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

| 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 | Do not routinely use sodium profiling with supraphysiological dialysate sodium concentrations and high (144 mmol/L) sodium dialysate concentration (2007) [13] |
| Potassiuma     | Individualize to avoid pre-dialysis plasma potassium >6 mmol/L or post-dialysis relative hypokalaemia or very rapid decrease in plasma potassium | Avoid <2 mmol/L | NA |
| Calcium        | Ionized calcium 1.25 (nominally 1.5) mmol/L | Around 0.5 mmol/L (1 mg/dL) | 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] |
| Bicarbonatea   | Individualize to correct acidosis and to avoid symptoms of transient metabolic alkalosis | Avoid >35 mmol/L | 40 mmol/L (if venous pre-dialysis bicarbonate persistently <20 mmol/l) (2007) [10] |
| Glucose        | NA 100 mg/dL | Individualize for pre-dialysis plasma bicarbonate 24 and post-dialysis 28 mmol/L | Avoid glucose-free in diabetics (2007) [13] |

**a** Consider using oral medication to achieve pre-dialysis targets.

NA, not applicable.
The optimal way to individualize haemodialysate bicarbonate concentration is a topic of ongoing debate. However, clinical trials are needed that provide insights into the post-dialysis serum bicarbonate in their patients. Typically, clinicians currently assess serum bicarbonate pre-dialysis and even less have observed those with magnesium within the normal range [17]. Considering higher and lower magnesium concentrations, including those 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 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.

| 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**         | 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? |

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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.)

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