Research Article

OMICS International

Effect of Personalized Dialysate Sodium Prescription on Plasma Sodium Concentration and Sodium Set Point in Conventional, Quotidian and Nocturnal Home Hemodialysis

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Abstract

Introduction and objectives: In thrice weekly conventional hemodialysis, dialysate sodium prescription can cause intradialytic plasma sodium shifts, and undesirable symptoms. However, changes in pre-dialysis plasma sodium setpoint are not observed. Whether these clinical observations are observed in quotidian or nocturnal home hemodialysis has not been prospectively evaluated.

Methods: A randomized crossover study of conventional, quotidian and nocturnal home hemodialysis patients was performed. Dialysate sodium was personalized 3 mmol/L above (HIGHDIALSOD) or below (LOWDialSOD) the SP, with 100 days for each crossover studies period.

Results: Plasma Na^+ decreased during hemodialysis in LOWDialSOD study period (136.8 to 135.0 mmol/L, p=0.002). Pre-Na^+ SP (137.4 to 136.8 mmol/L, p=0.03) and Pre-Na^+ SP slope (0.014 to -0.015 mmol/L/day, p=0.009) decreased from HIGHDialSOD to LOWDialSOD study periods.

Conclusions: Personalization of Dial-Na^+ to below SP leads to reductions in plasma sodium concentration during hemodialysis, in conventional, quotidian and nocturnal home hemodialysis patients. Furthermore, sodium set point changes in response to Dial-Na^+ prescription. This has the potential to lead to adverse outcomes in a patient population that is followed less frequently and stringently than the in-center hemodialysis population.

Keywords: Sodium set point; Dialysate sodium; Quotidian hemodialysis; Nocturnal hemodialysis; Plasma sodium

Introduction

Cardiovascular disease is the leading cause of mortality in hemodialysis patients [1,2]. Chronic volume and pressure overload are major contributing factors, leading to hypertension, left ventricular hypertrophy and death [3-6]. Several strategies to improve these risk factors have demonstrated success, including dietary sodium restriction [7,8], increasing hemodialysis frequency and duration, [9-14] and volume management guided by bioimpedance [15,16]. Of recent relevant interest to this topic is the dialysate sodium prescription [17-19].

Pre-dialysis plasma sodium concentration is relatively stable in thrice weekly conventional hemodialysis patients, and is thus termed the "sodium setpoint" (SP) [20-22]. When dialysate sodium concentration is less than SP, increased diffusive sodium removal occurs, leading to improvement in interdialytic weight gain, pre- and post-dialysis blood pressure [17,19,23-25] and perhaps also in cardiovascular outcomes and mortality [26,27]. However, marked reduction in dialysate sodium concentration gives rise to intradialytic

symptoms including intradialytic hypotension [28,29]. This may be mediated by intradialytic shifts in plasma sodium concentration [28].

While effects of personalized dialysate sodium prescription are well described in conventional thrice weekly hemodialysis patients, these outcomes have not been prospectively evaluated in quotidian or nocturnal home hemodialysis patients. Whether plasma sodium concentration changes during more frequent or longer hemodialysis sessions is unknown, and whether such changes impact the sodium set point has not been prospectively evaluated. Since these patients often dialyze at home, where their clinical follow-up is less frequent, it is essential to determine if set point changes over time. Three objectives were tested in a randomized crossover study, in conventional, quotidian and nocturnal home hemodialysis patients. Our first objective was to determine if personalized dialysate sodium prescription modified plasma sodium concentration from the start to the end of a hemodialysis session. Our second objective was to determine if a change in dialysate sodium concentration altered the pre-dialysis sodium set point. Our third objective was to determine if dialysis frequency or duration modulated changes in either plasma sodium throughout dialysis or sodium set point.

Methods

Study population

All patients in the home hemodialysis 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.

