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Invited critical review

Peritoneal dialysis and inflammation

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ABSTRACT

Peritoneal dialysis (PD) is a kidney replacement therapy for end stage renal disease (ESRD) patients. Despite being a lifesaving treatment, the rate of mortality in patients under PD is elevated, mainly due to the chronic peritoneal dysfunction which is characterized by inflammation, peritoneal fibrosis and neoangiogenesis. The inflammatory process is trigged and modulated by the type of the peritoneal dialysis solutions (PDSs) used during PD. Currently, different PDSs are commercially available: (i) the conventional solutions; (ii) solutions of neutral pH containing low concentration of glucose degradation products (GDPs); (iii) solutions with icodextrin; and (iv) solutions containing taurine. Therefore, the aim of this review is to describe the different types of peritoneal dialysis solutions used during PD and their relationship with systemic and intraperitoneal inflammation. Some studies suggested that solutions of neutral pH containing low concentration of GDPs, icodextrin and taurine have better biocompatibility and lower influence on the inflammatory process compared to the conventional one. On the other hand, the studies, in general, were performed with a small population and for a short period of time. Therefore, further well-designed and -controlled clinical trials with larger number of individuals are required in order to better understand the role of different peritoneal dialysis solution types in the development of inflammation in patients with chronic peritoneal dialysis.
Accordingly, studies that are more well-designed, well-controlled and with a larger number of patients are needed to explain and define the role of different types of PDS in the inflammation development in patients with chronic peritoneal dialysis.

Contents

1. Introduction

Peritoneal dialysis (PD) is a kidney replacement therapy for patients with end stage renal disease (ESRD). It is based on the properties of the peritoneal semipermeable membrane [1]. PD requires an infusion of a dialysis solution into the peritoneal cavity to enable ultrafiltration (UF) and solute transport across the peritoneal membrane [2]. According to the Kidney Disease Outcomes Quality Initiative (KDOQI) (2006) the dialysis is recommended when the patient reaches stage 5 of chronic kidney disease (CKD) characterized by a glomerular filtration rate (GFR) lower than 15 mL/min/1.73 m^2 associated with clinical signs of malnutrition, overloaded volume unresponsive to diuretics, or other signs and symptoms attributed to uremia. Particular clinical

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considerations and specific complications of kidney failure may prompt initiation of the therapy before stage 5 [3].

PD removes accumulated solutes such as urea, creatinine, potassium, phosphate, and water from the blood to the peritoneal dialysis solution (PDS). The peritoneal membrane (PM), functioning as a similar dialyzer, regulates the exchange of water and solutes between the interstitial capillaries and PDS [4]. The capability of the PM to transport solutes and its ability of ultrafiltration in PD patients are evaluated by the peritoneal equilibration test (PET). PET is a semi-quantitative approach to assess the transport capacity of the peritoneal membrane. It is determined by measuring the creatinine and glucose concentrations over the time in both plasma and dialysis solution [5]. This test classifies patients into four categories: (i) patients with high peritoneal solute transfer rates which are likely to have inadequate ultrafiltration to standard PD; (ii) patients with high-average peritoneal solute transport that are responsive to standard PD even after losing residual renal function; (iii) patients with low-average and particularly (iv) patients with low peritoneal transport who are likely to develop symptoms and signs of inadequate dialysis to standard PD, and may require high-dose peritoneal dialysis prescriptions [6].

Similar to the hemodialysis process, the rate of mortality in patients under peritoneal dialysis is elevated despite all recent technological improvement developed in this field. Although there are several factors associated with mortality in PD patients, one of the most important is inflammation [7]. Long-term peritoneal dialysis promotes chronic inflammation process, such as that related to catheter access infections, dialysate contamination, inadequate dialysis, high concentration of uremic toxins, release of plastic materials, and bioincompatibility of dialysis solution, mainly due to the high glucose concentration, to the acidic pH (~5.5) and to the lactate used to correct the metabolic acidosis [8].

Inflammation related to the use of PDS is normally followed by peritoneal fibrosis and neoangiogenesis. Thus, augmentation on the transport of small solutes is observed leading to UF failure over the dialysis treatment time [2,9]. However, how these changes in the peritoneal membrane are regulated remains to be unveiled [10].

The toxicity related with the sustained use of conventional peritoneal dialysis solution stimulated the discovery of alternative PDSs with higher biocompatibility and lower risk peritoneal membrane (PM) damage [2]. Biocompatibility can be characterized by the ability of PM to remain functional and without significant clinical alteration even after a long period of treatment [11].

The PDS can be divided into four major groups: (i) the conventional solution group, bioincompatible; (ii) the group with reduction of glucose degradation products and neutral pH; (iii) the group with the osmotic agent icodextrin replacing the glucose; and (iv) the group with the amino acid taurine instead of glucose as an osmolite. See Table 1 [12].(See Table 2.)

