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MINIREVIEWS

Increasing the use of biocompatible, glucose-free peritoneal dialysis solutions

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Abstract

A major concern inhibiting some clinicians from embracing peritoneal dialysis (PD) as the preferred first modality of dialysis is the effects of PD solutions on the peritoneal membrane. These anatomical and functional changes predispose to complications like peritonitis, encapsulating peritoneal sclerosis and ultrafiltration failure. In recent years, "biocompatible" and glucose-sparing PD regimens have been developed to minimize damage to the peritoneal membrane. Can the use of these more expensive solutions be justified on current evidence? In this review of the literature, we explore how we may individualize the prescription of biocompatible PD fluid.

Key words: Individualized prescription; Biocompatibility; Peritoneal dialysis; Glucose degradation products; Peritonitis; Ultrafiltration failure; Residual renal function

Core tip: There is increasing evidence of benefit for using biocompatible and non-glucose based peritoneal dialysis (PD) fluids. However, cost remains an impediment and perhaps there are selected groups of patients where the cost can be justified. We suggest that biocompatible solutions should be considered for patients with residual renal function and/or expected to remain on PD for a long period. They are particularly helpful for patients with drain-in pains. The targeting of diabetic patients for non-glucose solutions is intriguing given the recent IMPENDIA/EDEN study although vigilance is required to minimize unaware hypoglycemia. It remains to be seen if PD nephrologists are willing to take the same leap of faith that our hemodialysis (HD) colleagues took when they moved from Acetate-based HD solutions to Bicarbonate dialysate. It is possible that economies of scale will reduce the cost of the biocompatible solutions if we use them more frequently.

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INTRODUCTION

Peritoneal dialysis (PD) has been a popular modality of renal replacement therapy since it was introduced in 1978[1]. In comparison to hemodialysis (HD), PD provides a more gradual and continuous method of fluid and solute clearance, with improved preservation of residual renal function and minimal cardiac stress. PD is at least equivalent in terms of survival benefits in the initial phase of dialysis vintage[2]. Furthermore, PD is more cost effective than HD, especially when reduced erythropoietin stimulatory agent requirement and patient transport cost savings are considered[3].

Common complications of PD include peritonitis, technique and ultrafiltration failure. It has been proposed that newer "biocompatible" and "non-glucose" containing PD fluids can reduce these complications[4]. However, these newer PD solutions are more expensive, and the potential cost advantage of PD over HD may be attenuated. We have reviewed the literature to determine if the additional cost of these newer solutions can be offset by reducing complication rates.

It is generally accepted that conventional PD fluids alter the functional and anatomical integrity of the peritoneal membrane over time[5,6]. Glucose degradation products (GDPs), high lactate and low pH levels have been implicated in the pathogenesis of adverse dynamic changes in the peritoneal membrane[7], which then predispose to complications like peritonitis, technique failure, *etc*[8].

Biocompatible PD fluids are produced in multi-compartmented bags that separately store the acidic glucose solution and the bicarbonate buffer solution. This allows the glucose component to be heat sterilized at a low pH thus causing minimal or no caramelization and GDP generation[9]. At the point of use, the acidic glucose compartment is mixed together with the buffer solution to produce a more physiological pH solution, with minimal lactate and GDP concentrations.

ALTERNATIVES TO GLUCOSE AS OSMOTIC AGENTS

Glucose remains a popular osmotic agent in conventional PD solutions due to its low cost, relative safety and effectiveness. Increasing glucose concentration allows for greater ultrafiltration due to the larger osmotic gradient. However, increasing glucose concentrations also means increased glucose absorption, which may result in metabolic abnormalities like hyperglycemia, hyperinsulinemia, obesity and hyperlipidemia[10]. Non-glucose based osmotic agents such as icodextrin (used in Extraneal solution) and amino acids (used in Nutrineal solution) are often used in glucose-sparing regimens to reduce the metabolic impact of glucose absorption. The icodextrin molecule is large sized and does not cross the membrane easily, thus producing a prolonged osmotic gradient and sustained ultrafiltration. The enhanced ultrafiltration achieved with Extraneal results in better fluid balance with improved blood pressure control[11], and a reduction in left ventricular mass[12].

