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Conventional versus biocompatible peritoneal dialysis fluids: more questions than answers?

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Abstract

The most important challenge in peritoneal dialysis (PD) is long-term preservation of peritoneal membrane structure and function. Introduction of dialysis fluids into the peritoneal cavity induces changes. These changes are related to duration of dialysis, occurrence of peritonitis and components of the dialysis solution. Bioincompatibility is considered to be the major cause of the development of morphological changes of the peritoneal membrane. pH neutral PD fluids that are low in glucose degradation products (GDP) seem to better preserve the peritoneal membrane and have less systemic effects than the conventional ones. However, the long-term effects are not clear. An overview of the effects of conventional PD fluids and glucose-based PD fluids with neutral pH in *ex vivo* and *in vivo* animal and clinical studies is presented.

Keywords: biocompatibility; peritoneal dialysis fluids; peritoneal dialysis

Introduction

Today, about half of the patients who have received predialysis care choose peritoneal dialysis (PD) as their first dialysis modality [1]. Besides personal preferences, in the first 2 years, PD preserves residual renal function (RRF) better and possibly has a better patient survival [2]. However, long-term technique survival of PD is poor because of technical problems and peritoneal membrane failure; the latter is considered to be a consequence of bioincompatible characteristics of PD fluids. Therefore, the most important challenge in PD is long-term preservation of peritoneal membrane structure and function. Several studies have shown that introduction of dialysis fluids into the peritoneal cavity induces changes, ultimately leading to 'membrane failure'. Features of membrane failure include malfunction of local host defence mechanisms, signs of peritoneal sclerosis and neovascularization resulting in ultrafiltration failure (UFF). UFF remains one of the most important reasons for treatment dropout. The cumulative risk of UFF was reported to be 3% after 1 year and 40% after 6 years [3]. The incidence of UFF seems to increase with time on PD [4].

The above-mentioned observations in humans have been studied in more detail in animals: chronic daily instillation of conventional PD fluids leads to an angiogenic response in the omentum, mesentery, liver surface and parietal peritoneal wall [5–8]. In addition, detachment of the mesothelial cell layer, submesothelial extracellular matrix deposition and fibrotic alterations [9,10] were described after exposure to these dialysis solutions. These changes are related to duration of dialysis, occurrence of peritonitis and components of the dialysis solution. Although bioincompatibility, in general, is considered to be the major cause of the development of morphological changes of the peritoneal membrane ultimately resulting in UFF, the major culprit is not known. Conventional dialysis fluids are acidic (pH 5.5), contain supraphysiologic concentrations of lactate (35–40 mmol/L) and have a high osmolality (347–486 mosmol/kg H_2O) as a result of high glucose concentrations (75–215 mmol/l) that, after heat sterilization, turn into glucose degradation products (GDP). Which of them is most harmful remains the question. New PD fluid formulations have become available: they have different osmotic agents and buffers such as glucose polymer-based and amino acid-based PD fluids. This report focuses on the effects of conventional PD fluids and glucose-based PD fluids with neutral pH.

In vitro and ex vivo studies: effects of PD fluids characteristics on mesothelial cells and defence

Cells that are continuously exposed to dialysis fluids are mesothelial cells and (in part) macrophages. A majority of data on the *in vivo* effect of PD fluids are derived from *ex vivo* measurements of effects of PD fluids characteristics on cell function.

In a number of studies with animal and human mesothelial cells, apoptosis was observed after incubation with PD fluids [11–13]. This indicates an imbalance between proliferation and apoptosis of mesothelial cells. The characteristic or combination of characteristics in PD fluids that was responsible for the imbalance in these studies remained unclear.