Study design

A randomized crossover trial design was used. The average of the two most recent monthly pre-dialysis plasma sodium (Pre-Na$^+$) measurements defined the patient's sodium setpoint (SP). Patients were randomized to a dialysate sodium (Dial-Na$^+$) concentration group either 3 mmol/L above (DialNa$^+$ = SP^{+3} = HIGHDialSOD) or 3 mmol/L below (DialNa$^+$ = SP^{-3} = LOWDialSOD) 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 day period and then the study was completed.
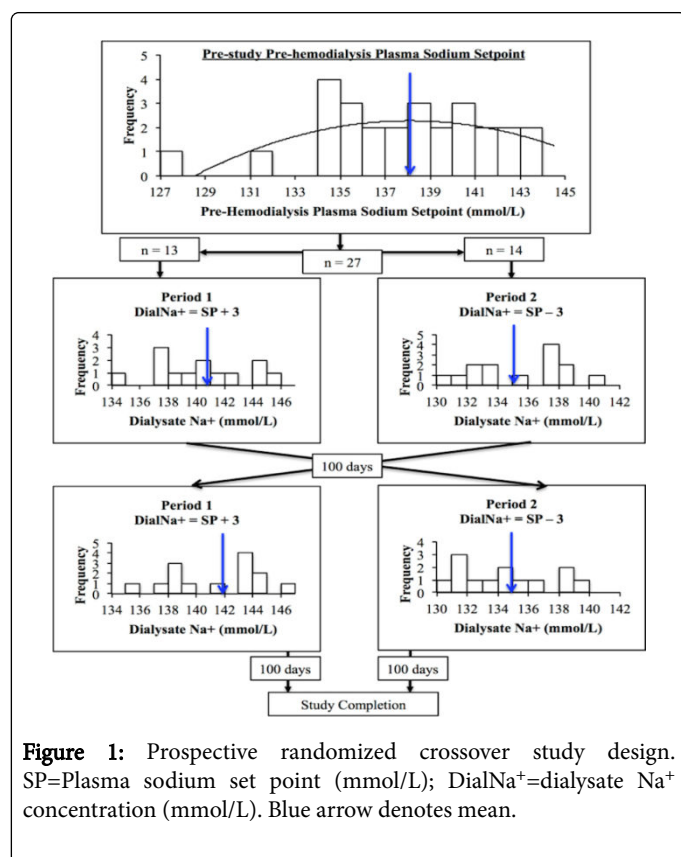
Figure 1: Prospective randomized crossover study design. SP=Plasma sodium set point (mmol/L); DialNa$^+$=dialysate Na$^+$ concentration (mmol/L). Blue arrow denotes mean.

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 hours of collection. Of interest in this study were pre-dialysis (Pre-Na$^+$) and post-dialysis (Post-Na$^+$) plasma Na$^+$. Only outpatient blood tests were considered, to eliminate the confounding effect of acute illness.

Na$^+$ concentration measurement

Plasma Na$^+$ concentration were 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 hemodialysis 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 [30].

Database creation

Demographic, clinical and hemodialysis data were collected from the electronic patient record (Power Chart by Cerner), home hemodialysis run sheets and the outpatient hemodialysis 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 hemodialysis (days). Residual renal function was calculated as previously described [31]. Hemodialysis records were used to record dialysis frequency (sessions per week) and duration (hours per session) throughout the study.

Dialysate to pre-dialysis plasma sodium gradient (DPNa$^+$) and post-dialysis (Post-Na$^+$) to pre-dialysis (Pre-Na$^+$) plasma sodium gradient (PPNa$^+$) concentration were also recorded. We decided a priori that a minimum of 3 observations per DPNa$^+$ and PPNa$^+$ would be required in each of HIGHDialSOD and LOWDialSOD study periods for a patient to be included in the final analysis.

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 Helsinki Declaration.
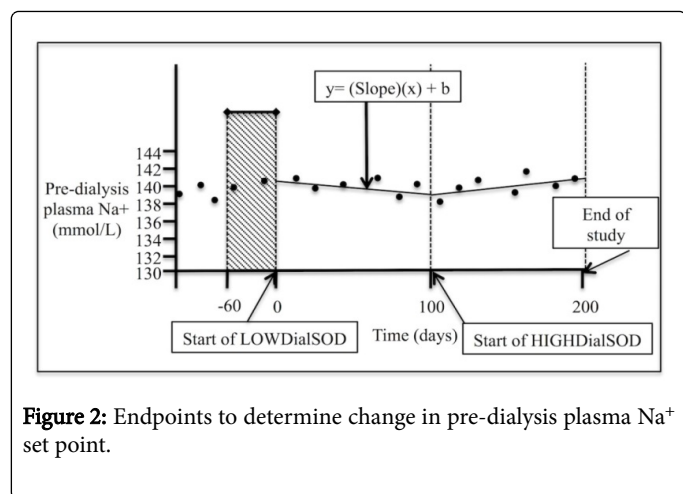
Statistics

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

The average pre- and post-dialysis plasma sodium concentrations were calculated for each patient for each study period. The group average pre- and post-dialysis plasma sodium concentrations were then compared between HIGHDialSOD and LOWDialSOD, using paired two-tailed student t-tests with a value of 0.05 considered for statistical significance.

