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Clinical Effects of Personalized Dialysate Sodium in Conventional, Quotidian, and Nocturnal Home Hemodialysis Patients: A Randomized Crossover Trial

Benjamin KA Thomson[1,2,3*], Lihua Li[2] and Robert M Lindsay[1,2,3]

[1]Division of Nephrology, Department of Medicine, London Health Sciences Centre and Western University, London, Ontario, Canada

[2]Kidney Clinical Research Unit, London Health Sciences Centre and Western University, London, Ontario, Canada

[3]Department of Medical Biophysics, Western University, London, Ontario, Canada

[*]**Corresponding author:** Benjamin Thomson, Division of Nephrology, Department of Medicine, 76 Stuart Street, Burr 3-38 Kingston Ontario, K7L-2V7, Canada, Tel: +6135496666; Fax: +613548-2524; E-mail: ben@benthomson.org

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Abstract

Background: In thrice weekly conventional haemodialysis patients, higher dialysate sodium concentrations may associate with adverse clinical outcomes. Whether increased frequency and duration of haemodialysis in quotidian and nocturnal patients alters these clinical outcomes is unknown.

Methods: A randomized crossover study was performed in conventional, quotidian and nocturnal haemodialysis patients. Dialysate sodium (Dial-Na^+) was personalized 3 mmol/L above (DIALHighSOD) or below (DIALLowSOD) the pre-dialysis plasma sodium set point (SP), with 100 days for each crossover study period.

Results: Interdialytic weight gain (IDWG)(2.15 *vs.* 1.90 L, p=0.002), IDWG as % of target weight (IDWG%)(2.78 *vs.* 2.39%, p=0.002), pre-dialysis systolic (143.3 *vs.* 138.3 mm Hg, p=0.001), diastolic (78.6 *vs.* 75.6 mm Hg, p=0.008) and mean arterial pressure (100.2 *vs.* 96.5 mm Hg, p=0.003), post-dialysis systolic (135.4 *vs.* 130.0 mm Hg, p=0.04), diastolic (75.8 *vs.* 72.4 mm Hg, p=0.006) and mean arterial pressure (95.7 *vs.* 91.6 mm Hg, p=0.009) were higher in DIALHighSOD than DIALLowSOD. Haemodialysis frequency was associated with decreased (R=-0.295, slope=-0.002, p=0.034) IDWG%, while the opposite was seen with haemodialysis duration (R=0.507, slope=0.002, p<0.001). Haemodialysis duration increased intradialytic change in diastolic blood pressure (R=0.280, slope=1.127, p=0.044), while haemodialysis frequency increased post-dialysis diastolic blood pressure (R=0.366, slope=3.464, p=0.008).

Conclusions: These results confirm that dialysate sodium concentration alters clinical outcomes in quotidian and nocturnal haemodialysis patients, and that dialysis frequency and duration correlate in opposing fashions in IDWG. Further studies are required to determine the effect of dialysate sodium on cardiovascular outcomes. This trial is registered at UMIN000026102.

Keywords: Dialysate sodium; Hypertension; Interdialytic weight gain; Intradialytic Hypotension; Quotidian haemodialysis; Nocturnal haemodialysis

Abbreviations:

BP: Blood Pressure; DialNa^+: Dialysate Sodium Concentration; DPNa^+: Dialysate To Pre-Dialysis Plasma Sodium Gradient; HIGHDialSOD: Study Period When Dialysate Sodium Is 3 Mmol/L Greater Than Patient's Sodium Setpoint; IDWG: Interdialytic Weight Gain; LOWDialSOD: Study Period When Dialysate Sodium Is 3 Mmol/L Lower Than Patient's Sodium Setpoint; PPNa^+: Post-Minus Pre-Dialysis Plasma Sodium Gradient; Pre-Na^+: Pre-Dialysis Plasma Sodium Concentration; Post-Na^+: Post-Dialysis Plasma Sodium Concentration; R: Pearson's Correlation Coefficient; SP: Pre-Dialysis Plasma Sodium Setpoint

Introduction

Cardiovascular death is the leading cause of mortality in haemodialysis patients [1]. A chronic state of volume and pressure overload is a major contributor [2-5] leading to hypertension, left ventricular hypertrophy [6-10], and death [11,12]. Considerable research has evaluated the effect of dialysis frequency and duration on clinical outcomes [6,13-15]. It is well established that longer haemodialysis sessions improve outcomes [13,14,16-19] including mortality [20-22]. How this improvement relates to volume and pressure control remains controversial.

