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Optimal Dialysate Sodium - what is the evidence?

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Abstract

Oligoanuric patients with end-stage kidney disease are dependent on hemodialysis to achieve and maintain the desired goal of euvolemia. The dialysis prescription, in addition to sodium and fluid restriction, is therefore a critically important factor in the care of hemodialysis patients. Various dialysate sodium concentrations have been favored throughout the history of dialysis, but the 'optimal' concentration remains unclear. In this manuscript we examine the historical context of changes to the dialysate sodium prescription, review the evidence of its associated effects, discuss 'individualization' of dialysate sodium and highlight the need for definitive trials that are powered for important clinical outcomes.

Keywords

sodium; dialysate; outcomes; hemodialysis

In 1854 the Scottish chemist Thomas Graham suspended a vessel of urine, bounded by a membrane derived from ox bladder, within a container of distilled water. He observed that the membrane permitted the movement of solute from urine to water, named this process 'dialysis', and even considered future therapeutic uses of this physiochemical observation for the treatment of patients with kidney failure.[1] Over time, and with several advances in medical practice and technology, the widespread use of hemodialysis to treat humans with acute and end-stage kidney disease became possible. One of the major requirements for the success and safety of hemodialysis was determination of the composition of dialysate - the fluid on the opposite side of the semi-permeable membrane to the patient's blood.

Hemodialysis tries to accomplish in an intermittent fashion (traditionally thrice-weekly) what the kidneys do continuously, including the removal of waste products and regulation of salt and water homeostasis. Most hemodialysis patients are counseled to limit dietary sodium intake. However, hemodialysis patients are estimated to consume between 1.7 and 5.5 grams of sodium per day,[2-5] with higher sodium intake having been independently associated with greater mortality.[3] In the absence of kidney function, hemodialysis patients

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rely on the dialysis procedure for sodium balance, achieved through convective clearance (i.e. ultrafiltration of excess plasma water and solutes accumulated since the prior treatment) and diffusion, which is partly dependent on the dialysate to plasma sodium gradient and is therefore modifiable. The achievement of optimal sodium balance is an important goal and can only be achieved with careful consideration of each patient's dietary intake and individual hemodialysis prescription.

This review aims to provide a historical context of how and why the dialysate sodium (DNa) composition has changed over the six decades or so that hemodialysis has been available for the treatment of acute and chronic kidney failure. We explore studies that examine both beneficial and detrimental outcomes associated with various DNa concentrations, including several recent observational reports that examine hospitalization and mortality, which have re-opened the discussion on the ‘optimal’ DNa composition.

Hemodialysis associated temporary osmotic gradients

Early studies of hemodialysis in dogs tested the hypothesis that some adverse symptoms associated with hemodialysis in humans, such as headache, cramping, abdominal pain and nausea (collectively described as dialysis disequilibrium), were caused by more rapid decline in extracellular versus intracellular urea concentrations, leading to temporary osmotic gradients that could cause fluid shifts into cells and the development of cerebral edema. Dossetor et al. recorded a transient gradient between the blood and cerebral parenchymal urea concentration during hemodialysis. This gradient positively correlated with the degree of cerebral tissue swelling (determined from intra-dialytic brain biopsies) suggesting intracellular movement of water down an osmotic gradient. The urea gradient rapidly dissipated after dialysis cessation.[6] Pappius et al. demonstrated that cerebrospinal fluid pressure increased during the hemodialysis of uremic dogs, suggesting that urea can temporarily act as an effective osmole. Moreover, they reported similar findings upon dialysis of non-uremic dogs who were dialyzed against a hyponatric dialysate, suggesting that changes in osmolality were more important than changes in urea concentration.[7] In three human subjects, Kennedy et al. reported significantly higher urea levels in the CSF compared with plasma immediately after hemodialysis, consistent with previous animal findings.[8]

Hemodialysis thus appears to be capable of inducing temporary osmotic gradients through rapid reductions in urea and/or sodium and other ions, which in turn may lead to trans-cellular fluid shifts and symptoms of disequilibrium during the actual dialysis session.[9, 10]