Nutrineal is an amino acid based PD solution which is generally considered equivalent to a 1.5% glucose bag with respect to osmotic power. Although the pH of the solution is 5.5 (low), it contains no glucose and hence is considered biocompatible. No study has shown any mortality benefit with this solution but improvements in nutritional parameters like albumin, transferrin and protein catabolic rate has been observed in some malnourished PD patients[13,14]. Both these non-glucose based PD solutions are licensed to be used once a day.

COST OF BIOCOMPATIBLE PD SOLUTIONS

Table 1 illustrates the cost difference between the various PD solutions. For convenience sake we have included the trade name of the PD fluids most commonly used in the United Kingdom. The catalogue prices of the non-conventional solutions are approximately 50% more expensive than the conventional ones. In the United Kingdom, based on these catalogue prices, continuous ambulatory PD compromising of daily 4 exchanges (CAPD × 4) of Dianeal would cost £5650/year, but × 2 Physioneal, Nutrineal, Extraneal would cost £10860/year. The incremental cost of switching a patient on automated PD from Dianeal to biocompatible glucose sparing regimen is similar. The cost incurred using 4 cycles of Dianeal (1.5%) overnight followed by last fill Dianeal (2.5%) is estimated to be £9420/year. A switch to 3 cycles of Physioneal, 1 cycle of Nutrineal and last fill Extraneal would cost an extra £5000/year (Table 2).

When extrapolating to a PD program of 150 patients the additional cost of prescribing biocompatible, glucose sparing regimen equates to £0.75 M/year. This calculation is somewhat spurious as it is based the on United Kingdom catalog prices which is not the actual price charged to the National Health Service. Nevertheless, as a comparator, the annual salary of a Band 6 nurse in United Kingdom ranges between £25700 to £34500. These figures present a significant dilemma as the same PD program could possibly employ 20 additional fully trained nurses at equivalent cost of changing to glucose sparing biocompatible fluids.

Table 1 Catalog prices of different peritoneal solutions

	United Kingdom (£)		Singapore ($)		Pakistan (Rs)	
CAPD fluid						
Conventional CAPD 2 litre bag						
Dianeal (1.5%)	3.87		10.66		774	
Staysafe (1.5%)	4.24		10.98		812	
Biocompatible CAPD 2 litre bag	£	Increment (%)	Sing $	Increment (%)	Rs	Increment (%)
Physioneal	7.32	89	12.5	17	1464	89
Nutrineal	8.5	120	14	31	1785	131
Extraneal	6.6	70	12.3	16	1200	55
Balance	4.63	9	12.1	10	1020	26
Automated PD Fluid						
Conventional APD 5 litre bag						
Dianeal (1.5%)	8.6		28		1400	
Sleepsafe (1.5%)	7.8		28		1450	
Biocompatible APD 5 litre bag		Increment (%)		Increment (%)		Increment (%)
Physioneal	12.2	42	39	39	2200	57
Sleep balance	12.5	60	40.5	45	2350	62

Source: Fresenius Dialysis Product Catalogue 2013 revised (United Kingdom, Singapore and South Asia); Baxter PD Product List 2014 (United Kingdom, Singapore and Pakistan). CAPD: Continuous ambulatory peritoneal dialysis; APD: Automated peritoneal dialysis; PD: Peritoneal dialysis.

Table 2 Estimated annual cost of peritoneal dialysis fluids based on United Kingdom catalog prices

	United Kingdom (£)	Increment (%)
CAPD		
Dianeal (1.5%) × 4	5650	-
2 × Dianeal, Nutrineal, Extraneal	8340	48
2 × Physioneal, Extraneal, Nutrineal	10860	92
APD		
Dianeal: 1.5% (× 4 cycles) with last fill of 2.5%	9420	-
Dianeal, Nutrineal, Extraneal: (× 3 cycles 1.5%, 1 cycle Nutrineal) with last fill Extraneal	11790	25
Physioneal, Nutrineal, Extraneal(× 3 cycles 1.5%, 1 cycle Nutrineal) with last fill Extraneal	14420	53

CAPD: Continuous ambulatory peritoneal dialysis; APD: Automated peritoneal dialysis.

