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CURRENT STATE AND FUTURE TRENDS IN PERITONEAL DIALYSIS*

R. Gokal, Department of Renal Medicine, Manchester Royal Infirmary, Manchester M13 9WL

Peritoneal dialysis is now an established form of renal replacement therapy for patients in end stage renal failure and has grown considerably in importance in the last two decades from its origins as a 'holding' procedure for haemodialysis (HD). The watershed came in 1976 with the introduction by Moncrief and Popowich[1] of the concept of equilibrium long dwell peritoneal dialysis: a technique which subsequently has become known as Continuous Ambulatory Peritoneal Dialysis (CAPD). Since then there has been an explosion of new information, research output and modifications of therapy on all aspects of peritoneal dialysis (PD), but a number of fundamental issues remain to be resolved and these will be discussed.

Current use and outcome results

Estimates put the total number of dialysis patients in the world at the end of 1994 at about 650,000. Of these, 15 per cent (nearly 100,000 patients) are managed on PD; furthermore, the number of PD treated patients throughout the world is steadily increasing at an annual rate of 15 per cent. This increase has been partly related to acceptance onto dialysis of high risk populations (elderly, and those with diabetes mellitus, cardiovascular and multi-system diseases). Diabetes as a primary cause of renal failure now accounts for up to 1/3 of all patients on dialysis programmes: a dramatic increase in recent years as previously diabetes was seen as a contra-indication to renal replacement therapy.

Selection of patients for a particular mode of dialysis should, ideally, be based upon medical, social and patient preference criteria. If this were so then it would be expected that the percentage of patients on the various possible modalities would be similar around the world. However, the utilisation of peritoneal dialysis in various countries ranges from 5 per cent to 90 per cent. Such a vast discrepancy in usage cannot be entirely related to medical, social and patient related factors. In a study by Nissenson *et al.*,[2] five non-medical factors were enunciated—not surprisingly perhaps, the most important reason for modality selection turned out to be financial and reimbursement policies. When physician or facility reimbursement differences were substantial, the utilisation rates varied concomitantly; in countries with fixed annual allocations, PD utilisation was high reflecting its lower costs and diminished maintenance costs as compared to HD facilities. In countries where financial aspects were less prominent, other factors such as physician bias and social mores took on greater importance. There is a higher PD penetration in countries where public money provides the majority of funds for dialysis.

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Patient outcomes on PD

Outcome analysis (using any of the accepted measures such as patient survival, hospitalisation rates and quality of life) is heavily dependent on patient selection, case mix and co-morbidity at the time of starting dialysis therapy. Whilst there are many studies which show that the survival of patients treated by HD and PD is similar,[3,4] these studies all suffer from patient selection biases and are often retrospective. Recent data from the United States, however, give cause for some concern. The United States Renal Dialysis Study (USRDS) data show a higher risk of mortality in patients treated by CAPD as compared to those using HD.[5] In an intention-to-treat analysis of patients on HD or PD (between 1987 and 1989), mortality rates were 21·3/100 patient-years on HD and 25·3/100 patient-years on PD. The all-cause death rate was 19 per cent higher on PD than HD for patients over 55 years of age. The CANUSA study[6] showed a survival at 2 years of 60 per cent (USA patients) compared to 82 per cent in the Canadian population. Lowry *et al.*[7] in the large dialysis data base from the NMC centres found an excess death risk of 32 per cent in PD treated patients compared to those treated by HD. These studies suffer from being either registry data or partially retrospective, not being corrected for major co-morbidities and may incorporate selection biases that are not identifiable. A randomised prospective study would be the only way to answer the question of whether survival is similar using PD and HD.