In patients undergoing conventional thrice weekly haemodialysis, pre-dialysis plasma sodium is stable over time [23,24] and is thus called sodium set point (SP). When the dialysate sodium concentration exceeds the SP, diffusion of sodium into the patient occurs, and a number of undesirable clinical outcomes result, including increased interdialytic weight gain (IDWG), blood pressure, and ultrafiltration rate [25-30]. These clinical outcomes are predicted by the magnitude not only

of dialysate to pre-dialysis plasma sodium gradient ($DPNa^+$), but also by the post to pre-dialysis plasma sodium gradient ($PPNa^+$) [30]. However, the relationship between $DPNa^+$ and clinical outcomes remains uncertain in patients who dialyze more than thrice weekly, or longer than four hours per session. Quotidian and nocturnal haemodialysis patients are exposed more frequently and longer to a diffusion gradient; how this alters clinical outcomes has not been prospectively evaluated.

Three objectives were tested in a randomized crossover study. The first objective was to determine how exposure to a higher $DPNa^+$ altered IDWG, pre- and post-dialysis blood pressure, and ultrafiltration rate, in a study population that included conventional, quotidian and nocturnal haemodialysis patients. The second objective was to determine the effect of dialysis frequency and duration on each of the same clinical outcomes. The third objective was to establish which of $PPNa^+$ or $DPNa^+$ better predicted clinical outcomes.

Materials and Methods

Study population

All patients in the home haemodialysis program of the Southwestern Ontario Regional Renal Program were considered. Patients were excluded if they were under the age of 18, pregnant, or not expected to survive 6 months (Figure 1). All patients used the Fresenius 2008K@homeTM haemodialysis machine.

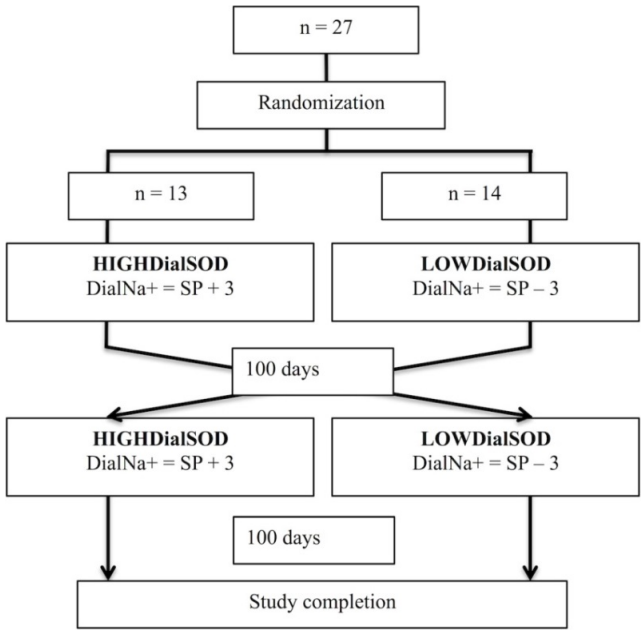

Figure 1: Randomized crossover study design. (DialNa $^+$=dialysate Na^+ concentration (mmol/L); SP=pre-dialysis plasma sodium setpoint (mmol/L))

