

Associations of a facility level decrease in dialysate sodium concentration with blood pressure and interdialytic weight gain

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Abstract

Background. Dialysate $[\text{Na}^+]$ is often overlooked as a contributor to hypertension in patients on haemodialysis (HD). We report observational experience with a facility level decrease in dialysate $[\text{Na}^+]$ from 141 mmol/l to 138 mmol/l, in the absence of concurrent change with respect to dietary sodium regulation.

Methods. The sample comprised all patients ($n = 52$) dialysing at a single HD facility over an 8-month period flanking the change in dialysate $[\text{Na}^+]$. Outcomes included repeated observations of blood pressure (BP), interdialytic weight gain (IDWG), pre-dialysis plasma $[\text{Na}^+]$ and adverse events. Predictors other than dialysate $[\text{Na}^+]$ included patient demographics, clinical characteristics and number of antihypertensive medications. The study used a longitudinal unbalanced panel design, and hierarchical linear and Poisson mixed models.

Results. In multivariate analyses, the change in dialysate $[\text{Na}^+]$ was associated with a statistically significant small to medium-sized decrease in pre- and post-dialysis systolic and diastolic BP, pre-dialysis plasma $[\text{Na}^+]$, but not IDWG. Change was greatest in the patient tertile with the highest initial BP. There was no change in the frequency of adverse events. Modelling dialysate $[\text{Na}^+]$ exposure as the diffusion gradient from dialysate to blood water did not improve the strength of associations.

Conclusions. A facility level decrease in dialysate $[\text{Na}^+]$ from 141 mmol/l to 138 mmol/l appears to be safe and well tolerated, and a useful means of improving BP control. The lack of change in IDWG probably reflects lack of dietary salt restriction, and but does raise the issue of volume-independent effects of sodium exposure on BP.

Keywords: dialysate sodium; haemodialysis; hypertension; interdialytic weight gain

Introduction

Dialysate is a crucial component of haemodialysis (HD), being the vehicle for regulation of solutes and water. One of the most important components of dialysate is sodium. Dialysate $[\text{Na}^+]$ has increased from 130–135 mmol/l to 140–145 mmol/l over the last 50 years due to cumulative clinical experience of less intradialytic cramps, headache and hypotension, especially in the context of the trend to progressively shorter treatment times [1–7].

It has been suggested that higher dialysate $[\text{Na}^+]$ increases blood pressure (BP), interdialytic weight gain (IDWG), ventricular hypertrophy (LVH) and ultimately even mortality [8,9]. Although these data are not sufficient to demonstrate causality, the putative effects of higher dialysate $[\text{Na}^+]$ are, however, biologically plausible and consistent with key observations of opinion leaders in the field [1,10].

Concern about the clinical impact of dialysate $[\text{Na}^+]$ in our own HD population prompted a review of prescribing patterns at our regional renal service based in Auckland, New Zealand. We observed a broad range of empirical dialysate $[\text{Na}^+]$ settings between facilities (from 137 mmol/l to 143 mmol/l), and in February 2005 a decision was made to standardize default dialysate $[\text{Na}^+]$ across the service to 138 mmol/l, in the absence of sodium profiling.

The primary objective of this study was to determine the associations between dialysate $[\text{Na}^+]$ and BP and IDWG, at a single HD facility, where dialysate $[\text{Na}^+]$ underwent a collective reduction from 141 mmol/l to 138 mmol/l. The secondary objective was to determine the corresponding associations between dialysate $[\text{Na}^+]$ and pre-dialysis plasma $[\text{Na}^+]$ and intradialytic adverse events.

Methods

Sample and sampling frame

The study was conducted with the Department of Renal Medicine at Middlemore Hospital, Auckland, New Zealand.

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The department provides regional nephrology and renal replacement therapy services to a population of approximately 330 000, the majority of whom are of New Zealand Maori and Polynesian ethnicity. As of 31 December 2004, there were 390 patients on dialysis, 296 of whom were treated with HD and the remainder treated with peritoneal dialysis.