There is no doubt that most studies show that the rate of transfer of PD patients to HD is much higher than the reverse transfer. The best 'technique' survival studies come from the Italian multicentre and single centre studies[3,8,9] which show roughly a differential at 6 years of about 10 per cent in favour of the HD population. Long term studies in patients on CAPD for greater than 5 years show that only a small percentage of the starting population are still being treated with CAPD,[10,11] the major reasons for this being still peritonitis, psycho-social, catheter-related factors and inadequate dialysis. The latter now accounts for over 25 per cent of total drop-outs to HD. If one is to improve the outcome of patients on PD and routinely achieve long term therapy using PD, then these factors need to be addressed. Currently, a reasonable number of patients are being treated with PD for an excess of 5 years but those who last beyond 10 years are but a handful.

Peritoneal membrane changes

Dobbie[12] has shown that the most significant changes to the histology of the peritoneum over time in patients on PD are diabetiform duplication of the basement membrane of the mesothelium and capillary endothelium, the thickness of which is directly related to the frequency of peritonitis. Changes of fibrosis and sclerosis from peritonitis are indeed well recognised, and severe peritonitis or repeated inflammatory episodes may well be a prelude to sclerosing and encapsulating peritonitis.[13]

However, there is still major concern about the damage to the peritoneum arising from the constant use of unphysiological PD solutions (high osmolality, low pH and glucose as an osmotic agent). It is difficult to ascertain, *in vivo*, the damage that these unphysiological solutions may cause to the peritoneal membrane and to the cells within the peritoneal cavity. *In vitro* data would suggest, however, that the damage is quite substantial.[14] Recent interest has focused on

the production of advanced glycosylated end products (AGE) from the non-enzymatic reaction of proteins with glucose and the possible effect that they may have on peritoneal membrane function.[15,16]

Considerable research has been undertaken to attempt to make PD solutions more physiological. Replacement of glucose with other osmotic agents has been tried. The most promising of these appear to be glucose polymers such as icodextrin: molecular weight 20,000 which are isosmotic to uraemic plasma and capable of producing prolonged ultra filtration (UF) over twelve hours.[17] Amino acids as a replacement for glucose provide another advantage, including acting as a valuable protein source in malnourished patients.[18] The replacement of lactate with bicarbonate solutions (either in two-chambered bags, or with glycylglycine which produces a stable solution and therefore does not require a two chambered bag) may also result in securing a more physiological solution.[19,20] It is possible that the combination of these osmotic agents, together with bicarbonate, could lead to an isosmotic solution with normal pH and an ultrafiltration profile that can be varied to suit the patient's needs.[21]

Several attempts have been made to try and correlate morphological changes in the peritoneal membrane with physiological measurements. Rippe *et al.*[22] have advocated a 3 pore theory with *trans cellular pores* (<5 Å) accounting for the bulk of ultrafiltration (UF) mediated through crystalloid osmotic agents; the identification of a water channel aquaporin[23] is evidence to this theory; *small pores* (40–60 Å) the dominant transcapillary pathway for water-soluble solutes and water, and across which the Starling equilibrium balance between hydrostatic and colloid osmotic pressure is established; and *large pores* (not identified yet) which may represent lymphatic channels. Agents like glucose polymer continue to produce UF because they act at the small pore level.

The most physiological and practical application of transport theories has been the development of the peritoneal equilibration test (PET),[24] which allows the crude classification of the peritoneal membrane transporter status in a patient to high, low or average. This status is linked to the UF capacity and therefore can be utilised to diagnose the cause of UF failure, solute transport failure and, to some extent, prescribe dialysis therapy. Several studies have shown that the D-P creatinine ratio, derived from PET tests, does increase with time indicating the development of a hyperpermeable membrane and gradual loss of ultra filtration capacity;[25] to some extent this is unrelated to peritonitis.

Adequacy of dialysis and nutrition

Inadequate dialysis now represents a major problem for PD and is probably the most vital stumbling block in our attempts to provide long-term PD. Whilst adequacy can be assessed in several ways, the capacity to maintain fluid balance and to remove adequate amounts of solutes now form the usual basis of adequacy assessment. Many studies based on urea KT/V and creatinine clearances have advocated targets to maximise therapy.[26] However, there is still an apparent lack of correlation between the level of solute clearance and clinical outcome.[27] The recent prospective CANUSA study of 680 new patients starting CAPD[6] did show a link between adequacy and outcome. Partly based on this and other reported series, a consensus is developing that a KT/V urea of 1·7 and weekly creatinine clearance of 50 litres should be minimum targets, but higher values (KT/V > 1·9, creatinine clearance > 60) may be more desirable.