Study design

A randomized crossover trial design was used (Figure 1). Before randomization, all patients used a standard dialysate sodium concentration of 140 mmol/L. There is no consensus about the number of measurements of pre-dialysis plasma sodium concentration necessary to determine a patient's "set point." However, standard blood work is performed on a monthly basis with study patients. To prevent any single measurement from being weighted too heavily in the determination of this set point, and to assure that the set point was determined from a recent time period when each patient was stable and healthy, the average of the two most recent monthly pre-dialysis plasma sodium ($Pre\text{-}Na^+$) measurements defined the patient's sodium setpoint (SP). Patients were randomized to a dialysate sodium ($Dial\text{-}Na^+$) concentration group either 3 mmol/L above (HIGHDialSOD period), or 3 mmol/L below (LOWDialSOD period) their SP (Figure 1). Dialysate sodium concentration range was restricted to between 130 and 150 mmol/L, because of concerns of clinical effects. After 100 days, patients crossed over study periods. Patients were followed for another 100 days period, and then the study was completed. The study design did not include a washout period before or between study periods; a similar study confirmed a washout period is not necessary to confirm change in clinical outcomes [31].

Patients were told that dialysate composition was being modified to determine effect on quality of life. A quality of life questionnaire was completed at initiation, middle and end of the study period, but evaluation of the questionnaire was not the study's objective. The QOL survey was used to blind patients to the study objective, so that patients would not focus and modify dietary sodium or water intake. On the other hand, study investigators were not blinded.

Blood sample collection

Pre-dialysis and post-dialysis blood samples were collected biweekly from the arterial blood line, using a standard slow blood and stop dialysate method. Locking solution (2 mL of 4% citrate) and a small amount of blood (~2 to 5 mL) are spent prior to blood collection. The samples are centrifuged and refrigerated until delivered to the laboratory, within 12 h of collection. Of interest in this study were pre-dialysis ($Pre\text{-}Na^+$) and post-dialysis ($Post\text{-}Na^+$) plasma Na^+. Only outpatient blood tests were considered, to eliminate the confounding effect of acute illness.

Na^+ concentration measurement

Plasma Na^+ concentration was measured using Roche Modular P Chemistry Analyzer (Roche Diagnostics, Laval, Quebec, Canada) with indirect ion selective electrodes. Dialysate Na+ concentration was determined using online conductivity measurements in the Fresenius H series haemodialysis machine. Dialysate conductivity is strongly correlated to dialysate sodium concentration (r^2=0.997; Dialysate Na^+=9.46 × Dialysate Conductivity+6.5), as previously described [32].

Database creation

Demographic, clinical and haemodialysis data were collected from the electronic patient record (Power Chart by Cerner),

home haemodialysis run sheets and the outpatient haemodialysis unit paper chart. Background factors of interest included patient age, sex, diabetes status, height (cm), weight (kg), residual renal function (mL/min × 1.73 m^2) and vintage of haemodialysis (days). Residual renal function was calculated as previously described [33]. Haemodialysis records were used to record target weight (kg) and dialysis frequency (sessions per week) and duration (hours per session) throughout the study.

Outcomes collected included interdialytic weight gain (IDWG), pre- and post-dialysis systolic and diastolic blood pressure, and ultrafiltration volume. Blood pressure was performed using the integrated Fresenius Home@K blood pressure monitor with a blood pressure cuff personalized to assure patient fit. Home haemodialysis patients are instructed to measure blood pressure at the beginning and end of haemodialysis treatments, and every 30 minutes during treatments. The cuff is fitted to their arm size, and records blood pressure with the patient relaxed while on haemodialysis. Patients were instructed to report episodes of intradialytic hypotension. Patients were seen in outpatient clinic at a minimum of every three months, during which time other intradialytic or interdialytic symptoms were discussed. Patients also knew to contact the home haemodialysis unit at any time if any urgent concerns arose. IDWG was calculated as the difference between the post-dialysis patient weight and the next dialysis session's pre-dialysis patient weight. Dialysate to pre-dialysis plasma sodium ($DPNa^+$) and post- to pre-dialysis plasma sodium ($PPNa^+$) concentration gradients were recorded. We decided a priori that a minimum of 3 observations per study period would be required for each outcome, for a patient to be included in the final analysis. Blood pressure was measured and recorded by patients at home, with automated blood pressure machines, as previously described [34].