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The low pH and high osmolality in PD fluids have an inhibitory effect on proliferation of mesothelial cells and their functions because of the production of cytokines and prostaglandins [14]. Adding fresh PD fluid to residual PD fluids with normal pH within the peritoneal cavity resulted in a pH value of 7 after ~10 min [15]. In an *ex vivo* experiment, the combination of low pH and high concentrations of sodium lactate in PD fluids did result in suppression of respiratory burst activation, a cell host defence mechanism, which is not because of either low pH or lactate concentration alone [16]. Inhibition of the respiratory burst activation was related to the extreme sensitivity of NADPH oxidase to low intracellular pH. This was reduced to >70% at pH 5.0. In this situation, the presence of lactate and glucose can lead to pseudo-hypoxia. These findings suggest that the clinical importance of low pH alone might be overestimated and that other factors are more important. The high osmolality in PD fluids is mainly because of glucose concentrations. Glucose inhibits proliferation of human mesothelial cells in a dose-dependent way [17]. Other hyperosmotic solutes, which were used in the same concentrations as glucose (mannitol and glycerol), did not decrease proliferation of the mesothelial cells as much as glucose did. This implies that the toxicity on proliferation of the mesothelial cells depends not only on the hyperosmolality but also on some metabolic effects. Basal cytotoxicity *in vitro* tests on PD fluids show that all major commercial brands of PD fluids are cytotoxic to cell proliferation, ranging from 53 to 75% inhibition of cell growth. This was found to be as a result of GDP and not because of interference with the PVC plastic of the bag as previously thought [18].

As the combination of low pH, lactate and the presence of GDP in PD fluids seems toxic to mesothelial cells, experiments were conducted with fluids that might be more biocompatible, such as isosmolar solutions with glucose polymers. These solutions show better phagocytic capacity for common peritonitis-causing bacteria, and a significantly higher chemiluminescence response was found [19]. Other studies demonstrated that exposure to solutions that consisted of a combination of lactate and bicarbonate buffer was less cytotoxic to the migratory capacity of normal human polymorphonuclear granulocytes. Bicarbonate and lactate alone reduce cellular function [20,21]. Bicarbonate/lactate-buffered PD fluids also improve *ex vivo* peritoneal macrophage TNFα secretion, which might improve host defence status [22].

Recent *ex vivo* findings suggest that human mesothelial cells not merely suffer, but are partly culprits for peritoneal injury. In long-term PD, new fibroblast-like cells arise from local conversion of mesothelial cells, which invade the submesothelial tissue and contribute to peritoneal fibrosis and angiogenesis. This can ultimately lead to peritoneal membrane failure [23].

Thus, the combination of low pH, lactate and the presence of GDP in PD fluids seems cytoxic to and weakens defence mechanisms of mesothelial cells in *ex vivo* and *in vitro* studies.

Animal studies: effect of PD fluids on mesothelium and peritoneal membrane

To avoid limitations of *in vitro* studies, animal models of PD have been developed. Rat, rabbit and occasionally mouse models have been used to examine physiological effects of PD fluids on mesothelium and the peritoneal membrane.

Mesothelium

Daily intraperitoneal injections of 3.86% glucose PD fluid in rats caused hyperplasia of mesothelial cells after 6 weeks [24]. Di Paolo [25] and Gotloib [26] had similar results in rabbits and mice, respectively, and concluded that the alterations observed after long-term exposure of the mesothelium to PD fluid are mainly caused by the high concentration of glucose, whereas the eventual role of low pH seemed marginal. The basement membrane of omental capillaries also shows marked lamination after 20-week daily exposure to hypertonic glucose (3.86%) PD fluid. This was in contrast to the same period of exposure to Ringer's lactate solution [27]. These data suggest a relation between glucose and damaging effects to the peritoneal mesothelial layer in long-term PD. However, concerning this issue, animal studies differ in their results. In chronic peritoneal exposure studies in mice, mesothelial viability and integrity of the peritoneal membrane was examined by trypan blue staining and by assessing mesothelial denudation. The mesothelial viability was better upon 30-day exposure to bicarbonate-buffered PD fluids [28] or 12-week exposure to lactate/bicarbonate-buffered PD fluids [29]. Other researchers [25,30,31], however, did not find any differences in mesothelial morphology between both types of fluid in rats and rabbits.