Statistics- objective 2

A change in SP was defined in two ways (Figure 2). Firstly, the average Pre-Na$^+$ differed between HIGHDialSOD and LOWDialSOD study periods. Secondly, the slope of Pre-Na$^+$ over time differed between study periods. Differences were detected using paired two-tailed student t-tests with a value of 0.05 considered for statistical significance.

Figure 2: Endpoints to determine change in pre-dialysis plasma Na+ set point.

Statistics- objective 3

Pearson correlation coefficients were calculated to determine if changes in SP were modulated by hemodialysis frequency or duration. Y axis included either change in pre-Na$^+$ or slope of Pre-Na$^+$ from HIGHDialSOD to LOWDialSOD study periods. X axis included hemodialysis frequency or duration. Slope of correlation was calculated and two-tailed p values were determined with a value of 0.05 for statistical significance.

Results

There were 43 patients screened for this study (Figure 1), 16 of whom were excluded for reasons that included pregnancy (n=1), age less than 18 (n=1), life expectancy less than 6 months (n=3) or declining participation (n=11). A total of 27 patients started and completed both 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 (23/26) being less than or equal to 2 mmol/L.

Mean and median SP was 138.1 and 138.5 mmol/L, with an interquartile range of 135.5 to 141.0 mmol/L (Figure 1 and Table 1). The study population was 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 hours. More than half of patients had no residual renal function, with a mean of 0.51 and median 0.00 mL/min.

	Mean	Median	Standard Deviation	Interquartile Range
Number Patients	27			
Pre-dialysis plasma sodium set point (mmol/L)	138.1	138.5	3.8	135.5-141.0
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	172.0	12.4	165-176
Body mass index (kg/m^2)	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 BP (mm Hg)	136.6	131.0	23.8	121-148
Diastolic BP (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

Table 1: Background demographic and clinical data.

Objective 1

Pre-Na+ and Post-Na$^+$ did not differ in HIGHDialSOD study period (137.4 to 137.8 mmol/L, p=0.45). However, plasma Na$^+$ fell throughout dialysis (136.8 to 135.0 mmol/L, p=0.002) in LOWDialSOD study period (Figure 3).
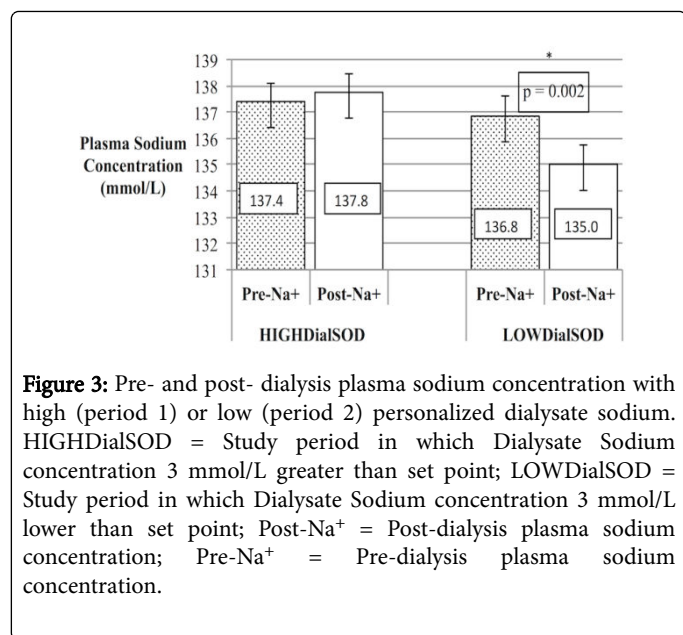
Figure 3: Pre- and post- dialysis plasma sodium concentration with high (period 1) or low (period 2) personalized dialysate sodium. HIGHDialSOD = Study period in which Dialysate Sodium concentration 3 mmol/L greater than set point; LOWDialSOD = Study period in which Dialysate Sodium concentration 3 mmol/L lower than set point; Post-Na$^+$ = Post-dialysis plasma sodium concentration; Pre-Na$^+$ = Pre-dialysis plasma sodium concentration.