Historical context of dialysate sodium concentrations

Sodium is the major cation of plasma in humans and therefore the major cationic constituent of dialysate. Before volumetric control was available, ultrafiltration was primarily achieved by using high dialysate glucose concentrations to promote plasma water removal by the process of osmosis. Sodium removal was achieved by utilizing hypotonic dialysate with DNa concentrations in the 125-130 mmol/L range, facilitating sodium removal by diffusion.[11, 12] As dialysis technologies advanced dialysate glucose concentrations and

treatment times were reduced. However, with shorter sessions and acetate-based dialysate, clinicians noted a greater occurrence of symptoms consistent with disequilibrium syndrome. Based on prior observations from animal and human studies these findings were attributed to more rapid changes in intra-dialytic plasma osmolality induced by the shorter dialysis sessions.[12]

Higher DNa concentrations (~140 mmol/L) became more common during the transition from acetate-based to bicarbonate-based dialysate. These changes appeared to lead to improved tolerance of the dialysis procedure. In fact patients could not distinguish between acetate (itself associated with hypotension and adverse symptoms[13]) and bicarbonate dialysate treatments when both had a DNa of 140mmol/L.[14] With increasing preference for bicarbonate based dialysate from the 1980′s onwards, the new 'standard' DNa of 140mmol/L was incorporated into the vast majority of chronic prescriptions,[12] and resulted in convection becoming the predominant route of sodium removal with thrice-weekly prescriptions.[15]

Dialysate sodium - association with patient symptoms

Many early studies assessed the efficacy of the new 'standard' DNa in terms of patient symptoms, making comparisons with the historical lower DNa (~130 mmol/L). One of the earliest reports from Stewart et al. in 1972 outlined their experience with higher (145 mmol/L) versus lower (132 mmol/L) DNa on the frequency of muscle cramps in nine patients on a low sodium diet (20-50 mmol/day). These patients dialyzed twice weekly for a total of 16-22 hours per week. In alternating treatment assignments (A->B->A->B) over a 15 month period they noted a significant decrease in the frequency of cramps for higher versus lower DNa (47.5 vs. 22.5%, $p<0.001$).[16] Changes in IDWG were not reported and adherence to dietary restrictions was not assessed.

Soon after, Port et al. examined 17 maintenance dialysis patients. Eight (five of whom were incident) received a fixed lower DNa of 133 mmol/L, while the remaining nine patients (four of whom were incident) were infused with hypertonic saline to minimize reductions in plasma osmolality. They underwent four-hour sessions with acetate based dialysate, blood flow of 250 mL/min and dialysate flow of 1000 mL/min. Disequilibrium-type symptoms did not occur in any individuals from the hypertonic saline group, compared with 69% in the standard group. These results correlated with blinded interpretation of intra-dialytic electroencephalographic recordings (22% having greater abnormalities in the hypertonic saline group vs. 77% in the fixed lower DNa group). Of note, greater IDWG (0.5 kg per day vs. 0.05 kg per day) was reported in the hypertonic saline group, although formal statistical comparisons were not provided.[17] Other concerns with this study included the inclusion of incident patients, different numbers of treatments in each arm and lack of measurement of dietary sodium intake.

In another study Wilkinson et al. reported that higher DNa of 136 mmol/L (compared with 130 mmol/L) was associated with a markedly reduced incidence of cramps. In this report, the authors noted the improvement in symptoms came at the expense of increased thirst, weight gain and slight increase in blood pressure.[18] Thus, even at this early stage, the

potential adverse effects of higher DNa --thirst, inter-dialytic weight gain and higher blood pressure-- did not go un-noticed by patients or their physicians.

Dialysate sodium - intra-dialytic blood pressure stability versus thirst, IDWG and pre-dialysis hypertension

While aiming to strike an appropriate balance between improved patient symptoms and tolerability on one hand, and higher IDWG and blood pressure on the other, some clinicians wished to examine the potential of higher DNa to improve cardiovascular stability in certain patient subgroups.[19] Thus, as hemodialysis became increasingly available for older, sicker and diabetic patients, many investigators began to experiment with even higher 'supra-physiological' DNa concentrations, with the aim of maximizing hemodynamic stability and further improving treatment tolerance.