EVIDENCE OF BENEFIT AND USE OF BIOCOMPATIBLE PD SOLUTIONS

Faced with the reality of current financial constraints can we individualise the use of biocompatible PD fluids?

The balANZ trial[15] was a large well conducted RCT exploring the clinical benefits of biocompatible solutions. Using biocompatible fluids, a significant 33% reduction in peritonitis rates was achieved although other studies have not yielded similar results. We have to consider if employing additional nurses would be more cost effective than biocompatible solutions in reducing peritonitis rates[16].

The balANZ study also suggested that biocompatible solutions may better preserve residual renal function (RRF). Although the primary end point did not reach statistical significance, the rate of decline of RRF was lower in the biocompatible PD fluid arm and time to anuria which was a secondary end-point did reach statistical significance. The importance of delaying onset of anuria should not be underestimated and would support using these more expensive solutions in patients with residual renal function.

One of the strongest drivers for the use of biocompatible solutions is the hope that PD membrane will be preserved, thereby delaying PD technique failure and reducing the development of encapsulating peritoneal sclerosis (EPS). Dialysate concentration of Cancer Antigen 125 (CA-125) is proposed to be an indicator of peritoneal mesothelial cell health[17]. There is evidence to suggest that biocompatible solutions preserve CA-125 levels, implying that they might prevent peritoneal membrane damage induced by the bioincompatible nature of the PD solutions[18,19]. Those most at risk of EPS may benefit from using biocompatible solutions. The incidence of EPS complication increases with time on PD[20]. There is consensus that EPS is very rare in people who were on PD for less than 3-4 years. The Pan-Thames EPS study[21] showed that more than 70% of the patients who developed EPS had a PD vintage of more than 5 years. If one is to use biocompatible solutions to reduce EPS risk, it should be prescribed at outset of PD. One might argue that elderly patients with high co-morbidity and short life-expectancy are unlikely to develop this complication. Perhaps more controversially, young patients with good match prognosis

