



Haemodialysis

EDITORIAL COMMENT

Haemodialysate: long neglected, difficult to optimize, may modify hard outcomes

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Abstract

In two recent CKJ reviews, experts (Basile and Lomonte and Locatelli *et al.*) have reviewed haemodialysate composition. A long-neglected issue, observational studies have associated the composition of haemodialysate to adverse outcomes. However, the scarcity of clinical trial-derived information results in limited guideline recommendations on the issue. Indeed, guidelines have more frequently indicated what not to do rather than what to do. In this setting, expert opinion becomes invaluable. In designing haemodialysate composition, a balance should be struck between the need to correct within a time frame of around 4 hours the electrolyte and water imbalances that take 48 to 72 h to build, with the need for gradual correction of these imbalances. The issue is complicated further by the impact of individual variability in dietary habits, medications and comorbidities. In this regard, a personalized medicine approach to individualization of haemodialysate composition offers the best chance of improving patient outcomes. But how can haemodialysate individualization be achieved, and what clinical trial design will best test the impact of such approaches on patient outcomes?

Key words: CKD-MBD, end-stage kidney disease, outcomes, renal replacement therapy, sudden death

Chronic kidney disease (CKD) is one of the top fastest growing causes of death worldwide [1]. This is an awkward position when end-stage renal failure is treatable by dialysis or transplantation [2]. Lack of access of millions of persons to renal replacement therapy is a major contributor to mortality [3]. However, current dialysis techniques may be optimized in order to increase patient survival and quality of life. In this regard, there is a current debate on the timing of dialysis initiation, especially for the elderly, which is reflected in widely differing practices throughout Europe and which may also be impacted by optimization of dialysis [4]. Indeed, renal replacement therapy complications were the primary cause of death in 2.1% of patients in the 2000s [5]. Furthermore, observational studies have associated haemodialysate composition with mortality [2]. Thus, high haemodialysate bicarbonate and low haemodialysate potassium

have been associated with increased mortality [6, 7]. However, there is very little information derived from clinical trials. This may be one of the reasons for the striking absence of recommendations on haemodialysate composition from most recent guidelines on haemodialysis prescription and adequacy. In this regard, there are no recent suggestions for haemodialysate potassium concentration and the only recent guideline to mention haemodialysate bicarbonate advocates increasing the bicarbonate concentration to 40 mmol/L as a means of achieving the target pre-dialysis serum bicarbonate concentration (Table 1) [8, 9, 10]. Other guidelines explicitly indicate what concentrations to avoid, but do not recommend the actual concentrations to use [11–13]. At this relatively early stage of understanding the optimal haemodialysate composition, expert opinion becomes invaluable, not only to provide guidance for current practice, but also and above

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Table 1. Optimal or recommended haemodialysate composition

Molecule	Basile and Lomonte [8]	Locatelli et al. [9]	Guidelines [10–13]
Sodium	138–140 mmol/L	Individualize to attain zero balance for the interdialytic and dialysis periods. Use a conductive kinetic model Avoid <2 mmol/L	Do not routinely use sodium profiling with supraphysiological dialysate sodium concentrations and high (144 mmol/L) sodium dialysate concentration (2007) [13] NA
Potassium ^a	Individualize to avoid pre-dialysis plasma potassium >6 mmol/L or post-dialysis relative hypokalaemia or very rapid decrease in plasma potassium		
Calcium	Individualize not to lower serum calcium, especially in sessions at risk for end-dialysis hypokalaemia	Ionized calcium 1.25 (nominally 1.5) mmol/L	1.25–1.50; 1.50 mmol/L if haemodynamic instability (2007, 2009, 2010) [11–13]
Magnesium	Individualize to normalize plasma magnesium	Around 0.5 mmol/L (1 mg/dL)	Avoid low (0.25 mmol/L) concentration if haemodynamic instability (2007) [13]
Bicarbonate ^a	Individualize to correct acidosis and to avoid symptoms of transient metabolic alkalosis	Avoid >35 mmol/L Individualize for pre-dialysis plasma bicarbonate 24 and post-dialysis 28 mmol/L 100 mg/dL	40 mmol/L (if venous pre-dialysis bicarbonate persistently <20 mmol/L) (2007) [10]
Glucose	NA		Avoid glucose-free in diabetics (2007) [13]

NA, not applicable.