Peritoneum

A rat experimental model in 10 nonuraemic rats, which were dialyzed twice daily for 4 weeks with high glucose concentration fluids, showed healing of the peritoneum after catheter implantation. Still, hyaluronic acid levels in the dialysate increased and a tendency to thickening of the peritoneum was observed when compared to nondialyzed animals [32]. In a long-term exposure model in rats by Zareie *et al*. [33], instillation of the current lactate-based PD fluid had deleterious effects on the peritoneal tissue. Exposition of the mesothelium to low pH lactate buffer solutions increased the number of mast cells, milky spots and milky spot areas, which are considered to be consequences of immune activation. A clear thickening of the endothelial cell layer, suggestive of endothelial activation, and an increase in the number of blood vessels were also found. Addition of glucose to this buffer (filter-sterilized PD fluid) especially strengthened the induction of fibrosis and the number of omental vessels. In addition to low pH and glucose, the presence of GDP (heat-sterilized PD-fluids) showed a further increase in the number and size of milky spots, parietal blood vessels, loss of mesothelial cell integrity, the number of Fc-receptor positive cells, a thickening of the

mesenteric submesothelial extracellular matrix and an increase in the number of rolling leucocytes. Interestingly, acidification of bicarbonate/lactate PD fluid did not contribute to peritoneal worsening [34], which confirms the findings earlier mentioned in *ex vivo* studies. During chronic exposition to bicarbonate/lactate solutions with fewer GDP and neutral pH, the increase in milky spots and the formation of new blood vessels were reduced [5]. By means of a total histological score by light microscopy, reduced peritoneal fibrosis upon bicarbonate-buffered PD fluid dialysis has also been suggested [35], together with a diminished non-specific inflammatory response and increased production of inflammatory cytokines upon endotoxin challenge [36].

In another PD model for rats, a standard lactate-buffered PD solution was compared with a bicarbonate/lactate-buffered solution during a 12-week study period [37]. In rats treated with a standard low pH solution, an increase was demonstrated in vascular endothelial growth factor (VEGF), micro-vascular proliferation and submesothelial fibrosis. Furthermore, an accumulation of advanced glycation end products (AGEs) and an up-regulation of the receptor for AGEs were found. The peritonitis rate was not different between rabbits that had been treated for 4 weeks by lactate/bicarbonate-buffered PD fluid, but the severity of peritonitis was significantly higher in the lactate group. Likewise, the dialysate leukocyte count had only declined significantly in the lactate group [30].

Therefore, in animal models, mainly glucose and GDP are associated with submesothelial thickening, fibrosis, neoangiogenesis, the presence of AGEs and the poorer inflammatory response. Low pH *per se* in PD fluids does not seem damaging. The difference in peritonitis incidence between the conventional and the more biocompatible PD fluids has not been established.

Animal studies: peritoneal transport

Experiments have been performed in rabbits and rats to study the direct effects of neutral pH bicarbonate-buffered PD solutions on peritoneal transport, appetite and microcirculation. These data point in the same direction, namely, an improved ultrafiltration [38,39], no vasodilation of peritoneal arterioles [40], improved appetite [41] and leukocyte recruitment [42] by bicarbonate-buffered PD fluids compared to lactate-buffered PD fluids.

Park *et al*. [29] demonstrated that in rats, peritoneal ultrafiltration had decreased after 12-week exposure to the conventional PD solution, but administration of a neutral bicarbonate/lactate-buffered PD fluid resulted in less loss of peritoneal ultrafiltration. However, contrasting results were reported by Suzuki *et al*. [35], who showed increased glucose absorption in rats along with decreased creatinine and protein clearance upon dialysis with bicarbonate-buffered PD fluid, which imply an increased peritoneal permeability compared to conventional lactate-buffered PD fluid. Wieczorowska *et al*. [31] suggested reduced transperitoneal protein transport after 4-week treatment in rats with a bicarbonate-buffered PD solution. In the study by Pawlaczyk *et al*. [36], no differences were seen in the transport characteristics between bicarbonate/lactate- and lactate-buffered PD fluids in rats.

Therefore, at present, it is not clear whether bicarbonate-buffered PD fluids improve peritoneal transport physiology in chronic peritoneal exposure animal models. However, this might be related to the animal model, as it is difficult to achieve statistically significant differences in peritoneal transport data in small laboratory animals such as the rat. However, the data summarized so far indicate that at least in *in vitro* studies and in preclinical rat PD models, the new generation of pH neutral, two-chamber PD fluids are more biocompatible than conventional acidic PD fluids.