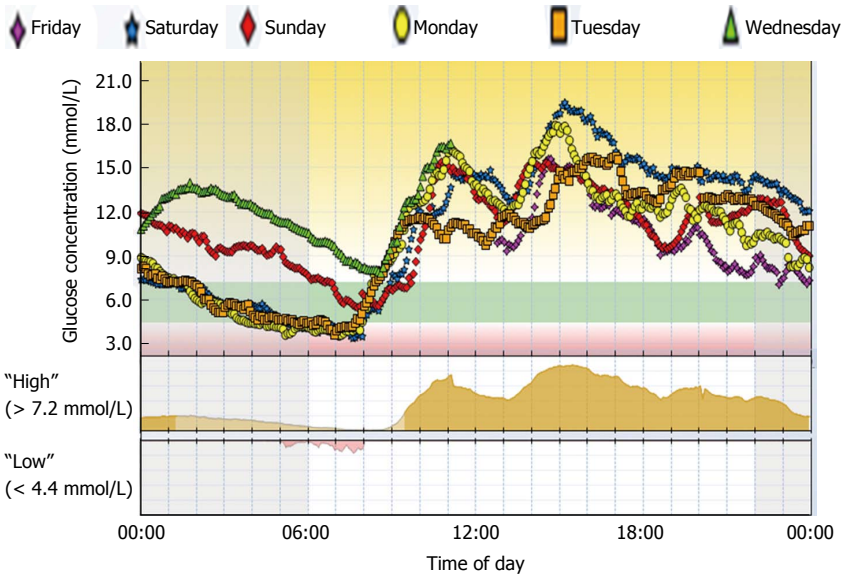

Figure 1 Continuous Glucose monitoring (6 d) of a Diabetic patient on peritoneal dialysis using Extraneal at night (22:00 to 06:00) not only showing hyperglycemia during the day (after 10 am) when glucose peritoneal dialysis solutions used, but also showing significant and regular episodes of hypoglycemia (unaware) suffered by the patient overnight. Continuous Glucose Monitoring demonstrates the merits and risk of using non-glucose based PD solutions (Extraneal). On one hand the overnight Extraneal dwell (from 22:00 to 06:00 h the next day) controlled the blood sugar effectively in comparison to the glucose based PD fluid dwell (from 06:00 till 22:00 h the same day). On the other hand Extraneal is putting the patient at risk of hypoglycemia (between 05:00 and 08:00 h). It is noteworthy that diabetic end stage renal disease patients have an increase incidence of hypoglycemia unawareness. PD: Peritoneal dialysis.

index for transplantation (especially patients with live donors) are also less likely to remain on PD long enough to develop EPS.

Infusion pain with PD fluids is known to affect treatment compliance and quality of life[22]. This pain is ascribed to the low pH of conventional PD solutions and the use of biocompatible PD fluids instead has shown to alleviate this discomfort in a randomized controlled trial[23].

GLUCOSE BASED *VS* NON-GLUCOSE BASED PD FLUIDS

The use of hypertonic 3.86%-glucose bags appears to precede the development of ultrafiltration failure (UF) and impaired osmotic conductance which are important predictors of PD technique failure and EPS[24]. Replacing 3.86% hypertonic solutions with Extraneal would be a reasonable strategy. The role of icodextrin for patients who have high transport characteristics exhibiting UF failure is well established, and recommended in the International Society of Peritoneal Dilaysis guidelines. However, it is not clear if reducing glucose exposure further by substituting Nutrineal for 1.36% glucose solutions will have clinically significant effects on peritoneal membrane preservation. Whilst inadequate solute clearance and ultrafiltration failure are undoubted causes of PD technique failure, patient and carer "burn out" is probably equally important. In this situation, biocompatible solutions will not help but diverting resources to providing more nursing support may be more effective in helping such patients continue on PD.

There are other obvious reasons for minimizing glucose load in the PD solution. Li *et al*[25] (on behalf of the IMPENDIA and EDEN study groups) reported a significant improvement in glycemic and lipid control with the use of glucose sparing PD fluids in the diabetic population. Could better glycaemic control have been achieved through more meticulous diabetic treatment if the additional resources were devoted to providing a comprehensive diabetic service? We suggest an additional caveat: not only should we be concerned about hyperglycaemia but hypoglycemia unawareness might be more dangerous leading to cardiac instability (an association between unaware hypoglycaemia and prolonged electrocardiogram QT-dispersion has been found in non-dialysis patients[26]). Hypoglycaemia unawareness is certainly something that we have found in diabetic patients that undergo routine continuous glucose monitoring. Figure 1 provides an example of diurnal hourly variations in interstitial glucose concentrations in a diabetic patient using nocturnal icodextrin to minimize overnight glucose exposure.

CONCLUSION

It is very ironic to note that HD faced a similar dilemma when a transition from acetate to bicarbonate buffered dialysate was proposed. Prescribing bicarbonate dialysate was equally controversial as it was more expensive and generally all the supportive data came from *in vitro* studies while *in vivo* studies provided very

little support. Nevertheless, a calculated rational leap of faith was taken and over time bicarbonate buffered HD dialysate has become cost-effective. Furthermore, the superiority of bicarbonate over acetate-based buffer was demonstrated during this time. Although we strongly believe in the potential benefits of PD biocompatible fluids, we acknowledge the pragmatic hesitancy of our colleagues due to associated high premium costs. In such a stalemate situation an approach to individualizing the prescription of biocompatible PD solutions is sensible. There is evidence to support its use in selected patients groups such as those with residual renal function with good life expectancy or patients with drain-in pain. The use of non-glucose PD solutions to improve diabetic control is perhaps more controversial but one hopes that cost will fall as uptake of these solutions increase. We are quite hopeful that in the imminent future the story of biocompatible PD fluids will have a similar conclusion to that of the bicarbonate buffered dialysate in HD.

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