Considering the role of inflammation and its prevalence of approximately 61.9% among PD population including the clinically stable patients, we aim to describe the different types of peritoneal dialysis solutions available for clinical use and their relationship with systemic and intraperitoneal inflammation in this review [13,14].

2. Inflammation related to conventional PDS

Conventional PDS contains high glucose and lactate concentrations as osmotic gradient enhancer and buffering agent, respectively [15]. The concentrations of glucose are between 1.5% and 4.25% through 2.3% and 2.5%.

Glucose is the main factor of bioincompatibility of the conventional PDS due to its direct metabolic effect of hyperosmolarity. Additionally, the chemical instability of glucose during sterilization by heat and storage generates elevated concentrations of toxic GDPs (methylglyoxal, glyoxal, and 3-deoxyglucosone) increasing the deleterious effects of PDSs [2,9].

Chronic exposure to high glucose load in conventional peritoneal dialysis solution induces significantly the inflammation state of the PM. This type of solution stimulates the production of several pro-inflammatory factors such as: vascular endothelial growth factor (VEGF), fibroblast growth factor or transforming growth factor-β (TGF-β) and advanced glycation end-products (AGEs) that induce an upregulation of the receptors for AGE (RAGEs) [16]. Together, these factors contribute to the occurrence of neoangiogenesis and mesothelial fibrosis. Additionally, glucose degradation products intensify the inflammation through induction of oxidative stress, which thus causes damage to human peritoneal mesothelial cells (HPMCs), finally leading to apoptosis and mesothelial denudation [16].

During the PD with conventional peritoneal dialysis solution, GDPs' diffusion from the peritoneal cavity to the systemic circulation results in the loss of human peritoneal mesothelial cells' viability and function [17] and also in the formation of AGEs in the blood [18]. The high concentrations of glucose degradation products which are advanced glycation end-product precursors trigger an inflammatory response in PM inducing the HPMC apoptosis [19] and fibrosis of the peritoneum submesothelial layer. The binding of AGEs with their receptors increases the production of TGF-β [20].

Vincent et al. [9] evaluated the peritoneum histomorphological changes of mice using the conventional solution with 4.25% glucose. The authors observed mesothelial cell transformation prior to cubic and submesothelial layer thickening of the parietal peritoneum. These peritoneal alterations begin with mesothelial and submesothelial changes, and culminate with peritoneal fibrosis and vasculopathy. After months or years of PD in humans, fibrosis is almost a constant finding. Furthermore, another study also suggested the changes in the

Table 1
Characteristics of PDS (adapted from [12]).

	Conventional PDS			Low-GDP PDS				Icodextrin
	CAPD	Dianeal	Gambrosol	Bicavera	Balance	Gambrosol TRIO	Physioneal	Extraneal
Sodium (mmol/L)	134	132	132	132	134	132	132	132
Chloride (mmol/L)	102.5	102/96/95	96/95	104.5	100.5	96	101/95	96
Calcium (mmol/L)	1.25/1.75	1.75/1.75/1.25	1.75/1.35	1.75	1.25/1.75	1.75/1.35	1.75/1.25	1.75
Magnesium (mmol/L)	0.5	0.75/0.75/0.25	0.25	0.5	0.5	0.25	0.25	0.25
Glucose (%)	1.5/2.3/4.25	1.36/2.27/3.9	1.5/2.5/4.0	1.5/2.3/4.25	1.5/2.3/4.25	1.5/2.5/3.9	1.36/2.27/3.86	0
Osmolarity (mOs/L)	356–509	344–486	353–492	358–511	358–511	356–483	344–484	284
Lactate (mmol/L)	35	35/40/40	40	0	35	40	10/15	40
Bicarbonate (mmol/L)	0	0	0	34	0	0	25/25	0
PH	5.5	5.5	5.5	7.4	7	5.5–6.5	7.4	5.5
Formaldehyde (mmol/L)	5.4 ± 0.4	6.8 ± 0.2	6.4 ± 0.5	<3.3	<3.3	<3.3	3.4 ± 0	3.6 ± 0.7
3-DG (mmol/L)	142 ± 0.8	167 ± 0.3	175 ± 4	163 ± 0.2	17.6 ± 0.3	20.2 ± 2.4	93.3 ± 5.0	7.5 ± 0.4
3,4-DGE (mmol/L)	16.2 ± 0.8	11.3 ± 0.5	13.1 ± 1.1	<2.4	<2.4	<2.4	14.3 ± 2.5	<2.4

DG = Deoxyglucosone; 3,4-DGE = Di-Deoxyglucosone-3-ene.