Clinical studies

UFF is the main reason for discontinuation of PD therapy [43]. Several clinical studies have been conducted to investigate parameters reflecting technique survival and peritoneum preservation in patients using conventional PD fluids versus the new more physiological, biocompatible ones.

Tranaeus *et al*. [44] designed a large randomized clinical trial comparing lactate-buffered PD fluids to bicarbonate/lactate solutions. They showed reduced pain on infusion. Rippe *et al*. [45] had similar though not significant results. Topley's group demonstrated that bicarbonate/lactate solutions might improve peritoneal host defence [22]. The previously mentioned study groups [44,45] did not show differences in the occurrence of peritonitis between the two solutions.

With respect to ultrafiltration, a significant increase in ultrafiltration after 6 months was seen by Tranaeus's group, but these results were in contrast to those of Rippe *et al*., who did not find any increase in ultrafiltration over a period of 2 years. The Eurobalance study even found less ultrafiltration in the group that used the new PD fluids [46].

Thus far, differences in peritoneal creatinine, urea clearance and Kt/V have never been seen. In the Eurobalance study, renal creatinine and urea clearances were higher when patients had undergone 3-month treatment with PD fluids that were pH neutral, lactate buffered and low in GDP [46].

Several publications underline the importance of RRF for the morbidity and survival of PD patients [47–49]. Williams *et al*. [46] also showed that urine volume was higher in patients treated with the new PD fluids. This was not shown in the NEPP (Nutrineal, Extraneal, Physioneal, Physioneal) study, which compared conventional fluids with a regimen low in glucose and GDP with icodextrin and amino acids [50].

In peritoneal biopsies and postmortal studies in long-term PD patients, a predominant finding was revealed that was the development of peritoneal fibrosis that had a deleterious effect on membrane function [51,52]. Over the last 15 years, interest has increased in the identification of potential markers that can be measured in the dialysis effluent that can provide information concerning the state of the peritoneum *in vivo*. Rippe *et al*. [45] also investigated peritoneal mesothelial and interstitial integrity by analysing effluent dialysate. After 2 years, a decrease in hyaluronan acid (marker of inflammation) and an increase in CA 125 were

found in pH neutral PD fluid. CA 125 reflects peritoneal mesothelial cell mass in stable PD patients [53]. Jones *et al*. [54] had similar results after 6 months and found no changes in CA 125 and hyaluronan acid in the lactate group. No differences were found in markers of fibrosis (procollagen I peptide and TGF-ß1). In the NEPP study, CA 125 levels in the effluents were higher in the group using NEPP, suggesting a better preservation of the mesothelium [50]. However, levels of VEGF, hyaluronic acid and Il-6 were also higher. Williams *et al*. [46] demonstrated higher levels of CA 125 in the effluent of patients using Balance®, a low GDP and neutral-pH PD fluid. Hyaluronic acid was lower but VEGF and TNFα were not different.

Currently there are not many data on the effects of biocompatible solutions on survival. In a retrospective observational study, Lee *et al*. [55] showed an advantage in survival rates in those who used Balance® compared to conventional fluids (74% versus 62% at 28 months). A limitation in this study was the difficulty to interpret survival based on observational data.

In conclusion, at present, the long-term effects of pH neutral PD fluids that are low in GDP are not clear. They seem to better preserve the peritoneal membrane and have less systemic effects than the conventional ones. None of the previously mentioned studies investigated local and systemic markers of inflammation, transport characteristics, RRF as well as technique survival in the same cohort of patients. It is also not always clear whether patients had used biocompatible fluids before being included in the study. Furthermore, most of these studies, except for one, had a follow-up of only 6–12 months. The effects on peritoneal transport, technique survival and patient survival remain unanswered. Today, there is still a lack of quality prospective studies that directly compare these solutions to conventional glucose/lactate-based PD fluids. To answer questions that remain, such studies are of utmost importance.

Conflict of interest statement. None declared.

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