

Future technologies and techniques in peritoneal dialysis—opportunities and challenges ahead

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Abstract

In the last 5 years, we have started to witness the emergence of new technologies and techniques that offer the potential for improved patient outcomes but which often still lack clinical demonstration and/or confirmation in well-designed, multicentre studies. These include biocompatible solutions, glucose sparing regimens, low-sodium solutions, bimodal solution formulations and continuous flow peritoneal dialysis (CFPD). This review discusses the potential benefits ascribable to each of these technologies and an analysis of the challenges that have to be surmounted before anyone of these candidate technologies can be declared as established. The demonstration of either hard clinical endpoints or validated surrogate endpoints is very feasible in terms of sample size requirements for some outcome measures, such as preservation of RRF, but will be much more challenging for other endpoints such as preservation of UF capacity.

Keywords: future; peritoneal dialysis; technologies; techniques

Introduction

Over the last 3 decades, we have seen the development of many new technological advancements in peritoneal dialysis, beyond the prototypical CAPD prescription, that have provided significant clinical benefit to patients. Salient examples of these established advancements include the introduction of the flush before fill principle, twinbags, topical antimicrobials for exit site care, icodextrin for the long dwell and APD technology. In the last 5 years, we have started to witness the emergence of new technologies and techniques that offer the potential for improved patient outcomes but which often still lack clinical demonstration and/or confirmation in well-designed, multicentre studies. These include biocompatible solutions, glucose

sparing regimens, low-sodium solutions, bimodal solution formulations and CFPD. This review discusses the potential benefits ascribable to each of these technologies and an analysis of the challenges that have to be surmounted before anyone of these candidate technologies can be promoted to the ordained list of advancements in PD declared above.

Biocompatible PD solutions

The scientific literature is replete with a plethora of cell-based *in vitro* assays and animal models suggesting that both glucose and glucose degradation products may play an important role in the longitudinal changes of peritoneal membrane structure and function that is seen in some patients. This subject has been recently reviewed and so will not be discussed in detail here [1,2]. However, it is worth noting that despite the body of suggestive pre-clinical evidence that glucose degradation products *per se* are important mediators of membrane change, to the extent that this notion has become dogma, there still remains an absence of robust demonstration of clinical benefit with low-GDP glucose-based solutions. Ironically, perhaps the best evidence to date of a membrane protective effect with any new PD formulation is with icodextrin from the European Automated Peritoneal Dialysis Outcome Study (EAPOS). In a secondary analysis of this observational cohort of functionally anuric patients treated in 28 centres across Europe, icodextrin use was associated with a membrane protective effect [3]. In this study, patients treated with icodextrin did not experience a decline in UF capacity over the 2-year observation period, unlike the full glucose prescription group and despite starting therapy with worse membrane function.

It is also instructive to realize that another dogma, one that states that all patient's membranes deteriorate over time on PD, is not supported by the literature. At least three large longitudinal studies have now been published that delineate only modest changes in membrane functional parameters in incident patients over the first several years using conventional glucose solutions [4–6]. Scrutiny of these studies portend that randomized clinical trials powered on such modest changes in peritoneal functional parameters will require large numbers of patients to be enrolled and followed up for several years and, thus, may be logistically

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Table 1. Sample sizes for comparing outcome parameters between control and test groups (incident patients)

Outcome parameter	Study duration	Patients/group
UF capacity 50 ml difference @ 5 years SD 200 ml	5 years	750
UF capacity 50 ml difference @ 4 years SD 200 ml	4 years	600
UF capacity 40 ml difference @ 3 years SD 200 ml	3 years	700
UF capacity 40 ml difference @ 3 years SD 260 ml	3 years	1240

80% power with a type 1 error of 0.05, 25% annual dropout.

impractical. To exemplify the challenge, Table 1 provides a sample size scenario chart for incident patients to be able to detect a 40 or 50 mL difference in UF capacity between a biocompatible solution and control. Clearly the sample size varies depending upon the assumptions made for the standard deviation seen in UF capacity in the population under study, the study duration, etc., but even under an optimistic scenario, it can be seen that 700 patients per group would need to be followed up for 3 years.