Ethics

Ethics approval was granted by the Western University Health Sciences Research Ethics Board. Informed written consent was obtained from all patients. The study was conducted in accordance with the 1964 Declaration of Helsinki.

Table 1: Background demographic and clinical data.

	Mean	Median	Standard Deviation	Interquartile Range
Number Patients	27			
Age (years)	54.2	54.9	11.6	48-62
Sex (% female)	40.7			
Diabetes (%)	33.3			
Weight (kg)	82.9	83.1	22.7	69-92
Height (cm)	169.9	172	12.4	165-176
Body mass index (kg/m2)	28.6	27.7	6.6	25-32
Dialysis Frequency (sessions per week)	4.4	4.0	1.3	3-6
Dialysis Duration (hours per session)	4.8	4.0	2.1	3-7
Vintage (days)	2539	1654	2720	745-3159
Residual renal function (mL/min)	0.51	0.00	1.25	0.00-0.00
Systolic Blood Pressure (mm Hg)	136.6	131.0	23.8	121-148
Diastolic Blood Pressure (mm Hg)	75.6	73.0	12.2	68-84
Hemoglobin (g/dL)	113.2	111.0	15.6	106-121
Albumin (g/L)	40.8	41.0	3.4	40-42
Pre-dialysis Plasma sodium (mmol/L)	137.3	138.0	3.5	135.5-143.0

Statistics

Data were analyzed using the Statistical Package for Social Sciences version 19.0. The mean, median, standard error and interquartile range were calculated for all background demographic and clinical factors.

Statistics-objective 1: Each patient's outcomes were averaged for each study period. Patients' outcomes were then averaged for each study period, and compared using paired two-tailed student T-tests, with a α value of 0.05 considered for statistical significance.

Statistics-objective 2: Pearson correlation coefficients were calculated between each clinical outcome and firstly haemodialysis frequency, then haemodialysis duration. Each patient provided two data points in the analysis, one from each study period. Two-tailed p values with α of 0.05 were used for statistical significance.

Statistics-objective 3: Pearson correlation coefficients were calculated between each clinical outcome and firstly $DPNa^+$, then $PPNa^+$. Two-tailed p values with α of 0.05 were used for statistical significance.

Results

There were 43 patients screened and approached to participate in the study protocol, 27 of whom consented to participate in the study. A total of 27 patients started and completed both study periods. The mean and median observations were greater than 40 for all clinical outcomes (Interdialytic weight gain, Pre-dialysis and Post-dialysis Blood pressures, Ultrafiltration rate), and greater than 3.0 for each of $DPNa^+$ and $PPNa^+$, in both HIGHDialSOD and LOWDialSOD study periods. No patient had fewer than 3 $DPNa^+$ or $PPNa^+$ measurements in either study period; thus, all patients were included in data analysis. The mean difference between the two averaged monthly Pre-Na^+ samples, at the beginning of the study, was 0.92 mmol/L, with the majority of differences (24/27) being less than or equal to 2 mmol/L.

The study population's background factors included an average age of 54.2 years, with 40.7% female and 33.3% diabetic (Table 1). Dialysis frequency averaged 4.4 sessions per week, with a median of 4.0 weekly sessions. Dialysis duration averaged 4.8 hours per session, with a median of 4.0 h. There were 9 short hours daily, 4 frequent nocturnal, 8 intermittent conventional, and 6 intermittent nocturnal haemodialysis patients, as previously defined [35]. The mean and median pre-dialysis plasma sodium concentration (Pre-Na^+) was 137.3 and 138.0 mmol/L, respectively. More than half of study patients had no residual renal function, with a mean of 0.51 and median 0.00 mL/min.

