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Peritoneal dialysis: The unique features by compartmental delivery of renal replacement therapy

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ABSTRACT

Despite decades of research, the clinical efficacy of peritoneal dialysis (PD) remains enigmatic. We may wonder why the modality fail in some patients but perhaps the more proper question would be, why it works in so many? We know that the contribution of residual renal function (RRF), more so than in hemodialysis, is critically important to the well-being of many of the patients. Unique features of the modality include the relatively low volume of dialysate fluid needed to provide effective uremic control and the disproportionate tendency for both hypokalemia and hypoalbuminemia, when compared to hemodialysis. It is currently believed that most uremic toxins are generated on the interface of human and bacterial structures in the gastrointestinal tract, the intestinal biota. PD offers disproportionate removal of these toxins upon "first-pass", i.e., via PD fluid exchanges before reaching the systemic circulation beyond the gastrointestinal compartment. Studies examining the net removal gradient of protein-bound uremic toxins during PD are scarce, whereas RRF receives considerably more attention without effective interventions being developed to preserve it. We propose an alternative view on PD, emphasizing the modality's compartmental nature, both for its benefits and the limitations.

Introduction

Based on the small solute clearance it provides and after the re-analysis of the National Cooperative Dialysis Study [1], peritoneal dialysis (PD) should not provide what we have come to call "adequate dialysis". Attempts to show the benefits of higher weekly dialysis clearance rates during PD have also failed [2,3]. Historically, the "slow but steady" nature of peritoneal dialysis, providing a more continuous clearance of uremic solutes, and the better preservation of residual renal function (RRF) have been cited as reasons for modality's clinical efficacy. Nonetheless, in the subset of patients without RRF, this apparent discrepancy between a seemingly inadequate small solute clearance and clinical efficacy becomes more striking. A chronic maintenance PD patient who has lost RRF may equilibrate serum creatinine between 10 and 15 mg/dL in many cases. In most predialysis patients, these numbers would translate into a glomerular filtration rate (GFR) of ≤ 5 mL/min/1.73 m^2, a number clearly unacceptable for most stage-5 chronic kidney disease (CKD) patients. Several large clinical trials have challenged the assumed direct correlation between the small solute clearance achieved by peritoneal dialysis and the hard measures of clinical outcomes. Attempts to show the benefits of setting weekly Kt/V targets (> 2.1) are reminiscent of similar efforts in conventional hemodialysis and have proven to be of no benefit [2,3]. Rather, what most of these studies have shown is the enormous importance of RRF beyond the small-solute clearance it provides [2–4]. Yet, clinical experience suggests that many patients live well on peritoneal dialysis even for some time after losing residual function. These patients appear to have adequate volume control and are devoid of uremic symptoms.

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Thus, to paraphrase the late U.S. president John F. Kennedy, we perhaps should not ask why peritoneal dialysis does not work for some people; rather, why does it work in so many? We believe that pursuing this paradox may get us closer to answer this clinical conundrum. It is certainly the time-honored understanding that not all clearances are created equal. While measured GFR performs reasonably well to follow the gradual CKD progression through stage 3–4 range, it becomes unreliable to predict clinical uremia in the very low range (< 15 mL/min/1.73 m^2). In our clinical experience, an intercurrent illness results in increased metabolic activity and catabolic state to prompt clinical uremia in very low estimated (e) GFR states, with a seemingly stable or minutely changed serum creatinine concentration. Despite the early notions which stressed the importance of avoiding high peak concentrations of small uremic toxins in the serum irrespective of how clearance was provided – eventually finding expression in the concept of "standard Kt/V" [5] – the modality effect may be quite important. To explain the apparent discrepancy between the efficiency of small solute clearance and clinical symptoms in PD, one should consider the differential rate of the generation and consequent compartmental distribution of uremic toxins in the body. Uremic toxins are generated disproportionally in various body compartments. While some tissues (muscles, liver) are more active in this regard than others (fat tissue) [6], the single most important site of uremic toxin generation seems to be the interface of human epithelial tissue with intestinal bacterial biota in the gastrointestinal (GI) tract [7]. A pivotal study in end-stage renal disease (ESRD), examining patients with or without a colon, found that colectomized patients had much less uremic toxins generation [8]. Perhaps we should consider viewing PD as a "compartment dialysis" of the visceral organs [9], a modality delivering disproportionately large clearance to the tissue compartments of the gut and liver, the very compartments generating the most uremic toxins. Conceptually, this compartment effect may in fact be the largest contributing factor explaining prevention of clinical uremia during PD. Based on this theory we believe this compartment effect would be partially disengaged (albeit not fully disconnected) from the modality's ability to provide small solute clearances, including removal of urea and creatinine. We think this conceptual difference is woefully unexplored and likely to explain the unique effectiveness of PD despite limited small solute clearance. The quantitative removal of various unconventional markers of uremia such as uric acid, p-cresol, oxalic acid or other indoles in the PD fluid compared to serum levels has not been studied so far. On the contrary, hemodialysis (HD) could be viewed as a "blood space compartment dialysis" or "vascular compartment dialysis," providing disproportionate clearance of the intravascular space and equilibrating with the rest of the extracellular space with some delay. This arrangement is dependent on equilibration rate of uremic toxins between compartments relative to the rate of solute removal. Accordingly, the success of HD will be contingent upon hemodynamic stability making the equilibration between compartments possible. Net ultrafiltration, the effort to remove the excess fluid accumulated between HD sessions will potentially compromise overall circulation volume and blood pressure. Intradialytic hypotension, one of the most frequent adverse effects of HD, is expected to negatively influence uremic toxin equilibration and as well the life-span of RRF.