Fixed higher DNa

Cybulsky et al. studied fixed lower (133 mmol/L) versus higher (144 mmol/L) DNa in a mixture of normotensive, hypertensive and anephric patients in a 12-month cross-over trial. They reported a reduction in IDH in the normotensive and anephric patients, without an increase in overall blood pressure. However, they proposed that blood pressure may further increase in patients who were already hypertensive.[20]

Barre et al. also noted no major change in pre-dialysis SBP in five male anephric patients, who were not on any blood pressure medications at baseline. They randomized these patients to acetate-based dialysate with relatively high fixed DNa concentrations of 145, 150 or 155 mmol/L in random sequence, one month at a time over a 6-month study period. No significant changes were found in pre-dialysis blood pressure or intra-dialytic symptoms. However, progressively greater IDWG was recorded with higher DNa prescriptions (2.2 kg, 2.6 kg and 2.9 kg respectively).[21]

Thein et al. analyzed 52 patients over a four month period before and after a facility-wide lowering of DNa from 141 to 138 mmol/L. The mean baseline SBP was 151.8 mmHg, with an average use of 0.8 anti-hypertensive medications per patient. They reported that lower DNa was associated with modest reductions in pre-dialysis SBP, but not with changes in IDWG, which the authors ascribed to lack of dietary sodium restriction enforcement.[22]

Variable DNa/Sodium modeling

Sodium modeling algorithms were developed due to increasing concerns about potential 'sodium loading' and the associated increases in thirst, IDWG and pre-dialysis blood pressure. These strategies involve tapering the DNa concentration (starting high with progressive lowering via linear, stepped or exponential decline) during the dialysis procedure so that the terminal dialysate sodium concentration is similar to or lower than that of the patient's serum sodium.

Some reports were favorable and found beneficial effects in terms of blood pressure stability, without increases in IDWG or thirst. For example, Dumler et al. enrolled 10 stable patients

on acetate-based dialysis in a 4-week cross-over trial of sequential high/low (150/130 mmol/L) versus fixed (140 mmol/L) DNa. They reported a 50% reduction in the incidence of cramps and 11 mmHg lesser decline in SBP with the sequential high/low DNa regimen. They did not observe any change in IDWG.[23] The degree of co-morbidity and dietary patterns were not reported in this study, making it difficult to assess its generalizability. Raja et al. examined 10 stable chronic hemodialysis patients, using acetate based dialysate, for 2-weeks on each of the following protocols: A) fixed DNa=135; B) fixed DNa=140; C) high->low stepwise DNa 145->135; and D) low->high stepwise DNa 135->145mmol/L. The frequency of hypotensive episodes (SBP <90 mmHg) was significantly reduced from B and C vs. A and D (21% vs. 39%), but no significant change was found in IDWG.[24]

Of note, the prior two studies were of small sample size, relatively short duration and used acetate-based dialysis, thereby limiting their generalizability to modern treatments. In a larger and longer study using bicarbonate based dialysate, Achiardo et al. randomly assigned 39 stable patients over a 9-week period to week-long therapy with either fixed standard (140mmol/L), stepped (149 mmol/L for the majority of the treatment, then 140 mmol/L), modeled linear decline or modeled exponential decline modeling (149->140mmol/L). They recorded a 50% reduction in the frequency of hypotensive events (SBP <90 mmHg) in the sodium modeling vs. non-modeling groups, again without significant changes in pre-dialysis SBP or IDWG.[25] Of note the session length was relatively short (mean 126 mins) in this study.

On the other hand, despite the hypothesis that lowering of the DNa concentrations with sodium modeling algorithms might tip the risk/benefit ratio in a more favorable way, several studies have reported associations with greater IDWG and pre-dialysis SBP. Sadowski et al. randomly assigned 16 stable non-diabetic individuals (aged 16-32 years) to four two-week blocks consisting of random assignment to either: exponential modeling (DNa=148->138mmol/L); linear modeling (DNa=148->138mmol/L); stepped (DNa=148 mmol/L for majority of treatment and 138 mmol/L for last 30 min); or fixed DNa (138mmol/L). As a combined group, all modeling strategies were associated with a significant reduction in post-dialysis hypotension compared with fixed DNa (13% vs. 20%; $p<0.05$), though there appeared to be trend towards greater thirst and IDWG.[26]

Oliver et al. enrolled 10 stable patients to a randomized cross-over study of standard (DNa=142 mmol/L) vs. profiled (DNa 152->142 mmol/L and profiled UF) dialysis for two weeks per arm. Hypotensive events or symptoms were less frequent in the profiled treatments (30.6 vs. 20.4%), but pre-dialysis weight was greater by an average of 0.3 kg. In a longer duration cross-over study by Flanigan et al. (3.5 months per arm), 40 patients were assigned to either fixed DNa of 140mmol/L or sodium modeling (exponential decline from 155->135 mmol/L), with higher UF rates permitted in the modeled group (1.6 vs 1.2 L/hour). The modeled group experienced a significant reduction in anti-hypertensive drug use, despite absence of significant changes in 24-hour BP parameters or ultrafiltration volume.[27]

An important point to note with sodium modeling algorithms is that the time-averaged concentration of DNa is much higher than that reflected by the terminal DNa concentration.[10] Based on the heterogeneity of the patient samples and mixed results of the

presented studies and others, it appears that higher DNa (fixed or modeling) may be of benefit in selected patients, but comes with the potential downside of greater IDWG, thirst and potentially greater pre-dialysis SBP.

