

How Do Changes in Water Quality and Dialysate Composition Affect Clinical Outcomes?

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Key Words

Haemodialysis · Dialysate composition · Water quality

Abstract

Dialysis relies upon the transfer of waste products and electrolytes across a semi-permeable membrane contained in the dialyser facilitated by the dialysis fluid, a fast-flowing electrolyte solution prepared continuously by the mixing of treated water with a concentrated electrolyte solution. Both the water, the buffer and electrolyte composition play important roles in modulating complications associated with treatment. With respect to water, historically the focus was on chemical contaminant content, but more recently has shifted to microbiological quality due to the role that such quality plays in the pro-inflammatory state. The composition of the dialysis fluid is crucial in normalization of electrolyte composition of plasma water, homeostasis and acid-base balance, and should be individualized to the patients' requirements in the same way as blood and dialysate flow rates are individualized to ensure optimal comfort and minimal complications associated with the procedure.

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Introduction

During haemodialysis and related therapies, removal of waste products from the blood, normalization of electrolyte levels and adjustment of acid-base status of the patient takes place primarily by diffusion across a semi-permeable membrane contained in the dialyser either into or from dialysis fluid. The dialysis fluid is manufactured continuously during treatment and is derived from mixing treated tap water with electrolytes and a buffer. Water quality and the composition of the dialysis fluid influence a number of dialysis-related complications (fig. 1). In this article, the clinical impact of changes in water quality and dialysis fluid composition on outcomes of patients undergoing regular dialysis therapy are discussed.

Water for the Preparation of Dialysis Fluid

As the average dialysis patient undergoing three times weekly haemodialysis treatment is exposed to around 24,000 liters of dialysis fluid per annum, the water used in the preparation of dialysis fluid undergoes supplementary treatment to ensure that its chemical and microbiological content meets requirements laid down in international and national standards [1].

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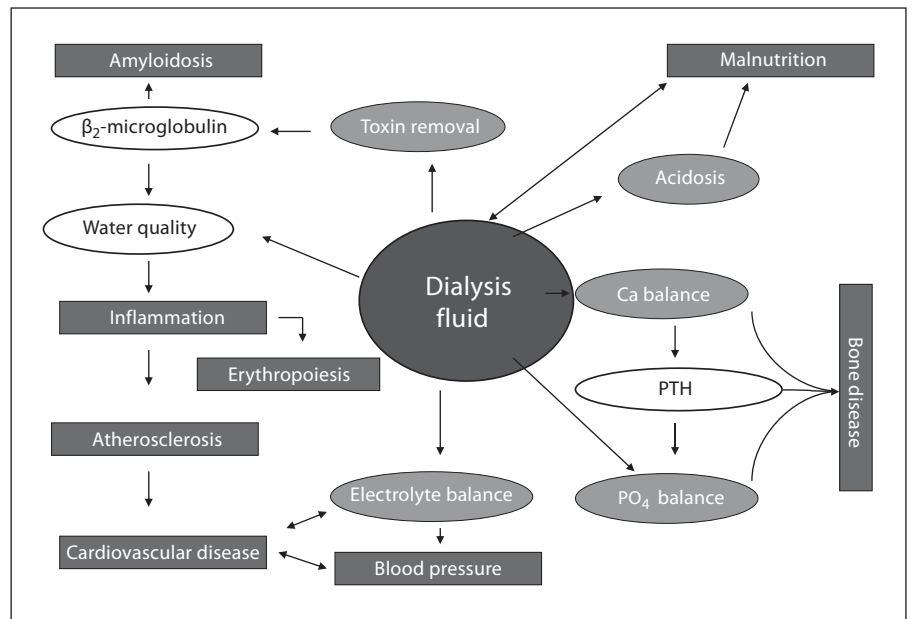


Fig. 1. The role of dialysis fluid composition in dialysis-related complications. PTH = Parathyroid hormone.

Historically, the focus was on chemical contaminant content of the water, but this has recently shifted to microbiological quality. Microbiological contamination of the water derived from a variety of causes has been linked to the pro-inflammatory state, which, with the acute-phase response, interacts with the haematopoietic system at several levels. This leads to a reduced erythropoiesis, accelerated destruction of erythrocytes leading to functional iron deficiency and resistance to erythropoiesis-stimulating agents [2].

The microbiological quality of water in dialysis units is critically dependent upon the presence of biofilm in the distribution network [3]. Achievement of high microbiological quality necessitates attention to the cultivation medium, incubation temperature and incubation time, since an insensitive technique will demonstrate low or no growth and influence the interval periods between disinfection and cleaning, allowing the development of biofilm in the distribution network, which once established is difficult to eradicate [4].

Further control and reduction in bacterial content of the dialysis fluid can be achieved by attention to the design of the distribution network and the materials used to pipe the water, ensuring that they are compatible with hot water or ozone disinfection. For example, the use of polyvinylidene fluoride or cross-linked polyethylene (PVC), the use of dry powder cartridges or bags for the preparation of bicarbonate-buffered dialysis fluid and the use of a bacteria-retentive and endotoxin-retentive

filter for final purification of the dialysate immediately before it enters the dialyser. When such filters are used, whilst effective against larger bacterial fragments or endotoxin, they can permit the passage of short DNA fragments which have been shown to trigger Toll-like receptors on monocytes inducing cytokine production [5].