Data for analyses were retrospectively collected from a single satellite HD facility in the region, which was chosen on the basis of being the only one where: (i) default dialysate [Na⁺] prior to standardization was ubiquitous for all HD patients and treatments in the facility, and (ii) no sodium profiling was utilized.

Data were analysed from each of the 4-month periods flanking the change in default dialysate [Na⁺]. The duration of these periods was chosen on the basis of previous studies indicating three months or more as the time to steady state haemodynamic status and interdialytic diet and fluid intake [11,12]. Patient data included demographics, diabetes mellitus status and cause of end-stage kidney failure. Treatment data included details of the HD regimen, pre- and post-dialysis BP, IDWG, pre-dialysis plasma [Na⁺], number of antihypertensive medications, number of treatments requiring normal saline infusions for intradialytic hypotension or cramps and the number of treatments requiring emergency medical attention.

The sample comprised all patients dialysing at the facility during the 8 months, including those transient patients who either joined or left the facility midway through the period of observation. This sampling frame avoids potential selection bias, since some drop-ins and drop-outs could plausibly have been related directly to health state: due to deaths, serious illness or patients moving into institutional care. Restricting analyses to those dialysing for the entire period of observation is inadvisable, potentially resulting in an incomplete 'unrepresentative' sample with characteristics and statistical estimates that differ between patients for whom data are available versus those for whom data are unavailable [13].

Blinding was not part of the study design, and data were collected and analysed with full knowledge of the patients' dialysate [Na⁺] by the patients, and medical and nursing staff.

Haemodialysis regimen

HD was performed on a thrice weekly basis for all patients using Gambro® AK200S machinery (Gambro AB, Lund, Sweden), with bicarbonate based dialysate (Bicart® powdered cartridge system) and synthetic high and low flux haemodialysers (Polyflux® polyamide membranes). Mean ± SD HD session length was 4.5 ± 0.43 h.

Default dialysate [Na⁺] was 141 mmol/l for all treatments in the audited HD facility prior to 1 February 2005, and 138 mmol/l thereafter. This change was made to all machines within a week of 1 February 2005. There was no change in the type of machinery or consumables over the period of observation, or nursing staff in the facility at any level.

Outcome definitions

The primary outcomes (dependent or outcome variables) in this study were BP (pre- and post-dialysis, systolic and diastolic) and IDWG. The secondary outcomes were

pre-dialysis plasma [Na⁺] and intradialytic adverse events (normal saline infusions for cramp or hypotension and requirement for urgent medical advice or attention).

Exposure definitions

The primary exposure (independent or explanatory variables) in this study was dialysate [Na⁺] (141 mmol/l vs 138 mmol/l). This parameter was also modelled separately as pre-dialysis sodium diffusion gradient (ΔNa^+) defined as the sodium ionic activity (γ_{Na}) in dialysate minus that in pre-dialysis plasma [14–16]. Plasma γ_{Na} was estimated from plasma [Na⁺] by direct ionometry (ABL725 blood gas analyzer, Radiometer, Copenhagen) corrected by a factor of 0.967 to account for the Donnan effect from negatively charged plasma proteins [15]. Dialysate γ_{Na} was estimated from dialysate conductivity multiplied by 10 (H.D. Polaschegg, personal communication, 29 May 2006, [17–19]).

Confounding by patient age, sex, race, diabetes mellitus status, post-dialysis body weight, and number of antihypertensive medications was assessed through multivariate modelling described subsequently.

Statistical methods

This study uses a longitudinal, panel design, with repeated clinical observations obtained from the same patient over time. The panel design is effective for studying change over time and increases power of analysis in longitudinal data.

Data from the study cohort were collapsed (mean, median or count as appropriate) by patient and month to provide the cross-sectional time series. Specifically, all BP recordings for each patient during each observation period were used for summary measures. Variables for statistical modelling were, therefore, monthly summary measures of dependent and independent variables (n cases, over t time periods, for a total of $n \times t$ observations). The resulting data produced an unbalanced panel, as a result of missing observations pertaining to patients who were dialysing at the facility during some parts of the period of observation, but not during others.