There is now also a clear realisation that declining residual renal function has a major impact on the ability to deliver adequate dialysis.[6,26,27] The impact is enormous, not only on survival but also in terms of the nutritional status. Further it is now apparent that inadequate dialysis has resulted from applying a standard 4 × 2 litre per day regime to most patients on CAPD irrespective of weight of the patient, peritoneal permeability status and residual renal function.[27,28] The standard daily CAPD regime of 4 × 2 litres is incapable of providing adequate dialysis for patients over 60 kg who do not have any residual renal function. This limits the applicability of this standard CAPD regime to small individuals or to those with significant residual renal function, which therefore needs to be monitored.

Various techniques may be employed to improve the regime. The ability to increase dialysis 'dose' is limited—a maximum tolerated installation volume should be attempted. If this fails then a change to automated peritoneal dialysis (APD) using a cycling machine is almost inevitable. Various computer programmes are available to aid the prescription of dialysis on APD (various regimes exist—NIPD, Tidal, CCPD, all with alternating 'wet day' or 'dry day'). Some patients, especially low transporters, may need a 'wet day' and in this context, the use of glucose polymers to enhance the UF and solute clearance with a daytime dwell of 12–14 hours would seem to be ideal. It would be pertinent practice to commence these patients on the maximum volume of fluid that they can tolerate at the time of starting CAPD so as to maximise solute clearance. To maintain residual renal function, continuation of frusemide therapy has shown to be of benefit, at least in one long term study.[10]

Malnutrition is a particular problem in CAPD treated patients, with up to 30 per cent or so being mild to severely malnourished.[29] Serum albumin is also a strong predictor of survival in patients being treated by PD[30] and there is again a link between diminishing residual renal function and an increasingly malnourished state.[31] Various ways have been advocated to improve nutrition, including better dietary intake and advice, and the intra-peritoneal use of 1 per cent amino acid solutions has now been shown to be of benefit.[18] Further advances on the horizon are the use of growth hormone and insulin-like growth factors.

Peritonitis and catheter problems

With the increasing use of disconnect systems, peritonitis rates have improved such that the target rate of one episode every 2–3 years should be readily achieved.[32] Many centres now achieve peritonitis rates considerably better than this, and national registries throughout the world have shown positive impacts of disconnect systems. This has had an impact also on technique survival in some centres as well as survival of patients.[4]

However, a much greater problem is that of catheter-related complications and failures.[33] The need for a dedicated expert team of catheter inserters is vital.[33] Various catheter designs have also been employed; it seems that the catheters with a built-in bend or angle (swan neck catheter or the pail neck Cruz catheter) may well prove to be the catheters of choice, although no prospective randomised study data are available.[35] Work by Twardowski *et al*[36] on the morphological changes of the exit site and tunnel have delineated risk factors for infection in these areas. Overall, catheter design, materials, and insertion techniques need to be improved to bring about better results.[34]

Quality of life

With a greater number of elderly and diabetic patients coming on to dialysis programmes, objective and subjective assessment of outcome for patients on dialysis is becoming an important aspect of therapy.[37] Comparative psycho-social adaptation seems to be marginally better on CAPD than on HD,[38] but large and longer term studies from Italy reveal that loneliness, lack of help and patient 'burn out' are major factors contributing to patient drop-out from PD.[8,39] It is evident that social, leisure and sexual activity are seriously affected in up to two thirds of CAPD patients.[38]

CONCLUSION

After nearly 20 years of CAPD therapy there has been a remarkable increase in basic knowledge and encouraging clinical developments that have led to better dialysis for many PD patients. Nevertheless, some areas of major concern remain such as inadequate dialysis, catheter-related problems and quality of life. These need to be addressed as a matter of urgency to allow better therapy to be given to our patients.

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