Sodium modeling in patients prone to intra-dialytic hypotension

It is possible, and indeed likely, that hypotensive prone patients may have a different response to DNa prescriptions than non-hypotensive prone patients. Therefore, Sang et al. analyzed 414 sessions from 23 patients (five diabetic) with varying degrees of intradialytic hypotension The protocol involved randomization to 2-week blocks of fixed standard DNa (140 mmol/L), linear modeling (155->140mmol/L) or stepwise modeling (155mmol/L x 3 hrs; 140mmol/L for one hour). All sessions lasted four hours and used constant UF. The mean number of hypotensive episodes per 2-week period (defined as SBP decline of 50 mmHg, any BP drop with symptoms requiring an intervention; any SBP <90 mmHg) was significantly less in the linear (1.3 ±1.9) and stepped protocols (0.8 ±1.3) compared with the standard fixed DNa (0.7 ±1.4). However, compared with the standard fixed regimen, the linear and stepped modeling protocols were associated with significantly greater thirst, IDWG (3.7 and 3.9 vs 3.2 kg) and pre-dialysis SBP (145 and 152 vs 143 mmHg). Six patients who were not analyzed left the study due to excessive thirst. The authors postulated that ramping may only be beneficial in those with baseline symptoms or predisposition to hypotension.

Song et al. performed a complex two-stage protocol of several DNa and UF profiling algorithms in 11 IDH-prone patients (>30% of sessions in the prior six months complicated by either SBP<90 mmHg, drop in SBP >30 mmHg or hypotension requiring a clinical intervention). Sodium-balance positive algorithms were associated with fewer intra-dialytic symptoms (including IDH) and less UF failure, but at the expense of greater IDWG compared with controls (DNa=138mmol/L and constant UF rate).[28]

Levin et al. randomized 16 symptomatic and non-symptomatic patients into a double-blind cross-over trial involving DNa of 140 mmol/L with constant UF versus stepwise sodium modeling (155-160 tapering to 140 mmol/L), each over a three-week period. This short study found no differences in IDWG or pre-dialysis SBP, but greater thirst with sodium modeling. Patient preference was markedly greater for the modeled arm compared with the standard arm (94% vs. 25%).[29]

Dialysate sodium - hospitalization and mortality

Despite decades of research examining intermediate outcomes such as symptoms, IDWG and pre-dialysis blood pressure, it is only recently that associations with hospitalization and morality have been examined. The first report from Mc Causland et al. examined 2272 chronic hemodialysis patients from a medium-sized dialysis provider in the United States. In addition to reporting a wide variety in the prescribing patterns of DNa between and within centers, they found that higher DNa (>140 mmol/L or modeling, compared with ≤140mmol/L), was associated with 0.16 kg greater IDWG, but not with higher pre-dialysis SBP. The association of DNa with mortality appeared to differ according to the pre-dialysis serum sodium concentration (SNa), such that higher DNa was significantly associated with

greater mortality only in those with higher SNa. Conversely, there was a trend toward lower mortality for those with lower pre-dialysis SNa when dialyzed against higher DNa.[30]

Hecking et al. published similar findings from the larger DOPPS dataset. When stratified by tertile of pre-dialysis SNa, they found that those in the lowest tertile (<137 mmol/L) had lower mortality (HR 0.77; 95%CI 0.60-0.98) when dialyzed with higher DNa (>140 mmol/L), compared with DNa=140 mmol/L.[31] In a subsequent analysis, they found no evidence for greater mortality associated with higher DNa (HR 0.98; 95%CI 0.95-1.02 per 2 mmol/L higher DNa), but actually a *lower* associated hospitalization rate (HR 0.97; 95%CI 0.95-1.00 per 2 mmol/L higher DNa), despite 0.17% greater associated IDWG. When analyses were restricted to centers in which >90% of individuals were prescribed the same DNa (to minimize confounding by indication) they found a reduced mortality risk with higher DNa (HR 0.88; 95%CI 0.83-0.94).[32] The authors speculated that the beneficial effect may be secondary to greater cardiovascular stability associated with the use of higher DNa, again raising the possibility that in select individuals, the potential benefits of hemodynamic stability may offset the potential downsides of greater thirst, IDWG and pre-dialysis SBP.