Analyses used hierarchical linear (continuous) or Poisson (count) mixed models. To account for internal correlation between repeated patient observations, a random effect model was used for each dependent variable that included all data from all time periods simultaneously, with observations over time from the same patient sharing the same random effects, assuming different random effects for different patients. To account for non-response bias, regression coefficients were estimated using the maximum likelihood method. All of the confounding independent variables discussed earlier were considered initially, and reduced models estimated after removing those that were not significant.

The associations of dialysate [Na⁺] with outcomes were assessed both in terms of statistical significance, and also magnitude of effect. The former was assessed at a level of $P < 0.05$. Effect size was assessed using Cohen's d , computed as the difference between the means between the two comparison groups, divided by their pooled SD (as the root mean square of the two SD). This calculation is suitable for correlated designs involving repeated measures such as panel data, avoiding the over-estimation of the actual effect

size that arises by the calculation of this statistic from the paired *t* or chi-square statistic. For the models estimated using pre-dialysis ΔNa^+ , Cohen's *d* was calculated from the effect size correlation calculated as the product moment correlation (*r*) between the observed pre-dialysis ΔNa^+ and the predicted dependent variable from the final multivariate model, according to the formula Cohen's $d = 2 * r / \sqrt{(1 - r^2)}$. Cohen used the arbitrary values of 0.1, 0.3 and 0.5 to indicate small, medium and large effects, respectively, and these values can be used to the effect size: nil-to-small, small-to-medium, medium-to-large and large-to-extreme [20,21].

Where necessary, comparisons between groups were made using Student's *t*-test, Mann-Whitney U-test and non-parametric *K*-sample test (with a continuity correction) for continuous variables or chi-square test for categorical ones. Analyses were conducted using STATA 9.2 (StataCorp, College Station, TX, USA).

Ethical considerations

Formal approval for the research process was granted by the National (New Zealand) Health and Disability Ethics Committee under the provisions made for retrospective review of patient notes and data.

Results

Baseline patient characteristics are shown in Table 1. The sub-group dialysing for the entire period of observation was different from the sub-group of drop-ins or drop-outs only with respect to angioaccess and race. No significant change was seen in the post-dialysis weight and number of antihypertensive

medications for the study population over the period of observation, as shown in Figure 1.

Patient BP, IDWG and pre-dialysis $[\text{Na}^+]$ by dialysate $[\text{Na}^+]$ exposure are illustrated graphically in Figures 2–5, stratified by tertiles defined at study entry. For instance, a patient with a pre-dialysis systolic BP in the upper tertile for the population at study entry would be assigned to this category, and their corresponding BP represented in the same tertile after the change in dialysate $[\text{Na}^+]$ exposure. Significant differences in primary and secondary outcomes by dialysate $[\text{Na}^+]$ exposure were observed only in patients in the upper and/or middle tertiles of the population, and not in those in the lower tertiles.

The frequency of adverse intradialytic clinical events by dialysate $[\text{Na}^+]$ exposure is illustrated in Figure 6. The small numbers of such events preclude meaningful statistical analysis, although inspection shows that they are spread approximately equally amongst all tertiles of BP at study entry.

The results of multivariate modelling are shown in Table 2. These core analyses were performed for all patients dialysing at the facility during the 8 months to minimize bias as described earlier. When dialysate $[\text{Na}^+]$ was modelled as a dichotomous variable, there was a statistically significant association with lower pre- and post-dialysis BP and pre-dialysis $[\text{Na}^+]$, but not IDWG. The magnitude of the effect as assessed by Cohen's *d* was small to medium for BP and nil to small for IDWG. When dialysate $[\text{Na}^+]$ was modelled as pre-dialysis ΔNa^+ , there was no relationship with pre- and post-dialysis BP or pre-dialysis $[\text{Na}^+]$, but a statistically significant association with lower IDWG. The magnitude of the effect was small