Albumin loss through peritoneal dialysis – a foe or a friend?

Hypoalbuminemia in PD can be a result of protein loss through urine or malnutrition [10], similarly to, though worse than chronic maintenance HD [11]. The more recent interpretation of low albumin as a negative inflammatory marker [12–14] emphasizes the need for adequate control of uremia and the maintenance of RRF [4]. PD also has a unique feature when compared with intermittent HD: the inevitable loss of albumin in the PD fluid. Historically, albumin loss in PD has been viewed exclusively only in negative terms. However, protein loss via PD may be linked with more effective removal of larger molecular weight or protein-bound toxins. Hence, the meaning of hypoalbuminemia may be different in PD patients compared to HD patients, where the association between hypoalbuminemia and mortality is defined at a different cut-off point and an alternative process with albumin loss is taking place, as well. We do not argue that hypoalbuminemia is not disadvantageous in PD; in fact, the contrary is true in PD as well [4]. Rather, albumin loss – as long as the synthesis of the new albumin is unimpaired and plasma levels are reasonably maintained – offers an unconventional "sink" to remove protein-bound uremic toxins from the GI compartment before reaching systemic absorption. To state it differently, PD patients achieve similar survival compared to HD patients despite lower albumin values. In our clinical experience, some of the most severe hypoalbuminemia we have witnessed took place in patients with hepatic vein thrombosis, leading to portal hypertension and increased albumin filtration gradient without necessarily impairing the albumin synthesis. Another good example would be the large albumin loss with cirrhotic subjects with PD – yet survival will be better than on HD [15,16]. An unexplored area of interest for future research may be colloid PD solutions affording targeted binding and removal of uremic toxins from the gastrointestinal compartment.

Peritoneal dialysis and hypokalemia

Compared to their peers on HD, otherwise stable patients on PD have another unique feature, i.e., a general tendency for hypokalemia [17–20]. Such tendency is not without clinical relevance as hypokalemia is a risk factor for mortality in ESRD patients on dialysis as well [17,18], perhaps to a greater degree than hyperkalemia. Hypokalemia may also pose a risk for peritonitis by slowing GI motility [18,21,22]. While the etiology of hypokalemia is insufficiently explored in this context, malnutrition [20,23,24] and poor nutritional intake of potassium [17] are generally thought to be contributing. The fact that hypokalemia in PD often remains recalcitrant to dietary intervention suggests that, in addition to poor intake, enhanced potassium loss may also be important in the pathophysiology. While PD fluids are customarily potassium-free, this alone is clearly insufficient to provide an explanation for hypokalemia in the subjects. Take, for example, the case of a patient on continuous ambulatory PD and significant hypokalemia (3 mEq/L). Assuming a customary regimen of 2-liter exchanges 4 times a day, a maximum daily net removal would be only $8 \times 3 = 24$ mEq! As oral potassium supplements are poorly palatable, and patients' long-term acceptance is limited, potassium-sparing diuretics may provide a viable alternative to combat this phenomenon. Aldosterone is known to enhance both renal and colonic potassium secretion [25]. In this context, it is interesting that we [26] and others [27–29] have demonstrated excellent safety and efficacy of potassium-sparing "diuretics" to normalize serum potassium in these subjects. At this juncture, it is unclear how enhanced potassium loss through the peritoneal membrane may affect the dynamics of solute clearance in PD; therefore, this potential relationship deserves further exploration.

Peritoneal dialysis and calcium metabolism

Surgical parathyroidectomy (PTX) is commonly performed for therapy-resistant secondary and tertiary hyperparathyroidism in ESRD patients [30,31], with post-PTX hypocalcemia being a common occurrence [32]. After surgical parathyroidectomy, PD patients' ability to respond to significant calcium (Ca)-losses into bone compartment ("hungry bone syndrome") is compromised in comparison to HD patients. Conceptually, there may be a disproportionate tendency for hypocalcemia after PTX for those patients undergoing PD compared to HD, assuming identical net bone compartment Ca-influx. While HD can be viewed as a highly effective "electrolyte clamp", albeit of limited duration, effectively delivering seemingly limitless amounts of Ca across gradients, PD is limited by the amount of Ca available in the exchange fluid. During hemodialysis, a large amount of blood is