From the longitudinal membrane function study by Davies [4], it can be observed that, in retrospect, the cohort of patients who developed UF failure clearly had a much more rapidly deteriorating UF capacity over time compared to the rest of the study population. If this population can be better defined at the start of dialysis using modern genotyping or phenotyping techniques, then a randomized control trial will likely much more feasible. The work of Szeto *et al.* is illustrative of the potential of polymorphism analysis for this area, where they have already described two single nucleotide polymorphisms in the VEGF gene associated with longitudinal membrane change [7].

Although biocompatible solutions formulations were not intentionally designed to provide systemic benefits, a reduction in plasma levels of advanced glycation end-products (AGE) has also been reported [8]. This observation in conjunction with an observed preservation of urine output in the same study has led to the hypothesis that low-GDP solutions via a systemic mechanism related to decreased AGE formation may preserve residual renal function in PD patients. Proof of this concept now relies upon the conduct of well-designed and adequately powered clinical trials. The sample size requirements for such a study are less demanding than the above scenarios for membrane function. For example, in order to detect a 30% difference in the rate of decline of residual renal function (RRF) in a population with an average starting RRF of 7 mL/min (which would equate to a difference of 0.5 mL/min after 2 years), a sample size of ~175 patients per group would be required. Clinical evidence to date is restricted to a single centre study has been described in which a significant preservation of RRF was reported with the use of a low-GDP solution [9]. However, the sample size for this study was a total of 31 patients

followed up for 18 months, rendering this an underpowered study and susceptible to statistical error.

Glucose sparing solution regimens

Icodextrin and amino acids are non-glucose osmotic agents that have been used in the clinical management of PD patients for over a decade, at least in some geographical regions. The benefits of improved UF during the long dwell with 7.5% icodextrin solution, and the effect of the amino acid solution on nutritional parameters have been the subject of much research. It has been only of late, however, that the benefits of glucose sparing offered by these formulations have started to be explored. Table 2 provides a summary of more recent clinical observations that suggest that both diabetic and non-diabetic patients may benefit from a glucose-sparing approach, in terms of the PD solutions prescription. By employing icodextrin to achieve a reduction in total carbohydrate absorption while maintaining adequate UF, it appears that a less atherogenic lipid profile can be attained and avoidance of weight gain is often observed versus glucose only patients [10–12]. At least two independent studies have also identified the potential for improving insulin sensitivity [13,14]. In diabetic patients, a well-designed, albeit small study by Marshall *et al.* [15] demonstrated much improved glycemic control with a glucose-sparing regimen, and Johnson *et al.* [16] have reported a preliminary observation of reduced haemoglobin (Hb) A1c, which was recently confirmed in a longitudinal study in Japanese CAPD diabetic patients [17]. Recent research illustrates the numerous avenues for further exploration of glucose-sparing regimens: beneficial changes in plasma adipokine levels [18], glucose and lipid oxidation [19], systemic haemodynamic effects [20,21] and improved gastric emptying [22]. The accumulated experience to date is promising, but clearly there is a need for further well-designed studies to confirm and to extend these observations.

Several alternatives to glucose have been evaluated over the past three decades, and have been reviewed extensively by Van Biesen *et al.* [23]. Aside from amino acids and polyglucose, experience has shown that it is very challenging to identify safe, effective and affordable osmotic agents [24]. Small molecular weight candidates more ideally suited for short exchanges, such as members of the mono or disaccharide or sugar alcohol families have typically suffered from hyperosmolar syndromes due to their rate of metabolism being slower than their absorption rate [24]. Larger molecular weight species, exhibiting colloidal properties, better suited for longer dwells often exhibit accumulation in plasma, liver or RES. A classic example of the latter is hydroxyethyl starch, which despite its potentially attractive oncotic pressure properties, has been shown to accumulate in the liver of patients with renal failure [25]. Therefore, given these challenges, what avenues still exist for future glucose sparing formulations?

It has been suggested by several investigators that the most practical way to maximize UF efficiency and minimize the potential for adverse metabolic consequences with osmotic agents for PD is to rely upon the toxicological principle of dose dependence. That is, the safety

Table 2. Selected clinical outcomes associated with glucose sparing prescriptions

