritoneal access failure is now reduced to approximately 5 to 10% (Fig. 37.2). Access-related dropout is low, and the improvement in catheter-related infections from mupirocin prophylaxis augur well for the continuing improvement in peritoneal infection. The type of catheter and method of implantation are probably less important than the meticulous care taken during implantation and subsequent care with immobilization and exit-site care; these

aspects are reviewed in the catheter guidelines of the International Society of Peritoneal Dialysis.[23]

Adequacy of Solute Removal

In spite of the original description by Popovich, et al[24] and the theoretical work of Teehan, et al[25] suggesting prescription formulations, CAPD has remained standardized to daily 4 × 2-L regimen with little, if any, individualization.[26] This is disconcerting, because such a standard prescription simply cannot be applied to patients of varying size, residual renal function, and peritoneal permeability. It is now clear that a prescription needs to take these three factors into account. Adequate dialysis regimens need to be arrived at by variation in the number, volume, and strength of exchanges and the dwell time of each exchange.

Guidelines on targets for solute clearance have now emerged, the most prominent of which has been the National Kidney Foundation–Dialysis Outcomes Quality Initiative (NKF-DOQI) guidelines.[27] The NKF-DOQI targets are a weekly Kt/V_{urea} of 2.0 and a creatinine clearance of 60 L per week per 1.73 m^2 for CAPD and slightly higher targets on automated PD (APD) regimens. These have been modified to lower the targets for creatinine clearance in low transporters to 50 L per week, in line with the Canadian guidelines; high transporters have a poorer outcome.[28] These have been based predominantly on the Canada-USA study,[29] which showed that the greater the solute clearance at start of dialysis, if maintained over the duration of the CAPD, the better the outcome. Although there is still considerable debate surrounding the evidence for such targets,[30] it is generally accepted that higher target values are desirable and should be achieved if at all feasible.[31] A Kt/V_{urea} of 1.7 and a creatinine clearance of 50 L/wk are absolute minimal targets, and all patients should be above these.

In developing countries, financial constraints have not yet allowed liberalization of prescriptions to meet these targets. However, results from Hong Kong suggest that lesser total daily exchange volumes can produce good outcomes.[32] The new millennium will see more studies and data from these countries to verify the needs of their patients in terms of adequacy and prescription-setting.

Automated PD

One way of achieving increased dialysis is by the use of APD. Use of APD is increasing rapidly indeed, it is the fastest-growing mode of dialysis. APD is a major advantage in patients with a hyperpermeable peritoneal membrane (high transporters) because these patients are unable to ultrafilter adequately on long-dwell regimens and experience fluid overload on standard CAPD. The short-dwell exchanges on APD can overcome the loss of ultrafiltration. Clearly, achieving targets of solute and fluid clearance is likely to favorably affect outcomes.

APD has also major advantages for the patient from the psychosocial point of view, and this is partly the reason for its popularity. In the West, there is a growing trend toward higher targets. These trends reflect the increasing emphasis on adequacy, and the practice of PD is bound to change with this increased emphasis on prescription setting to meet targets of adequacy; variations in the various regimens available to achieve these will considerably facilitate achievement of solute clearance targets. It would be interesting to see how these increased prescriptions are going to affect outcomes.

Questions where controversies exist and where prospective controlled studies are required include the following: (*1*) renal *versus* peritoneal clearances and the equivalence; (*2*) small solute clearance measured via creatinine clearance and Kt/V_{urea}—which is better?; and (*3*) solute clearance targets—are they the same or different for special patient groups, such as patients with diabetes, children, the elderly, and underweight and obese subjects?

PD Growth in India

Peritoneal Dialysis (PD) has come a long way since the introduction of continuous ambulatory peritoneal dialysis (CAPD) as a form of renal replacement therapy (RRT) for end stage renal failure (ESRF) over a quarter of century it has been in existence. There have been dramatic improvements in outcomes in patients treated by PD, such that it is now accepted as an equivalent therapy to hemodialysis (HD). In the last decade, CAPD has proven to be effective a treatment as HD, and in some instances may offer advantages over HD.[33] Currently there are more than 130,000 patients on PD worldwide, representing approximately 15% of the total world population requiring dialysis. The population in India exceeds one billion and is projected to become the reservoir of chronic disease like diabetes, hypertension and *chronic renal failure (CKD)*. However, in the absence of any renal registry, data on incidence of ESRD in India or other countries of south Asia is not accurate. Based on the estimates from tertiary care centre data, and collective experience of experienced nephrologist the incidence rates of ESRD in India probably varies between 150 to 225 per million with diabetic nephropathy as the leading cause of ESRD.[34] Further it has been estimated that less than 10% of all Indian ESRD patients receive any meaningful RRT.

PD has grown in India rapidly in the last five years from 1800 patients to more than 5000 till date. CAPD penetration in India is about 17%. Majority of patients are on twin bag system (Baxter India). Majority of patients are doing 3 exchanges per day. Most of the patients on CAPD in India are within the age group of 40-70 years.