^aConsider using oral medication to achieve pre-dialysis targets.

all, to help understand the issues involved, identify the key unmet needs and unanswered questions, and help plan the best way forward research-wise. Two recent CKJ reviews led by experts in the field, Basile and Lomonte [8] and Locatelli et al. [9] have reviewed haemodialysate composition.

Basile and Lomonte and Locatelli et al. review the haemodialysate concentrations of sodium, potassium, calcium, magnesium and bicarbonate, and the main conclusions are summarized in Tables 1 and 2 [8, 9]. Both authors emphasize that in designing haemodialysate composition, a balance should be struck between the need to correct within a time frame of around 4 h the electrolyte and water imbalances that took 48–72 h to build, with the need for gradual correction of these imbalances. Overall, correction of imbalances impacts more on the long-term outcomes of the patients. However, the speed of correction or overcorrection may have an acute impact in the form of arrhythmia, as is the case for hypokalaemia, and calcium haemodialysate prescriptions that decrease serum calcium, especially if both are associated with metabolic alkalosis resulting from high haemodialysate bicarbonate that further reduces ionized calcium and potassium. The issue is complicated further by the impact of individual variability in dietary habits, medications and comorbidities. In this regard, a personalized medicine approach to individualization of haemodialysate composition offers the best chance of improving patient outcomes. However, haemodialysate individualization may not be as easy as it sounds, and no trial has assessed the different possible strategies in terms of hard outcomes.

A common theme to decrease the speed of correction of the imbalances is to keep those imbalances to a minimum [8, 9]. Dietary counselling and oral medication may play a key role here. Thus, a low salt diet will decrease the need for ultrafiltration and for a negative sodium balance. This is an important but often forgotten concept and some health care personnel insist more on the amount of fluid ingested, although salt ingestion is the key driver of thirst. Similarly, a low potassium dietary intake or the use of potassium binders or even diuretics, as well as the prescription of oral bicarbonate will mitigate the need for low potassium or high bicarbonate haemodialysate. In this regard, haemodialysate prescription should be viewed as an additional tool, not just the only tool, in a holistic approach to patient care and correction of hydroelectrolyte imbalances. In any case, we should remember that haemodialysate individualization requires actual assessment of the individual patient needs. Thus, haemodialysate bicarbonate cannot be individualized if serum bicarbonate is not monitored before and after haemodialysis.

For sodium and potassium, the main issue is how to make a negative balance during haemodialysis that keeps the overall balance for the interdialytic-plus-haemodialysis-session period neutral in such a way that hypotension and arrhythmia are avoided by providing a smooth, adequate rate of removal. Volume status and serum potassium are used as targets. Calcium presents additional issues, given the highly variable calcium absorption from dietary sources or medications, the highly variable bone response and the different factors impacting on serum calcium, from serum albumin levels to acid-base balance and the use of medications such as cinacalcet. In Basile and Lomonte's words, 'Which is the ideal haemodialysate calcium concentration is probably an unanswerable question.' [8]. This is a sad realization for nephrologists who fill millions of prescriptions for haemodialysate calcium concentrations every year. Thus, a key priority here is to develop the techniques that will allow the routine estimation of calcium balance in the clinic in order to prevent long-term calcium loading or depletion. Probably as a

Table 2. Unsolved issues related to haemodialysate composition [8, 9, 14]**Sodium**

Benefits and harm of fixed (either low or high) haemodialysate sodium prescription

Impact on mortality of fixed, individualized or real-time-modelled haemodialysate sodium

Potassium

Role of potassium profiling to prevent arrhythmia in the first 2 h of haemodialysis

(Related: role of new oral potassium binders to allow a lower plasma-haemodialysate potassium gradient)

Calcium

How to assess and monitor calcium balance as a tool to guide haemodialysate calcium concentration

What haemodialysate calcium concentration maintains each individual patient in overall neutral calcium balance without promoting CKD-mineral bone disorder?

What is the role of calcium profiling?

Magnesium

What is the optimal target serum magnesium concentration?

Bicarbonate

Randomized trial to assess the impact of different haemodialysate bicarbonate concentrations on mortality

Other haemodialysate components

What is the role of haemodialysate containing ferric pyrophosphate citrate in the management of iron deficiency?