Patient population	Prescription	Observations	Author	Year
CAPD with hypertriglyceridaemia	Icodextrin versus glucose	Significant fall in triglycerides in the icodextrin group only	Sisca	2002
All PD patients	Icodextrin versus glucose	Gastric emptying time significantly shorter with the icodextrin group	Van	2002
All PD patients	Icodextrin versus glucose	No increase in non-fluid weight gain in the icodextrin group unlike the glucose group	Davies	2003
Diabetic CAPD	Icodextrin, amino acids and glucose versus all glucose	Significantly improved glycaemic control	Marshall	2003
All PD patients	Icodextrin and amino acids versus glucose	Improved glucose and lipid metabolism; increased glucose oxidation, decreased lipid oxidation	Martikainen	2005
CAPD patients	Icodextrin versus 3.85% glucose	Increased heart rate, stroke volume and thus cardiac output leading to increased blood pressure during dwell with glucose versus icodextrin	Selby	2005
Non-diabetic patients	Icodextrin versus glucose	Decreased plasma leptin, insulin and triglycerides in the icodextrin group. Increased adiponectin, HDL and improved insulin sensitivity in the icodextrin group also	Furuya	2005
Non-diabetic patients	Icodextrin observational design	Significant decrease over 1-year treatment in HbA1c in >8% HbA1c cohort, significant fall in total cholesterol, LDL and triglycerides	Babazono	2007

of any agent will be minimized with smaller daily doses, and thus, mixtures of osmotic agents are the logical approach. This concept was brought to clinical demonstration by Van Biesen and colleagues in 2004 using a mixture of 0.6% amino acids and 1.4% glycerol [26]. In this small, but well-designed, randomized control trial with 3 months of follow-up control patients used icodextrin for the long dwell and two 2.27% glucose exchange plus a fourth glucose exchange of choice while the test group replaced the two 2.27% glucose exchanges with two of the non-glucose amino acid/glycerol combination. The attractiveness of this approach lies in its ability to reduce the daily amount of absorbed glycerol versus that previously reported with glycerol when used as the sole osmotic agent in clinical studies [23], combined with a daily amino acid uptake that would be well tolerated and similar to a single 1.1% amino acid exchange. Glycerol, when used as the sole osmotic agents has been associated with a greater caloric load than glucose, a hyperosmolar syndrome in a few patients and an apparent increase in plasma triglycerides, although the latter has also been attributed to assay overestimation [23]. The daily mean glucose uptake for the control group in this study was 70.7 g at the 3-month time point versus a significantly lower value of 11.7 g for the amino acid/glycerol test group. Recently, Krediet *et al.* have evaluated the performance of a glycerol/amino acid/dextrose combination solution in a bicarbonate/lactate buffered formulation in a chronic infusion rat model [27]. This solution shows promise in terms of preserving membrane structure, and is reviewed in this supplement.

The concept of osmotic agent mixtures therefore offers a wide variety of options to include osmotic agents that were previously regarded as unsuitable when used as the sole osmotic agent. This is particularly so today, when the long dwell solution also can be icodextrin, which will permit

dialytic removal of a circulating osmotic agent and metabolites thus further reducing the risk of undesirable metabolic effects. As an example, xylitol was evaluated in the 1980s but was abandoned due to concerns over hyperosmolarity, lactic acidosis and hyperuricaemia [28]. An impressive reduction in HbA1c was seen, however, in poorly controlled diabetics, and side effects were only observed in the highest exposure group [28]. Consequently, xylitol is a potential example of an osmotic agent mixture candidate.

As with RRF, endpoints associated with improved metabolic control such as HbA1c, insulin resistance using clamp techniques, improvement in lipid profiles and truncal fat mass, while often requiring operational expertise, are feasible from a sample size perspective. The latter assumes that the control solution regimen is fully glucose based. These assumptions would have to be modified if current non-glucose solutions, such as icodextrin, are widely adopted as the standard of care.

Low-sodium solutions

Much research on the benefits of low-sodium solutions was conducted in the 1990s but did not materialize into a strong clinical need at that time. A new finding on sodium removal was reported in the early 2000s when Rodriguez-Carmona compared sodium removal between CAPD and APD patients in their centre and reported a significantly lower removal of sodium in APD patients as a putative consequence of sodium sieving during the short dwells [29]. The use of icodextrin for the long dwell was reported to overcome this deficiency (Table 3) [30], but despite this there still remains a desire by many clinicians to remove more sodium in all PD patients, to accommodate the high salt intake that still occurs in many patients and to assist in the management of hypertension. It is instructive, however, to review

Table 3. The effect of Icodextrin on daily sodium removal [30]

