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Peritoneal dialysis beyond kidney failure?

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ABSTRACT

Compared to extracorporeal modalities, peritoneal dialysis (PD) is less invasive and more cost-effective, wherein blood is dialyzed intra-corporeally against a solution instilled in the peritoneal cavity. Although PD is mainly indicated for patients with end-stage renal failure, it has also been used for several non-renal indications. The aim of this review is to provide an overview of the role of PD beyond kidney failure. The alternative indications of PD include hypothermia, congestive heart failure, hyperammonemia and poisoning with xenobiotics. The use of PD as a treatment for acute pancreatitis and psoriasis was initially proposed but could not be established; these indications are therefore classified as historically relevant. Recent developments have led to a potential application of PD during the management of stroke and as an oxygenation therapy with the use of oxygen carriers. Novel colloid-based dialysates with improved functionality with respect to detoxification and oxygenation are currently underway, though their efficacy has so far only been demonstrated in pre-clinical settings. Finally, insight into potential future developments of PD is given. Characterization studies are proposed to better understand the fate of non-recovered carriers following dialysate removal, their efficacy following multiple administrations and potential immune response to optimize their formulation, enabling their clinical translation.

1. Introduction

Peritoneal dialysis (PD) is an intra-corporeal, life-sustaining therapy by which blood circulating in the peritoneal membrane is dialyzed against a large fluid volume (*i.e.* the dialysate) that is instilled into the peritoneal cavity and left to dwell. Effective exchange of fluid and solutes is enabled by the large area of the highly vascularized peritoneal membrane [1], exposed to the dialysate containing an osmotic agent (often glucose) [2–4]. The PD solutions are categorized as drugs by health regulatory agencies [5] and therefore, the development process of a new PD fluid is long and costly.

The first human application of PD was described by Georg Ganter in 1923 for the treatment of uremia, at the same time as the early reports of hemodialysis (HD) [6,7]. Unlike HD, where patients are connected to an extracorporeal circuit and dialysis machine and require the administration of anticoagulants, PD does not require sophisticated equipment nor specialized centers, permitting simple and easy to implement daily home dialysis and access to treatment in less endowed environments [5,8]. A number of technical innovations have led to major developments in the clinical use of PD for the treatment of end-stage renal disease (ESRD). In a recent outcome study, these improvements resulted in a significant reduction in the mortality risk for patients starting with PD, and a similar survival rate as patients subjected to in-center HD [9]. The less invasive nature of PD favour its use over HD, especially in the pediatric population, where PD is the preferred dialysis modality given the large extracorporeal circuit volumes implied in HD [10,11]. Moreover, recent evidence indicating the lower societal costs and relative underutilization of PD [8] has prompted various governmental policies to encourage its use [12,13].

Traditional dialysate formulations employ glucose as a crystalloid osmotic agent. However, with repeated dialysis treatments, glucose and its degradation products can cause structural changes in the peritoneal membrane by local exposure [14–16]. Furthermore, the rapid absorption of glucose leads to an early disemination of the osmotic gradient and can cause adverse metabolic and cardiovascular effects, thereby limiting long-term PD [16,17]. The rapid absorption of glucose may be countered by shorter dwells using a cycling machine as in automated PD [18]. Alternatively, glucose can be replaced by other osmotic agents. The use of icodextrin, a high molecular weight glucose polymer and colloid osmotic agent, has improved PD formulations notably as it allows prolonged dwell time with sustained ultrafiltration (water removal) given its enhanced peritoneal retention [16,19]. Recent PD fluids under investigation include a hyperbranched polyglycerol-based solution [20] and a glucose-based solution supplemented with the cytoprotective dipeptide AlaGlu [21]. Solutions employing hyperbranched poly(glycerol) as an osmotic agent demonstrated more