Objective 2

Pre-Na$^+$ sodium setpoint decreased from HIGHDialSOD to LOWDialSOD study period (137.4 to 136.8 mmol/L, p=0.03) (Table 2).

The slope of Pre-Na$^+$ also decreased from HIGHDialSOD to LOWDialSOD study periods (0.014 to -0.015 mmol/L/day, p=0.009).

	Study Period		
Outcome	**HIGHDialSOD**	**LOWDialSOD**	**p**
Pre-dialysis plasma sodium (mmol/L)	137.4	136.8	0.03
Slope of pre-dialysis plasma sodium [(mmol/L)/day]	0.014	-0.015	0.009
HIGHDialSOD = Dialysate sodium concentration 3 mmol/L higher than pre-dialysis sodium set point; LOWDialSOD = Dialysate sodium concentration 3 mmol/L lower than pre-dialysis sodium set point			
Bolded text signifies statistically significant findings			

Table 2: Difference in absolute and slope of pre-dialysis plasma sodium set point with two personalized dialysate sodium concentrations.

Objective 3

The change in Pre-Na$^+$ across study periods was not correlated to hemodialysis frequency (R=0.264, p=0.193) or duration (R=0.032, p=0.877) (Table 3). Likewise, the change in slope of Pre-Na$^+$ across study periods was not correlated to hemodialysis frequency (R=0.172, p=0.401) or duration (R=0.067, p=0.745).

	Dialysis Frequency			**Dialysis Duration**		
Outcome	**R**	**Slope**	**P**	**R**	**Slope**	**P**
Pre-dialysis plasma sodium (Pre-Na$^+$)(mmol/L)	0.264	0.464	0.193	0.032	0.036	0.877
Slope pre-dialysis plasma sodium (mmol/L/day)	0.172	0.007	0.401	0.067	0.002	0.745
P=p-value; R=Pearson's correlation coefficient						

Table 3: Effect of hemodialysis frequency and duration on change across study periods in absolute and slope of pre-dialysis sodium set point.

Discussion

Reduction in dialysate sodium concentration can reduce IDWG, blood pressure and cardiovascular outcomes [17,19,24]. However, it may also give rise to intradialytic hypotension [28,29]. mediated by intradialytic shifts in plasma sodium concentration [28]. Whether personalized dialysate sodium prescription associates with intradialytic shifts in plasma sodium in quotidian or nocturnal home hemodialysis patients is previously unreported.

This randomized crossover study included patients with a spectrum of dialysis frequency (mean=4.4, interquartile range=3 to 6 sessions per week) and duration (mean=4.8, interquartile range 3-7 hours) (Table 1). There was a high number of females (40.7%) and diabetics (33.3%) and a wide spectrum of other demographic and clinical factors such as blood pressure, age and body habitus. Every patient had at least 3 recordings of PPNa$^+$ and DPNa$^+$ during each study period. The sodium set point (SP) varied widely in our study population (interquartile range 135.5 to 141.0, Table 1 and Figure 1). Thus, our study population was representative of a typical hemodialysis population, and outcomes were evaluated with rigor.

While the HIGHDialSOD plasma sodium did not change over dialysis (137.4 to 137.8 mmol/L, p=0.45), there was a significant decrease from Pre-Na$^+$ to Post-Na$^+$ in the LOWDialSOD study period (136.8 to 135.0 mmol/L, p=0.002) (Figure 3). This is consistent with Suckling et al. recent work [28]. While the magnitude of intradialytic plasma sodium change was small in our study, there is still reason for concern. Firstly, intradialytic decrease in plasma sodium is linked to intradialytic hypotension [28], which independently increases risk of death [29]. Secondly, ignoring patient-specific SP by facility level decreases in dialysate sodium concentrations will lead to significantly negative DPNa$^+$ gradients in some patients. Again, this increases the risk of intradialytic hypotension. Ultimately, selection of dialysate sodium should be personalized to the patient to limit adverse outcomes of a very positive DPNa$^+$, while simultaneously avoiding the complications of intradialytic plasma sodium shifts from a negative DPNa$^+$; this can only be done by regularly following the Pre-Na$^+$ and adjusting the Dial-Na$^+$ accordingly.