Objectives

Objective 1: IDWG (2.15 *vs.* 1.90 kg, p=0.002), IDWG as % target weight (2.78 *vs.* 2.39%, p=0.002), pre-dialysis systolic (143.3 *vs.* 138.3 mm Hg, p=0.001), diastolic (78.6 *vs.* 75.6 mm Hg, p=0.008) and mean arterial pressure (100.2 *vs.* 96.5 mm Hg, p=0.003) and post-dialysis systolic (135.4 *vs.* 130.0, p=0.04), diastolic (75.8 *vs.* 72.4, p=0.006) and mean arterial pressure (95.7 *vs.* 91.6, p=0.009) were significantly higher in HIGHDialSOD than LOWDialSOD study period (Table 2). No change in target weight, or intradialytic change in systolic, diastolic or mean arterial pressure was found. No episodes of intradialytic hypotension were reported, and thus this outcome was not considered in data analysis.

Objective 2: Haemodialysis frequency was inversely related to IDWG% (R=-0.295, Slope=-0.002, P=0.034), and positively correlated with post-dialysis diastolic blood pressure (R=0.366, slope=3.464, p=0.008) (Table 3). Haemodialysis duration was inversely correlated with ultrafiltration rate (R=-0.593, slope=-0.053, p<0.001) and positively correlated with IDWG (R=0.562, slope=0.184, p<0.001) IDWG% (R=0.507, slope=0.002, p<0.001) and intradialytic change in diastolic blood pressure (R=0.280, slope=1.127, p=0.044).

Table 2: Clinical Endpoints for Home Haemodialysis Patients in HIGHDialSOD and LOWDialSOD Study Periods.

	HIGHDialSOD STUDY PERIOD	LOWDialSOD STUDY PERIOD	P
Interdialytic weight gain (kg)	2.15	1.9	0.002
Interdialytic weight gain (% target weight)	2.78	2.39	0.002
Target weight (kg)	82.6	83.58	0.09
Ultrafiltration rate (L/hour)	0.49	0.44	0.006
Pre-hemodialysis			
Systolic blood pressure (mm Hg)	143.3	138.3	0.001
Diastolic blood pressure (mm Hg)	78.6	75.6	0.008
Mean arterial Pressure (mm Hg)	100.2	96.5	0.003
Post-hemodialysis			
Systolic blood pressure (mm Hg)	135.4	130	0.04
Diastolic blood pressure (mm Hg)	75.8	72.4	0.006
Mean arterial Pressure (mm Hg)	95.7	91.6	0.009
Intradialytic change			
Systolic blood pressure (mm Hg)	-7.9	-8.2	0.9
Diastolic blood pressure (mm Hg)	-3	-3.2	0.76
Mean arterial Pressure (mm Hg)	-4.6	-4.9	0.8

DialNa$^+$=dialysate sodium concentration; SP =setpoint; P values calculated as 2-tailed, paired student's T-test; Bolded text denotes statistical significance P<0.05

Table 3: Correlation between haemodialysis frequency and duration to clinical outcomes.

	HEMODIALYSIS FREQUENCY			HEMODIALYSIS DURATION		
CLINICAL OUTCOME	**R**	**SLOPE**	**P**	**R**	**SLOPE**	**P**
Interdialytic weight gain (kg)	-0.228	-0.119	0.097	**0.562**	**0.184**	**<0.001**
Interdialytic weight gain (% target weight)	**-0.295**	**-0.002**	**0.034**	**0.507**	**0.002**	**<0.001**
Ultrafiltration rate (L/hour)	0.143	0.02	0.301	**-0.593**	**-0.053**	**<0.001**
Pre-dialysis blood pressure						
Systolic (mm Hg)	-0.097	-1.46	0.493	0.003	0.028	0.983
Diastolic (mm Hg)	0.204	1.666	0.148	-0.006	-0.032	0.965
Mean arterial pressure (mm Hg)	0.067	0.624	0.636	-0.002	-0.012	0.989
Post-dialysis blood pressure						
Systolic (mm Hg)	0.039	0.571	0.784	0.17	1.546	0.229
Diastolic (mm Hg)	**0.366**	**3.464**	**0.008**	0.179	1.053	0.204
Mean arterial pressure (mm Hg)	0.248	2.5	0.077	0.194	1.217	0.168
Intradialytic change in blood pressure						
Systolic (mm Hg)	0.166	1.96	0.239	0.21	1.534	0.136
Diastolic (mm Hg)	0.262	1.698	0.06	**0.28**	**1.127**	**0.044**
Mean arterial pressure (mm Hg)	0.22	1.767	0.117	0.253	1.258	0.071