Should acetate or citrate accompany bicarbonate in haemodialysate?

consequence of the current uncertainties regarding haemodialysate calcium, Basile and Lomonte and Locatelli *et al.* reach what might look like different summary conclusions on the optimal concentration [8, 9] (Table 1). However, Locatelli *et al.* do point out that individualization may be considered in certain patients and suggest that in patients on cinacalcet the low serum calcium may lead to a high positive calcium balance when higher haemodialysate calcium is used. This is illustrated by a recent case report of lethal calciphylaxis despite long-term control of hyperparathyroidism with paricalcitol and cinacalcet, and low-normal serum calcium [15]. The long-term combination of oral 1.5–2.0 g elemental calcium daily with 1.5 mmol/L haemodialysate calcium may have contributed to progressive calcium overload. In our own experience, individualization of dialysate calcium concentration according to baseline pre-dialysis serum calcium may prevent major excursions in post-dialysis serum calcium and intact parathyroid hormone levels [16]. Thus, the mildest dialysis-induced changes in serum calcium and PTH were observed in patients with pre-dialysis serum calcium <8.75 mg/dL dialysed with 1.25 mmol/L haemodialysate calcium and in patients with pre-dialysis serum calcium >9.15 mg/dL dialysed with 1.50 mmol/L haemodialysate calcium.

The case of magnesium is striking. It is probably the less understood of haemodialysate components and serum magnesium is frequently not monitored in haemodialysis patients. Commercially available haemodialysate magnesium concentration is usually 0.25–0.75 mmol/L (a 3-fold difference!) and there are even solutions with 0 and 1 mmol/L. A key piece of missing information that can only be answered through clinical trials, is which is the optimal serum magnesium concentration. In this regard, observational studies recently reported a survival benefit for haemodialysis patients with mild hypermagnesemia, as opposed to those with higher and lower magnesium concentrations, including those with magnesium within the normal range [17].

Both Basile and Lomonte and Locatelli *et al.* concur with the need to individualize haemodialysate bicarbonate concentration [8, 9]. This is a key concept, since many dialysis units do not routinely assess serum bicarbonate pre-dialysis and even less have an idea of the post-dialysis serum bicarbonate in their patients. However, clinical trials are needed that provide insights into the optimal way to individualize haemodialysate bicarbonate concentration and what serum bicarbonate targets and haemodialysate bicarbonate concentrations improve outcomes.

Bicarbonate-based haemodialysate contains small amounts of acetate. An issue not discussed in the CKJ reviews is the possibility to replace this acetate with citrate (acetate-free haemodialysate). Limited clinical experience suggests that the short-term (months) use of such citrate-enhanced haemodialysate is safe and decreases haemodialysis-induced hypotension and malaise, the intra-dialytic shift in pH and base excess and post-dialysis plasma ionized calcium levels, increasing post-dialysis PTH levels, as compared with conventional haemodialysate, without affecting pre-dialysis values, and also caused an intra-dialytic increase in activated partial thromboplastin time [18–20].

Locatelli *et al.* further discuss haemodialysate composition in special situations, including long nocturnal haemodialysis, daily short haemodialysis, less frequent haemodialysis, on-line haemodiafiltration, as well as haemodialysate glucose concentration and the possibility to enhance the haemodialysate with additional phosphate or iron, such as ferric pyrophosphate citrate, in specific patient populations [9, 21, 22].

In conclusion, haemodialysate composition has been neglected for too long in an environment dominated by a restrictive concept of dialysis adequacy focused on the clearance of uraemic toxins as categorized by the K_t/V_{urea} . However, there is accumulating evidence that adequacy should be more broadly defined, encompassing not only the dose of urea clearance, but also the dose of each individual component of the haemodialysate. Observational data suggest that some currently used haemodialysate concentrations of potassium and bicarbonate are associated with increased mortality. Now, two updated and in-depth reviews by experts provide guidance for routine prescription of haemodialysate composition and identify key issues that should be addressed preferentially through well-designed clinical trials that embrace the complexity of end-stage kidney disease patients and the interplay between different haemodialysate components (Table 2) [8, 9]. Individualization is proposed for several haemodialysate components. However, routine, technical or knowledge limitations, or lack of monitoring of plasma parameters may preclude the widespread use of individualized haemodialysate.

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Conflict of interest statement

None declared.

(See related articles by Basile and Lomonte. A neglected issue in dialysis practice: haemodialysate. *Clin Kidney J* (2015) 8: 393–399 and by Locatelli et al. Optimizing haemodialysate composition. *Clin Kidney J* (2015) 8: 580–589.)