Clinical Impact of Water Quality

The chemical quality of water used in preparation of the dialysis fluid stipulated in current standards is readily attainable using current technology [4, 6]. Water companies are continuously reviewing their water treatment processes, and this may require review of the technology in use in dialysis units. For example, chlorine is being replaced by chloramines and monochloramine can increase the amount of bioavailable lead by interacting with domestic water piping [7].

It has generally been accepted that biological contamination of dialysate contributes to dialysis-related complications such as dialysis-related amyloidosis and malnutrition-inflammation-atherosclerosis syndrome [8]. Our own study in 2004 showed that following modification of the water treatment system to improve microbiological quality, there was alteration in the C-reactive protein levels of patients which translated into an improved mortality [9]. Since that time dialysis units under the management of the Renal Research Institute have em-

phasized water quality and use systems designed to achieve a water standard of less than 20 CFU/ml for bacteria and less than 0.06 EU/ml for endotoxin, levels lower than those set by the AAMI and closer to European recommendations [4, 10].

A number of published studies have shown that moving to ultrapure dialysis fluid, where ultrapure dialysis fluid is defined as dialysis fluid containing less than 0.1 CFU/ml of bacteria and less than 0.03 EU/ml of endotoxin, is associated with a range of clinical benefits such as reduction of plasma levels of β_2 -microglobulin and pentosidine [11], improvement of iron utilization, erythropoietin response and anaemia [12, 13]. The desire to remove larger molecules such as β_2 -microglobulin implicated in the development of dialysis-related amyloidosis has resulted in the increased utilization of treatment modalities such as haemodiafiltration, which not only enhances the removal of such molecules by convective transport across the membrane, but additionally requires the use of ultrapure dialysis fluid [14]. Although increasingly used, the clinical benefits of ultrapure dialysis fluid have not been established by large scale randomized clinical trials and this has resulted in a degree of scepticism in its universal application [15]. Furthermore, as increased frequency of dialysis also appears to reduce inflammation, its combination with the use of ultrapure dialysis fluid merits study.

Composition of Dialysis Fluid

The dialysis fluid electrolyte content matches the electrolyte content of plasma water; it also contains glucose and a buffer. Historically, bicarbonate was used as the buffer; however, interaction of calcium chloride and sodium bicarbonate produced calcium carbonate and made calcium unavailable for dialysis resulting in a switch to acetate. Today, with the availability of technology to overcome precipitation, the improved clinical tolerance of bicarbonate compared to acetate and a more physiological correction of acidosis, bicarbonate-buffered dialysis fluid is used universally. All bicarbonate-buffered dialysis fluid contains a small amount of acetate which acts as an acidifying agent in the form of acetic acid and lowers the pH value of the final mixture. A new formulation of fluid in which citric acid replaces the acetic acid as the acidifying agent is also available (Citrasate™ and DRYalysate™, Advanced Renal Technologies Inc., Seattle, Wash., USA).

Clinical Impact of Dialysis Fluid Composition

The composition of the dialysis fluid is crucial in normalization of electrolyte composition of plasma water, homeostasis and acid-base balance and impacts on a number of complications associated with dialysis therapy [16]. Many of the components of the dialysis fluid can be individualized or manipulated to improve patient tolerance and such individualization is increasingly used, given the age group and the presence of comorbid conditions in currently treated patients. Using existing technology, the accuracy of such an approach is around $\pm 2\%$. Patents exist for the more accurate individual component delivery and are likely to be incorporated into the next generation of dialysis machines.

Commonly altered components of the dialysis fluid to meet individual patient requirements are sodium, calcium, and potassium, the clinical impacts of which are discussed below.

Sodium

Historically, the sodium levels of dialysis fluid were maintained at levels below that in plasma water. As treatment efficiency improved and treatment duration decreased, there was an upward adjustment of the sodium levels to improve tolerability. Current technology permits the alteration of the sodium levels during dialysis (sodium profiling), either alone or in combination with fluid removal, to avoid or minimize osmotic disequilibrium. Although widely used, certain sodium profiles can lead to sodium gain during dialysis, leading to an increased interdialytic weight gain and hypertension [17, 18].

Ideally, the sodium concentration in the dialysis fluid should be matched to that in plasma water. Under these conditions the salt and water fluxes across the cell membranes and cellular salt loading were minimized, and intracellular tonicity preserved or minimized. Such an approach decreases thirst, interdialytic weight gain, treatment-related symptoms, and predialysis blood pressure but requires knowledge of the patients' plasma water sodium content, a parameter that may not be readily available at the time of commencing a treatment. To circumvent this problem, plasma conductivity may be used as a surrogate measure [19].