Individualization of the dialysate sodium prescription

Individualization of the DNa according to the pre-dialysis SNa may be an effective approach to limit diffusive transfer of sodium during hemodialysis. De Paula et al. randomized 27 non-diabetic and non-hypotensive prone patients to a single-blinded crossover study of fixed DNa (138 mmol/L) versus individualized DNa (set to the same value as the pre-dialysis serum sodium), for nine sessions on each assignment. They reported significantly lower IDWG (2.9 vs. 2.3 kg) and IDH (9 vs. 2%) for those in the individualized arm compared with the standard treatment, but lower pre-dialysis SBP only in those with uncontrolled SBP at baseline.[33]

Sayarlioglu et al. assigned 18 patients to DNa of 135 or 137 mmol/L depending on the baseline SNa. Those with baseline SNa<137mmol/L were assigned to DNa=135 mmol/L, while those with SNa>=137 mmol/L received DNa of 137 mmol/L. Lowering of the DNa resulted in a significant decline in pre-dialysis SBP (179.7 to 151.7 mmHg), IDWG (2.5 to 1.8 kg) and both left ventricular systolic diameter and inferior vena cava diameter as measured by echocardiography. It must be noted that the baseline BP's were relatively high in this cohort of patients.[34] While these studies are encouraging to some degree, they do not address the safety of individualization of the DNa in those with much lower pre-dialysis SNa (<135 mmol/L), who appear to be a high-risk sub-group that may actually benefit from higher DNa, based on observational reports.[30-32]

Practical issues with individualization - measurement of serum and dialysate sodium

Studies of hemodialysis patients have reported the median pre-dialysis SNa to be approximately 136-138 mmol/L (IQR 134-141 mmol/L).[30, 35] Obviously, a single facility wide choice for DNa will result in some individuals dialyzing against a DNa that is higher than their SNa and vice-versa. Therefore, a reasonable question is whether SNa should be measured prior to each session to allow a more tailored DNa prescription. Despite some evidence to suggest that SNa is relatively stable in individual patients over time, isolated

deviations in SNa can lead to a mean intra-individual range as high as 7.1 mmol/L.[36, 37] We also reported a relatively low serum sodium intra-class correlation coefficient of 0.56,[30] raising further questions about the acceptability of using averaged values to accurately individualize DNa.

Historically serum sodium was measured by flame photometry and reported as a substance concentration, i.e. the mass of sodium per unit volume of whole serum. However, sodium ions are restricted to serum water rather than whole serum, and so the traditional laboratory report of sodium concentration underestimates the true sodium concentration per unit of serum water. A further complicating factor is that not all sodium ions are capable of free movement. Thus, serum water sodium 'activity' is a more ideal physiochemical metric than concentration, and can be measured by ion sensitive electrodes (ISE). Indirect ISE requires a dilution step based on an assumption of the proportion of serum that is aqueous, similar to that required by flame photometry, and therefore is subject to the same predisposition with pseudohyponatremia. Direct ISE measurement of sodium activity is not limited by this assumption, but by convention is 'referenced' to historical flame photometric standards for ease of interpretation.[38-40] A further consideration is the Gibbs-Donnan phenomenon - negatively charged proteins accumulate at the surface of the dialysis membrane repel positively charged molecules, effectively reducing the available pool of free sodium ions for diffusive transfer.[41] Therefore, while serum water sodium activity may actually be higher than that inferred from standard laboratory measurements, this is counteracted by the Donnan effect at the dialysis membrane surface, which repels sodium and reduces diffusive transfer.[42]

Due to the above complexities, and the fact that many of these parameters are constantly changing during the course of the dialysis session, development of software programs to achieve a fixed sodium balance over the course of a hemodialysis session would require multiple measurements of ionized sodium in real-time.[43] This strategy is limited by practical and cost related limitations, necessitating the search for more acceptable alternatives including the investigation of plasma and dialysate conductivity as a surrogate for sodium flux.