	Na removal CAPD versus APD (<i>n</i> = 32)			APD pre- and post-ICO (<i>n</i> = 16)		
	CAPD	APD		APD	APD/ICO	
Total peritoneal UF (mls/day)	1310	1067	NS	1228	1450	NS
Na removal long dwells (mmol/day)	37	39	NS	29	58	0.02
Na removal short dwells (mmol/day)	66	21	0.04	64	63	NS
Total peritoneal Na removal (mmol/day)	143	76	0.02	98	148	0.001

the findings from the 1990s studies. Several clinical evaluations on a low-sodium solution were published, mainly with CAPD patients, evaluating a range of sodium concentrations from 90 to 126 mEq/L [31–33]. These studies, in aggregate, established the following: short-term exposure (up to 4 months) is well tolerated, sodium diffuses across the peritoneum slower than that predicted by its molecular weight and the use of low sodium may decrease blood pressure. However, a consistently clear observation was that glucose concentration had to be increased to replace sodium in order to maintain ultrafiltration in the CAPD mode. Consequently, the metabolic ‘penalty’ of a low-sodium solution in CAPD patients, at least, would be an increased glucose exposure to the membrane and glucose uptake if equivalent UF were required. Recent clinical studies with low-sodium solutions in CAPD patients have confirmed these earlier observations [34].

‘Bimodal’ solutions

Several researchers have described the concept of a bimodal long dwell solution that is one that combines a crystalloid and colloidal agent to improve ultrafiltration. The addition of glucose to icodextrin, for instance, was described originally by Mistry and co-workers during the clinical development of icodextrin, and has been pursued clinically in the recent years by Jenkins *et al.* and Freida *et al.* [35,36]. The latter groups have utilized different embodiments of this concept to demonstrate that enhanced UF can be obtained when 7.5% icodextrin solution is supplemented with glucose, thereby capitalizing upon the combination of crystalloid and colloidal osmotic pressure in a single solution. Carbohydrate absorption will naturally be greater during the long dwell with these solutions, although it has been proposed that their utility may be optimal for anuric APD patients, where the total daily carbohydrate absorption will not be higher if these solutions permit the use of 1.36% glucose solution for all short dwells. However, this aspect of bimodal solution performance remains to be clarified. Preliminary analysis suggests that the ultrafiltration efficiency of these bimodal formulations appears to be superior to icodextrin alone in anuric fast transporter APD patients, while the 24-h ultrafiltration efficiency of a bimodal therapy as compared to a conventional therapy regimen is unclear. Consequently, while these formulations show some promise for specific patients sub-groups, it still remains unclear if the additional carbohydrate uptake evident in the

long dwell can be offset by a reduction in the glucose prescription in the short dwell, and thus if there is a benefit over a regimen using icodextrin at higher glucose concentrations for the short dwells. The benefit of bimodals may ultimately lie in the avoidance of membrane exposure at higher glucose concentrations during short dwells.

Continuous flow peritoneal dialysis (CFPD)

CFPD is therapy that has several potential benefits that were succinctly reviewed by Diaz-Buxo in 2004 [37]. These include increased small solute clearances, increased ultrafiltration due to a constantly replenished osmotic gradient, biocompatibility as a result of the lower glucose concentrations potentially employable plus on-line bicarbonate generated dialysate, and finally, if solute clearances and UF were significantly enhanced, a possibility of dry periods throughout the therapy. However, progress has been disappointing for a variety of reasons. First and foremost, the high flow rates of CFPD can only enhance small solute clearances, and in the advent of Ademex, little benefit can be envisioned by using larger volumes of solution as required for CFPD, at a likely increase in cost. As middle molecule clearance is mainly dependent on time, CFPD would not offer an advantage, and certainly dry days would render it an inferior therapy to conventional modes of PD. Ultrafiltration control in CFPD is also technically challenging albeit not impossible—inflow has to match outflow very precisely to avoid large swings in under- or overfill. The technology requires the development of dual lumen catheters that can avoid recirculation of dialysate. Thus CFPD appears to have fallen victim to the adage ‘it seemed like a good idea at the time!’

Conclusions

The potential for improved clinical outcomes in the advent of new technologies in PD is promising, but significant challenges remain in terms of actual demonstration in well-designed multicentre clinical trials. The demonstration of either hard clinical endpoints or validated surrogate endpoints is very feasible in terms of sample size requirements for some outcome measures, such as preservation of RRF, but will be much more challenging for other endpoints such as preservation of UF capacity.

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