P=p value; R=Pearson's correlation coefficient; Bolded text for statistically significant findings

Objective 3: Increased DPNa$^+$ associated with increased IDWG (R=0.346, slope=0.001, p=0.012), pre-dialysis diastolic (R=0 284, slope=0.824, p=0.041) and post-dialysis diastolic (R=0.325, slope=1.084, p=0.019) and mean arterial (R=0.292, slope=1.030, p=0.036) blood pressure (Table 3). Increased PPNa$^+$ associated with increased IDWG (R=0.306, slope=0.001, p=0.029) and post-dialysis systolic (R=0.181, slope=-0.067, p=0.049) blood pressure.

Discussion

In conventional thrice weekly haemodialysis, positive sodium balance is associated with IDWG, hypertension, left ventricular hypertrophy, cardiovascular morbidity and perhaps mortality [5,26-30,36,37] although the relationship with mortality remains controversial [38]. The clinical effects of frequent or prolonged exposure to sodium concentrations have not been prospectively evaluated. Our study population included patients on quotidian and nocturnal haemodialysis prescriptions (Table 1). There were a high proportion of females (40.7%) and diabetics (33.3%), and a wide spectrum of other demographic factors such as age and body habitus. Furthermore, each patient had multiple measurements of each clinical outcome in each study period. Thus, our study population was representative of a typical haemodialysis population, and the clinical outcomes were rigorously evaluated.

This study confirms that in a patient group with quotidian and nocturnal haemodialysis patients, personalization of Dial-Na$^+$ higher than SP leads to several undesirable clinical outcomes, including IDWG, pre- and post-dialysis systolic, diastolic and mean arterial pressure (Table 2). This is consistent with previous trials in thrice weekly conventional haemodialysis patients [27-30]. However, there was no difference in intradialytic change in systolic, diastolic or mean blood pressure between HIGHDialSOD and LOWDialSOD study periods. Previous trials in thrice weekly conventional haemodialysis patients have demonstrated that low dialysate sodium increases risk for intradialytic hypotension [39-41]. However intradialytic hypotension occurs when increases in plasma volume from compartments outside plasma occur slower than haemodialysis reduces plasma volume [40,42]. Our study population had longer haemodialysis duration than previous trials (mean 4.8 hours, interquartile range 3-7 h (Table 1). Since plasma refilling is dependent upon the ultrafiltration rate, longer haemodialysis likely tapered this effect and decreased the dependence of intradialytic blood pressure changes on dialysate sodium concentration.

Whether and how dialysis frequency or duration modifies the clinical outcomes evaluated in this study is of clinical relevance. Our study confirms three important relationships. Firstly, haemodialysis frequency associates with decreased IDWG % (Table 3). Consider the common clinical situation of a patient