Calcium

Calcium plays an important role in the contractile process of both vascular smooth muscle and cardiac myocytes. Plasma calcium levels vary with serum albumin and are affected by pH and regulated by vitamin D, para-

thyroid hormone and calcitonin. Clinically used dialysis fluid concentrations range between 1.25 and 1.75 mmol/l with 1.5 mmol/l being the most common; however, even with this level there may be overload leading to the development of vascular calcification necessitating a reduction to 1.25 mmol/l [20]. With the more widespread use of calcimimetics, and the continued use of calcium-containing phosphate binders, there is the potential for further refinement of calcium levels in the dialysis fluid to minimize calcium gains.

Potassium

Approximately 98% of the potassium is located intracellularly. Alterations in plasma potassium levels during dialysis have an important effect on systemic haemodynamics and such changes are governed by the movement between the intracellular and extracellular spaces during dialysis, which in turn is influenced by changes in acid-base balance, as well as by the presence of glucose in the dialysis fluid [21].

Clinically used dialysis fluid contains between 1 and 3 mmol/l. In a recent analysis of mortality associated with potassium levels, Kovesdy et al. [22] suggested that patients with plasma levels in excess of 4.5 mmol/l should undergo dialysis with a dialysis fluid content of no greater than 2 mmol/l. Higher dialysis fluid content should be confined for use with a plasma level below 4 mmol/l.

Glucose

Glucose has been an integral component of the dialysis fluid since the 1960s. Historically, it was important for the creation of an osmotic gradient across the membrane thereby facilitating fluid removal. It also provided nutritional support to the patient and prevented hypoglycaemic episodes during treatment. Over time the removal of fluid could be more easily achieved by the use of hydrostatic pressure control across the membrane, and latterly by the use of volumetric displacement pumps. Despite this, glucose has been retained in the dialysis fluid and currently used dialysis fluids may contain up to 200 mg/l glucose. As a large proportion of patients undergoing treatment are elderly and diabetic, higher insulin levels, associated with the use of high dialysate glucose levels, can impair potassium removal during dialysis. Hyperglycaemia during dialysis should be avoided as it may activate inflammatory pathways and contribute to the pro-inflammatory state. Thus, reduction and optimization of dialysis fluid glucose content is highly desirable, and a recent study by Burmeister et al. [23] suggested that a level of around 100 mg/l (5.5 mmol/l) would be appropriate

for both diabetic and non-diabetic patients. The use of a glucose-free dialysate should be avoided as it places the dialysis patient at risk of hypoglycaemia, especially if the patient is debilitated or malnourished.

Buffer

Bicarbonate requirements of patients vary considerably as they are determined by the acid production in the interdialytic period, the buffer deficit in the body and the removal of organic anions during treatment. Moderate acidosis before dialysis appears to favour mortality, whilst higher levels of bicarbonate than used currently may be associated with improved nutrition and bone turnover [24].

Although a wide spread of predialysis serum bicarbonate levels is evident in dialysis patients, a dialysate bicarbonate concentration of 35 mmol/l is widely used. Individualization is possible and should be considered for those patients in whom the predialysis serum bicarbonate level is either below 20 mmol/l or above 30 mmol/l. In the former case, a gradual increase in dialysis bicarbonate levels is desirable as a full and rapid correction of metabolic acidosis carries with it the potential for intracellular acidosis [25].

All bicarbonate-buffered dialysis fluid contains small amounts of acetic acid as an acidifying agent. The availability of a formulation which uses citric acid may offer benefits to patients with increased risk of bleeding problems, or whose dialysers clot despite using large amounts of heparin.

Composition for Use in New Modalities of Treatment

Whilst conventional haemodialysis remains the most widely used treatment modality, an increasing number of patients are being treated using haemodiafiltration during which ultrafiltration beyond the desired weight loss is prescribed. This excess above the interdialytic weight gain is compensated by the infusion of a sterile and non-pyrogenic physiological solution derived from the dialysis fluid which undergoes additional filtration prior to infusion into the extracorporeal circuit. As previously discussed, this necessitates high-quality water. The infusion of large amounts of solution with the same electrolyte and buffer concentration as the dialysis fluid modifies the dynamics of ionic transmembrane exchanges and influences the final concentrations in patients. The potential effect of such infusion has not received extensive study, although the effect of acetate has been studied [26].

Interest in quotidian haemodialysis is also growing. Some advocate short high-efficiency daily haemodialysis and others long slow-flow nocturnal haemodialysis, used 5–7 times/week. In slow nocturnal haemodialysis, the use of a 1.25 mmol/l calcium-containing dialysate solution was associated with calcium loss leading to calcium depletion and subsequent hyperparathyroidism, necessitating an increase in the dialysis fluid calcium levels to 1.75 mmol/l [27].

Conclusions

Both the water quality and dialysis fluid composition play an important role in the modulation of both short- and long-term dialysis-related complications. In respect

to the former, constant and rigorous attention to water quality to ensure compliance with standards and to minimize the development of biofilm is desirable. With regard to dialysis fluid composition, the electrolyte composition of the dialysis fluid should be individualized to the patients' requirements in much the same way as blood and dialysate flow rates are individualized to ensure optimal comfort and minimal complications associated with the procedure. Alteration of the frequency and the duration of treatments will additionally require closer monitoring of the patient and the prevention of possible depletion of water-soluble vitamins [28].

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