References

- Ortiz A, Covic A, Fliser D et al. Epidemiology, contributors to, and clinical trials of mortality risk in chronic kidney failure. *Lancet* 2014; 383: 1831–1843
- GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 385: 117–171
- Anand S, Bitton A, Gaziano T. The gap between estimated incidence of end-stage renal disease and use of therapy. *PLoS One* 2013; 8: e72860
- Gonzalez-Espinoza L, Ortiz A. 2012 ERA-EDTA Registry Annual Report: cautious optimism on outcomes, concern about persistent inequalities and data black-outs. *Clin Kidney J* 2015; 8: 243–247
- Bray BD, Metcalfe W. Improving patient safety in haemodialysis. *Clin Kidney J* 2015; 8: 262–264
- Tentori F, Karaboyas A, Robinson BM et al. Association of dialysate bicarbonate concentration with mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2013; 62: 738–746
- Jadoul M, Thumma J, Fuller DS et al. Modifiable practices associated with sudden death among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Clin J Am Soc Nephrol* 2012; 7: 765–774
- Basile C, Lomonte C. A neglected issue in dialysis practice: haemodialysate. *Clin Kidney J* 2015; 8: 393–399
- Locatelli F, La Milia V, Violo L et al. Optimizing hemodialysate composition. *Clin Kidney J* 2015; 8: 580–589
- Fouque D, Vennegoor M, ter Wee P et al. EBPG guideline on nutrition. *Nephrol Dial Transplant* 2007; 22 (Suppl 2): ii45–ii87
- Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD–MBD). *Kidney Int* 2009; 76 (Suppl 113): S1–S130
- Goldsmith DJ, Covic A, Fouque D et al. Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) Chronic Kidney Disease–Mineral and Bone Disorder (CKD–MBD) Guidelines: a European Renal Best Practice (ERBP) commentary statement. *Nephrol Dial Transplant* 2010; 25: 3823–3831
- Kooman J, Basci A, Pizzarelli F et al. EBPG guideline on haemodynamic instability. *Nephrol Dial Transplant* 2007; 22 (Suppl 2): ii22–ii44
- Basile C, Pisano A, Lisi P et al. High versus low dialysate sodium concentration in chronic haemodialysis patients: a systematic review of 23 studies. *Nephrol Dial Transplant* 2015; doi:10.1093/ndt/gfv084
- Gonzalez-Parra E, Martin-Cleary C, Martin J et al. Calcific uraemic arteriopathy while on cinacalcet. *J Postgrad Med* 2011; 57: 51–52
- Gonzalez-Parra E, Gonzalez-Casas ML, Arenas MD et al. Individualization of dialysate calcium concentration according to baseline pre-dialysis serum calcium. *Blood Purif* 2014; 38: 224–233
- Sakaguchi Y, Fujii N, Shoji T et al. Hypomagnesemia is a significant predictor of cardiovascular and non-cardiovascular mortality in patients undergoing hemodialysis. *Kidney Int* 2014; 85: 174–181
- Daimon S, Dan K, Kawano M. Comparison of acetate-free citrate hemodialysis and bicarbonate hemodialysis regarding the effect of intra-dialysis hypotension and post-dialysis malaise. *Ther Apher Dial* 2011; 15: 460–465
- Grundström G, Christensson A, Alquist M et al. Replacement of acetate with citrate in dialysis fluid: a randomized clinical trial of short term safety and fluid biocompatibility. *BMC Nephrol* 2013; 14: 216
- de Sequera Ortiz P, Albalade Ramón M, Pérez-García R et al. Acute effect of citrate baths on post-dialysis alkalemia. *Nefrologia* 2015; 35: 164–171
- Gupta A, Lin V, Guss C et al. Ferric pyrophosphate citrate administered via dialysate reduces erythropoiesis-stimulating agent use and maintains hemoglobin in hemodialysis patients. *Kidney Int* 2015; doi: 10.1038/ki.2015.203
- Fishbane SN, Singh AK, Cournoyer SH et al. Ferric pyrophosphate citrate (Triferic™) administration via the dialysate maintains hemoglobin and iron balance in chronic hemodialysis patients. *Nephrol Dial Transplant* 2015; doi: 10.1093/ndt/gfv277