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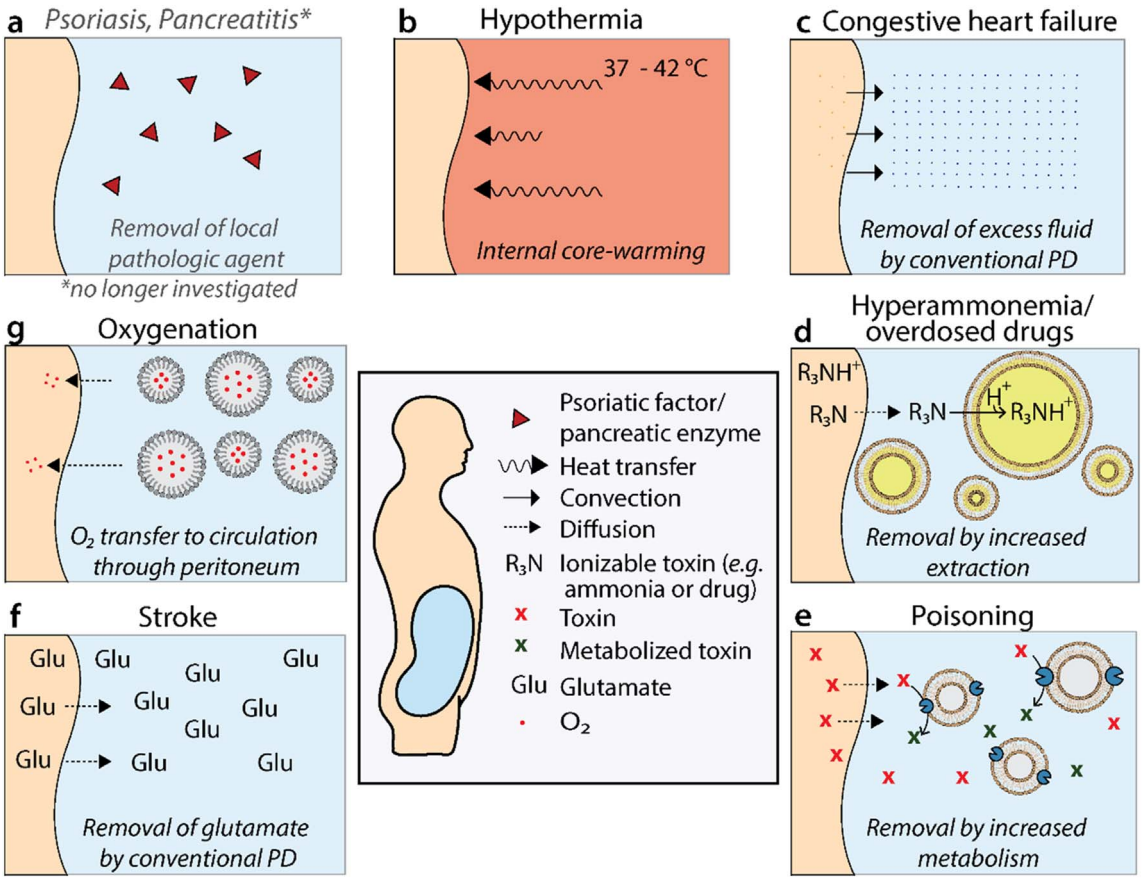

Fig. 1. Overview of PD's role during the management of non-renal indications. (a) Even though PD is no longer utilized as a therapeutic measure for psoriasis and pancreatitis, it has been suggested to act by clearing so-called psoriatic factors or trans-/exudated pancreatic enzymes from the peritoneal cavity. (b) In cases of severe hypothermia, dialysate fluids warmed to 37–42 °C can be administered for internal core-warming. (c) During the management of congestive heart failure, fluid overload is combated by removing excess fluid by convection driven by an osmotic force. (d) Hyperammonemia and poisoning can be treated by conventional PD, where endogenous and exogenous toxins are removed by diffusion. The functionality of these formulations can be augmented by supplementing conventional PD fluids with transmembrane pH-gradient liposomes to concentrate ionizable compounds within the liposomal core. (e) Alternatively, enhanced toxin metabolism can be achieved by supplementing PD fluids with liposomes loaded with specific toxin metabolizing enzymes. (f) Conventional glucose-based PD solutions have been shown to effectively reduce the infarct volume by increasing the brain-to-blood efflux of glutamate. (g) The peritoneal cavity can be used as an oxygenation organ by administering dialysate solutions constituting of OMBs.

effective fluid and waste removal, as well as superior peritoneal membrane preservation compared to a glucose-based dialysate solution in rodents [20,22,23], but their clinical characterization is still pending. AlaGlu-supplemented PD is currently being investigated by Zytoprotec under the trade-name PD-protec®, with which a first-in-man trial (NCT01353638) and Phase II study (EudraCT 2013-000400-42) have been successfully completed, demonstrating a reduced risk of peritoneal membrane failure and peritonitis [24,25].

Although PD is mainly indicated for the management of patients with ESRD, this technique has also been explored for the primary treatment of other conditions [26,27]. This review will provide an overview of PD's relevance during the management of non-renal indications with an emphasis on the administered dialysate formulations and strategies to increase the functionality of PD whenever pertinent (Fig. 1). The encompassed indications tested for PD treatment have been classified as either historically relevant, currently relevant or as potential future applications. The use of PD in ESRD as well as the peritoneal route for the administration of drugs have been discussed in depth in recent reviews [9,28–30] and will not be covered here.

2. Indications historically tested for treatment with conventional PD

2.1. Psoriasis

The therapeutic benefit of dialysis during the management of psoriasis was first described in the late 1970s and 1980s following the spontaneous improvement of psoriatic lesions in comorbid patients undergoing dialysis [31–33]. These observations prompted the initiation of clinical studies to investigate the underlying mechanism. A higher therapeutic benefit was accredited to PD compared to HD [34,35], which was further improved with multiple dialysate exchanges [32]. The underlying mode of action was hypothesized to involve the clearance of a psoriatic factor by dialysis (Fig. 1a) [36].

Glinski et al. [36,37] suggested the dependence of psoriatic lesions clearance on the removal of peritoneal polymorphonuclear leukocytes (PMNL), which were found to carry high levels of serine proteases capable of destructing the stratum corneum. A follow-up study by the same group confirmed the regression of psoriatic lesions by PD and leukopheresis, a procedure by which leukocytes are separated from the blood, supporting the involvement of cleared PMNLs [38]. However, when performed by another group, only moderate improvements of psoriatic lesions could be detected with leukopheresis [39]. Conversely, recent reports have described the emergence of psoriasis in patients undergoing PD for renal insufficiency [40]. To date, the connection