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...
Table 1. Optimal or recommended haemodialysate composition

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<tr>
<td>Sodium</td>
<td>138–140 mmmol/L</td>
<td>Individualize to attain zero balance for the interdialytic and dialysis periods. Use a conductive kinetic model to individualize sodium concentration so of sodium, potassium, calcium, magnesium and bicarbonate.</td>
<td>Do not routinely use sodium profiling with supraphysiological dialysate sodium concentrations and high (144 mmmol/L) sodium dialysate concentration (2007) [13].</td>
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<td>Potassium</td>
<td>Individualize to avoid pre-dialysis plasma potassium concentrations &gt;3 mmmol/L or post-dialysis relative hypokalaemia or very low (0.5 mmmol/L) post-dialysis potassium.</td>
<td>Avoid low (&lt;2 mmmol/L) to normal (2–3 mmmol/L) potassium concentrations.</td>
<td>1.25–1.50 mmmol/L haemodynamic instability (2007, 2009, 2010) [11–13]. Avoid low (&lt;2 mmmol/L) potassium concentrations (haemodynamic instability) 0.5–1.50 mmmol/L (2007) [13].</td>
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<tr>
<td>Calcium</td>
<td>Individualize to avoid hypocalcaemia or very high calcium concentrations.</td>
<td>Avoid &gt;35 mmmol/L of serum calcium for pre-dialysis plasma calcium &gt;2.50 mmol/L and post-dialysis calcium &gt;2.80 mmol/L.</td>
<td>C. Avoid low (&lt;1.50 mmol/L) to normal (1.50–2.50 mmol/L) calcium concentrations if haemodynamic instability (2007) [13]. Avoid low (&lt;1.50 mmol/L) calcium concentrations (haemodynamic instability) 1.50–2.50 mmol/L (2007) [13].</td>
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<tr>
<td>Magnesium</td>
<td>Individualize to correct acidosis and to avoid symptoms of transient metabolic alkalosis.</td>
<td>Avoid low (&lt;0.5 mmol/L) to normal (0.5–1.0 mmol/L) magnesium concentrations.</td>
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<td>Bicarbonate</td>
<td>Avoid concentrations &gt;35 mmmol/L of serum bicarbonate for pre-dialysis plasma bicarbonate &gt;40 mmmol/L and post-dialysis bicarbonate &gt;28 mmmol/L.</td>
<td>Around 0.5 mmol/L (10 mg/dL).</td>
<td>40–50 mmol/L (2007) [13].</td>
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NA, not applicable. *Consider taking and medication to achieve pre-dialysis targets. **Consider taking and 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
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 Kt/Vurea. 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

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