The average survival of PD patients has improved over the past decade and so is the incidence of peritonitis rates among Indian PD patients. Data from an unpublished resource suggest that the first year and two year survival is around 82% and 66% respectively. Total number of peritonitis episodes have gone down by more than 150 % in the last three year (since the data available is for the last three years) from 1 episode in 19 patients month to 1 episode in 36 patient month (source Baxter India). The mortality rates for peritonitis cases have reduced to less than 5% . The main cause of patient being dropped out of the therapy is cardiovascular related deaths among all age groups. Death due to myocardial infarction is still the leading cause of death among patients on peritoneal dialysis therapy. The positive points about PD therapy that have been established beyond doubt include:[30,33]

a. Lower cost than HD, especially in the western world
b. Similar survival to HD , and somewhat superior survival in the first 2 to 3 years
c. Treatment of choice for infants and younger children, especially automated PD
d. Considerable reduction in the incidence of peritonitis (due to disconnect system) and catheter-related infections (exit site treated with mupirocin)
e. Adequate solute clearance in all but the largest anuric patients.
f. Optimum treatment before transplant.

Results of well practiced PD , including training support and proper education to the patients has changed the survival outcomes to a great extent. Majority of patients are now able to continue their routine work while on the PD and quality of life has improved for such patients. With the introduction of new solutions Extraneal an icodextrin based PD solution (Extraneal Baxter) recently in the country, the technique and patient survival on peritoneal dialysis is expected to improve further and will help patients on the PD to achieve their ultrafiltration and improve their fluid balance.

Taking stock of the achievements of therapeutic discipline is a pre-requisite to continuous advancement. Social scientists agree that defining the 'Modern' is the harbinger of the 'Future.' Although North American nephrologists debate the issue of use of PD in the elderly, French nephrologists have been developing a successful model of offering dialysis care for the elderly using PD. The unique voluntary French registry described by Verger, et al illustrate their success in the pioneering implementation of assisted PD, a model of care that is being increasingly recognized as important in some North American circles.

The trend towards greater use of cycler-based therapy in the US is continuing and automated PD is the modern face of the therapy in the US and the world seems to be moving in a concordant fashion with greater use of automated PD becoming a global phenomenon. This is crucial to define patients outcome benefits with automated PD versus continuous ambulatory PD.

While it is firmly established that access-related morbidity and mortality are significantly lower in PD than in hemodialysis, the interest in further improvements in PD does not abate. If applied with dedication and care, this should further widen the advantage gap between PD and hemodialysis. Best demonstrated practices to be followed for optimization of catheter insertion and handling of catheter insertion and handling of catheter-related complications needs to be define. It not only covers familiar territory but also expands the options for patients so that access choice and insertion become more liberating and more appropriate to clinical characteristics, in a word how PD access can become 'personalized'. There is the logistic benefits of using an embedded catheter 'fistula equivalent' for PD for therapy planning, rather than remaining mired in the debate over a medical benefit (i.e., less infections, less leaks, etc.), which may have deprived patients from the benefits of such an approach.

For prevention of infectious complications on PD, the health of the peritoneal milieu and its ability to resist or rapidly clear contamination needs to be kept in mind. Use of a physiologic pH and bicarbonate/lactate solution is associated with lower peritonitis rates.

Use of PD for non-end stage renal disease patients has always been practiced by nephrologists, particularly in the management of congestive heart failure. Most of that recurrent clinical experience remains unpublished, but what has been reported leaves no doubt of the success of the intervention. As rates of severe treatment resistant congestive heart failure rise, there will be more demand of nephrologists participation and use of PD in the arena will rise. Mehrotra and Kathuria from the US and Khalifeh et al from Europe offer two perspectives on the issue of PD in this setting. The wide availability of icodextrin, which offers, sustained gentle ultrafiltration, greatly facilities the application of PD in this setting.

Observational studies had suggested that peritoneal transport characteristics may impact outcomes. Although this suggestion has been seriously challenged by ADEMED and other studies, it lingers from the earlier observations. Davies offers an intellectual breakthrough in this area by illustrating how a solid understanding of transport physiology coupled with the modern instruments of PD therapy (cycler use and icodextrin) can mitigate any influence of transport characteristics on patient outcomes. He presents a scientific framework for 'personalization' of PD where tailored therapy offers success.

The broad issue of metabolic penalty in PD, setting up a PD program, patient centric interventions, novel uses of the therapy, and the promise of genetic exploration are, areas of PD related clinical research. Holmes and Mujais introduce the topic of glucose sparing by offering a specific metric for the success of such an endeavor in the form of the ultrafiltration efficiency calculation. They illustrate the use of this quantifying tool in short and long dwell settings, the putative benefits of glucose sparing, and propose a strategy for clinical implementation of this pivotal concept. This is further expanded by the contribution of Park, et al that describes the use of amino-acid based solution, the determinants of success are the areas of future utility. Managing one metabolic penalty of glucose (hyperlipidemia) is a critical issue in patients on peritoneal dialysis.

In India, a nonavailability of facilities for maintenance HD units, 15 another factor which favors the PD as renal replacement therapy for patients staying in remote rural and urban areas. Establishing and maintaining a successful PD program addresses the rationale for greater utilization of home therapy and defines the elements of success necessary for the expansion. This is needs to be articulated to ensure ethical expansion of home therapy for achieving excellence in patient care in PD.

We need to define modern peritoneal dialysis to the near future. This is not the oracle of Delphi giving obscure generalities into which anything can be read. This is anticipatory planning by investigators who are themselves charting the new course of the science. Genotyping and

phenotyping in understanding and modifying outcomes and open the black box to the light of robust science, a truly inspiring achievement for identifying the modern as a way to chart the future.

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