An alternative to dialysate and serum sodium measurement - conductivity

Based on the linear correlation between sodium content and conductivity of fluids (including plasma and dialysate), it is possible to determine the DNa required to achieve any desired plasma water sodium concentration, without the need for repeated dialysate and plasma measurements.[44] Ionic mass balance studies have shown reduced net sodium removal with the use of higher DNa (144mmol/L) versus standard (140mmol/L) or individualized (adjusted to pre-dialysis plasma conductivity) prescriptions in both hemodialysis alone and hemodialysis with UF. Net patient gain of sodium was only observed when the DNa was 5 mmol/L greater than the pre-dialysis serum sodium.[45]

In a single-blind cross-over study of ten non-hypotensive prone patients, participants were randomized to either progressively lower targets of dialysate conductivity or plasma conductivity. There were no significant differences in terms of hemodynamic stability between the two treatments. However, the patient population was relatively stable at baseline

and the lowest target plasma conductivity allowed by the computer program was limited to 13.5 mS/cm (equivalent to sodium concentration of approximately 135 mmol/L).[46]

Studies have also been performed in less stable patients. For example, Coli et al. recruited 55 hypotensive or symptom-prone patients to a single arm study investigating the utility of the 'automatic adaptive system dialysis', which is based on a mathematical model of sodium and ultrafiltration profiling, over a six-month intervention period. They reported that the percentage of sessions complicated by IDH fell from 58.7% in the first month to 0.9% in the sixth month.[47]

Locatelli et al. randomized 50 hypotensive-prone patients to a cross-over trial of hemofiltration with endogenous reinfusion (HFR) vs. HFR + Aequilibrium. Aequilibrium is an automated program of sodium and ultrafiltration profiling that uses an online conductivity monitor to estimate plasma sodium during each treatment, thereby allowing achievement of a prescribed sodium balance for individual sessions. The frequency of the primary outcome of IDH (defined as SBP decline >25 mmHg with symptoms; any SBP <90 mmHg in those with pre-SBP>100 mmHg; 10% decline in SBP with symptoms in those with pre-SBP <90 mmHg), was significantly lower in the Aequilibrium group (17 vs. 22%, $p<0.01$), without significant difference in ultrafiltration volumes.[48]

Together these novel methods and interesting findings are setting the stage for future larger prospective studies of online conductivity monitoring. Given the opposing signals from observational studies to date (IDWG, thirst and hypertension one hand and decreased mortality and hospitalization on the other), it is imperative that future studies of DNa are designed and powered to investigate hard clinical outcomes.

Conclusion

There are several factors clinicians must take into account when prescribing the dialysate sodium concentration. The potential benefits of higher DNa—greater hemodynamic stability and reports from observational data of lower hospitalization rates and mortality—need to be considered against the potential benefits of lower DNa—lower pre-dialysis BP, less thirst, and reductions in IDWG. These conflicting issues are reflected by the wide variation of dialysate sodium use reported within the US and other countries.[30, 49] Attention should be paid to patient symptoms, nutritional status, and intra-dialytic hemodynamic stability with the overriding aim of striking balance between risk and benefit. The optimal DNa concentration remains unclear. Indeed, it is quite likely that a fixed, unit wide value is not optimal. As several large dialysis organizations consider lowering of the DNa, based largely on observational data of associations with less IDWG, pre-dialysis BP and 'sodium loading', it is our opinion that randomized controlled trials are needed to definitively assess DNa and whether and how DNa should be tailored to individual patients, e.g. based on pre-dialysis SNa or online conductivity monitoring. Dialysate composition should be treated like other interventional drugs or devices, and therefore studied in well conducted trials to determine its efficacy and safety.

There are a number of potential trial designs other than parallel-group randomized studies that could be considered. These include factorial design studies, (where two interventions can be evaluated at the one time, but the possibility of interaction must be accounted for); cluster randomization, (in which groups of patients are randomized rather than at an individual patient-level); cross-over trials, (in which patients serve as their own controls allowing reduction of between-patient variability in estimation of the effect estimates); pragmatic trials, (where easily implementable interventions can be tested on a large scale which assumes that the intervention is likely to have similar effects in all participants and does not require detailed characterization of individual participants thereby reducing costs). Irrespective of the design, trials should be adequately powered to assess effects on IDWG, thirst, patient symptoms, and more importantly, other hard clinical endpoints such as hospitalization and mortality.

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