undergoing thrice weekly conventional haemodialysis with persistent volume overload and recurrent intradialytic hypotension. Increased dialysis frequency could improve fluid removal [15,43,44] and a slightly positive $DPNa^+$ gradient would protect from intradialytic hypotension [39,41,45]. Our data provides evidence to support increasing haemodialysis frequency to decrease IDWG in such patients. Secondly, haemodialysis duration associates with an increased IDWG and IDWG%. While one might hypothesize that this relates to more prolonged exposure to a DNa^+ gradient, the gradient was positive in the HIGHDialSOD, but not in the LOWDialSOD study period. Therefore, this could reflect the common practice of avoiding food and drink during haemodialysis; this would disrupt dietary intake for conventional and quotidian, but not nocturnal patients. Thirdly, haemodialysis duration associated with increased intradialytic fall in diastolic blood pressure. Previous research has consistently shown that increased haemodialysis time decreases ultrafiltration rate and risk of intradialytic hypotension [22,27,39,46] contrary to this study's findings. However, nocturnal haemodialysis patients often sleep during haemodialysis, so post-dialysis blood pressure is measured in the morning in a relaxed state, unlike the shorter haemodialysis sessions in conventional dialysis. Therefore, the intradialytic blood pressure change may relate also to vasomotor tone, rather than ultrafiltration rates.

$DPNa^+$ was superior to $PPNa^+$ in predicting IDWG%, pre-dialysis diastolic, post-dialysis diastolic and mean arterial pressure (Table 3). This data is in contrast to a number of trials that suggest $PPNa^+$ to be more predictive [30,47,48]. Plasma Na^+ approaches Dial-Na^+ throughout hemodialysis, so intradialytic change in plasma Na^+ was predicted to be less than 3 mmol/L in our study, since Dial-Na^+ was randomized to be 3 mmol/L above (HIGHDialSOD) or below (LOWDialSOD) the SP. Indeed, mean $PPNa^+$ was quite low in our study (LOWDialSOD $PPNa^+$=-1.08 mmol/L; HIGHDialSOD $PPNa^+$=0.57 mmol/L), so $PPNa^+$ was too small to overcome the lack of precision in the plasma Na+ measurement. However, use of the $PPNa^+$ gradient has the disadvantage of using Post-Na^+ and therefore not being known prior to a hemodialysis session. Knowing that DPNa+ predicts clinical outcomes better than $PPNa^+$ when Dial-Na^+ is 3 mmol/L above or below the SP provides useful information, and helps guide selection of dialysate sodium to improve clinical outcomes. Furthermore, it makes measuring Post-Na^+ unnecessary so long as Dial-Na^+ is within 3 mmol/L of the Pre-Na^+.

This study does have limitations. Firstly, we did not record dialysis membrane surface area or blood glucose [49-52], each of which can impact diffusive sodium balance on haemodialysis. However, use of a randomized crossover design negated these effects, since each patient served as their own control, and since these factors were unlikely to change for any particular patient between study periods. Secondly, our study population was small. Despite this, an abundance of clinical endpoints and numerous pre- and post-dialysis sodium values were available from all patients on multiple dialysis modalities. We were still able to report important outcomes of statistical and clinical significance. Thirdly, while both intradialytic hypotension and IDWG correlate with increased mortality [4,5,42], higher dialysate sodium associates with decreased mortality in a subgroup of conventional haemodialysis patients [38]. Therefore, the precise relationship between clinical outcomes and survival still requires prospective evaluation in patients prescribed haemodialysis of varying frequency and duration. This is the first prospective evaluation of the effect of varying dialysate sodium concentrations on clinical outcomes in conventional, nocturnal and short hour's daily haemodialysis patients.

Conclusion

In conclusion, higher personalized dialysate sodium concentration lead to increased interdialytic weight gain, pre- and post-dialysis blood pressure, and ultrafiltration rates in a patient population that includes conventional, quotidian, and nocturnal haemodialysis patients. While haemodialysis frequency associates with decreased IDWG%, the opposite relationship is seen with haemodialysis duration. Furthermore, longer haemodialysis leads to greater falls in diastolic blood pressure, counter to previous research findings. $DPNa^+$ gradient is preferable to $PPNa^+$ to predict clinical outcomes so long as the Dial-Na^+ is personalized within 3 mmol/L of the SP. Further work is needed to establish the effect of personalizing the dialysate sodium concentrations on long-term cardiovascular outcomes in quotidian and nocturnal haemodialysis patients.

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