Net diffusive intradialytic ionic sodium flux reflects several competing mechanisms. Sodium concentration in serum water ranges from 6 to 9 mmol/L higher than in whole serum. This is because plasma water constitutes about 93% of total plasma, whereas it is 100%

of total dialysate volume [32]. However, this difference is compensated by the Gibbs-Donnan effect, in which anionic plasma proteins are not diffusible through the dialysis membrane, and therefore create an electric field attracting sodium, reducing diffusible sodium by 4 to 5% [33]. Sodium ions complex with anions in both serum water and dialysate, further reducing diffusible sodium in both compartments [34]. These forces cause the actual plasma sodium concentration to be higher than measured; when DNa^+ is greater than PNa^+, a neutral ionic mass balance persists so long as $DPNa^+$ is not greater than 5 mmol/L [35]. Thus, when DNa^+ is personalized to be lower than measured PNa^+, the actual $DPNa^+$ will be less than measured. This explains why there was either an intradialytic plasma sodium or SP change in the HIGHDialSOD period, when a DNa^+ was chosen to be only 3 mmol/L higher than PNa^+. On the other hand, an intradialytic plasma sodium and SP change were observed in the LOWDialSOD period, since the personalized DNa^+ (of 3 mmol/L lower than PNa^+) led to a $DPNa^+$ that was even lower than -3 mmol/L, since actual PNa^+ was greater than measured.

There are other potential mechanisms for the observation that SP changed in LOWDialSOD but not HIGHDialSOD period. Firstly, serum albumin concentration didn't change between both study periods; thus, maintenance of trans-dialysis membrane electrical potential during the LOWDialSOD period required increased movement of cationic serum sodium out of the blood into the dialysate. On the other hand, during the HIGHDialSOD period, maintenance of electric potential favored retention of sodium in the plasma. Secondly, the osmotic gradient from dialysate to plasma is greatest at the start of dialysis, when plasma osmolality contains retained osmoles such as urea. This favors water movement from dialysate to plasma; when dialysate osmolality is reduced by using a lower dialysate sodium concentration, this effect is accentuated and increased water movement occurs from dialysate to plasma. This effect has been previously described [36-38].

While Pre-N+ is stable as a "set point" in thrice weekly conventional hemodialysis patients [20-22], this has not been prospectively evaluated in quotidian or nocturnal home hemodialysis patients. A retrospective study by our research group found that conversion from thrice weekly conventional to quotidian hemodialysis associated with a reduction in SP, when $DPNa^+$ was neutral or negative [39]. We confirm a change in SP prospectively in this study, as mean pre-Na^+ (137.4 vs. 136.8 mmol/L, p=0.03) and slope of pre-Na^+ (0.014 vs. -0.015 mmol/L/day, p=0.009) (Table 2) differ between HIGHDialSOD and LOWDialSOD study periods. While the magnitude of the change in pre-Na^+ is small, this is both statistically and clinically important. Firstly, decreases in sodium setpoint are independently associated with increased mortality [40,41]. Secondly, hemodialysis units that use facility wide dialysate sodium prescriptions will lead many patients to having highly negative $DPNa^+$ and thus more exaggerated decreases in SP. Thirdly, in units that personalize dialysate sodium by following Pre-Na^+, repeated decreases in Dial-Na^+ to maintain a negative $DPNa^+$ could cause repeated and undesirable decreases in SP. Finally, this raises the possibility that hemodialysis prescription might be modified to increase SP in vulnerable patients. More research will be required to determine the pathophysiologic mechanism of a change in SP in these patients, and to determine the impact on cardiovascular outcomes.

There are limitations to this study. Firstly, we did not measure blood glucose, lipids or paraprotein levels, each of which can impact plasma sodium measurement [42-44]. However, use of a randomized crossover study 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. However, our patients are highly compliant, having participated in multiple previous research trials [13,14]. This enabled the recording of numerous pre- and post-dialysis sodium values from all patients on multiple hemodialysis modalities. We were thus able to report statistically and clinically significant outcomes.

Conclusion

In conventional, quotidian and nocturnal home hemodialysis patients, the personalization of Dial-Na^+ to lower than the SP decreases plasma sodium throughout hemodialysis. Furthermore, Dial-Na^+ can modify the Pre-Na^+ "set point". Further research is needed to determine the effect on cardiovascular morbidity and mortality.

Acknowledgements

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