Table 1. Baseline patient characteristics, presented as mean (standard deviation)

| | Patients remaining throughout the entire observation period | Patients not remaining throughout the entire observation period | <i>P</i> -value |
|--|---|---|-----------------|
| Number of patients | 42 | 10 | – |
| Age (years) | 52.4 (10.8) | 49.1 (13.1) | 0.48 |
| Sex (M/F) | 26/16 | 7/3 | 0.23 |
| Diabetes mellitus | 42.9% | 33.3% | 0.55 |
| Angioaccess | | | 0.009 |
| Arteriovenous fistula | 88.1% | 50% | |
| Arteriovenous graft | 2.4% | – | |
| Venovenous | 9.5% | 50% | |
| Race | | | 0.041 |
| White | 2.4% | 10% | |
| Polynesian | 38.1% | 70% | |
| New Zealand Maori | 47.6% | 20% | |
| Asian | 11.9% | – | |
| Number of antihypertensive drugs per patient | 0.8 (0.8) | 1.1 (1.2) | 0.44 |
| Interdialytic weight gain (kg) | 2.4 (0.8) | 2.2 (0.8) | 0.38 |
| Pre-dialysis systolic blood pressure (mmHg) | 151.8 (19.4) | 159.6 (18.0) | 0.25 |
| Pre-dialysis systolic blood pressure (mmHg) | 84.4 (10.6) | 88.4 (10.2) | 0.28 |
| Post-dialysis diastolic blood pressure (mmHg) | 139.1 (15.8) | 147.3 (28.7) | 0.40 |
| Post-dialysis diastolic blood pressure (mmHg) | 78.7 (9.2) | 90.6 (24.5) | 0.15 |
| Pre-dialysis plasma $[\text{Na}^+]$ (mmol/l) | 139.7 (2.6) | 138.6 (2.6) | 0.24 |
| Pre-dialysis Na^+ diffusion gradient (mmol/l) | 1.3 (2.6) | 1.8 (2.4) | 0.60 |
| Extemporaneous saline infusions per month | – | 1 | 0.039 |
| Emergency medical attention per month | – | 1 | 0.039 |

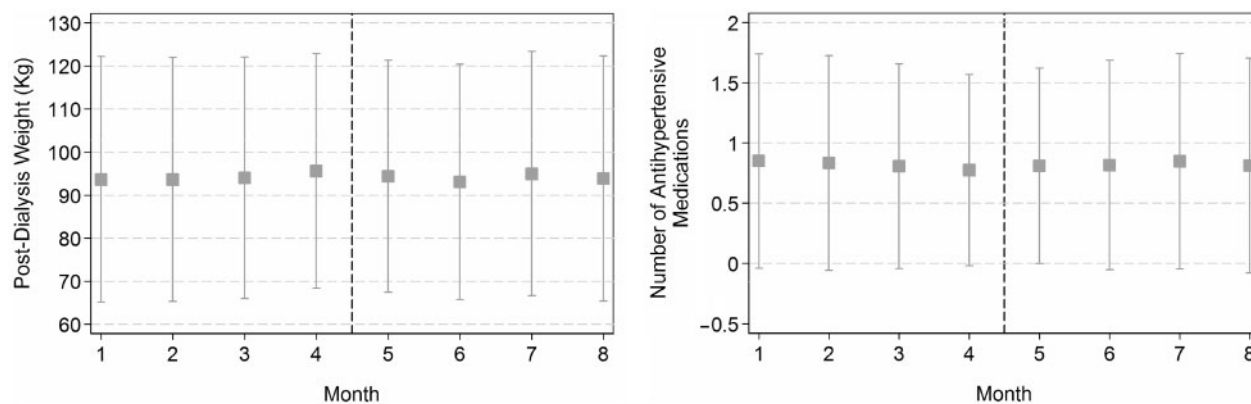


Fig. 1. Post-dialysis weight and number of antihypertensive medications by month of observation (markers represents means, error bars represent SDs, with change in dialysate [Na⁺] indicated by the dashed vertical lines).

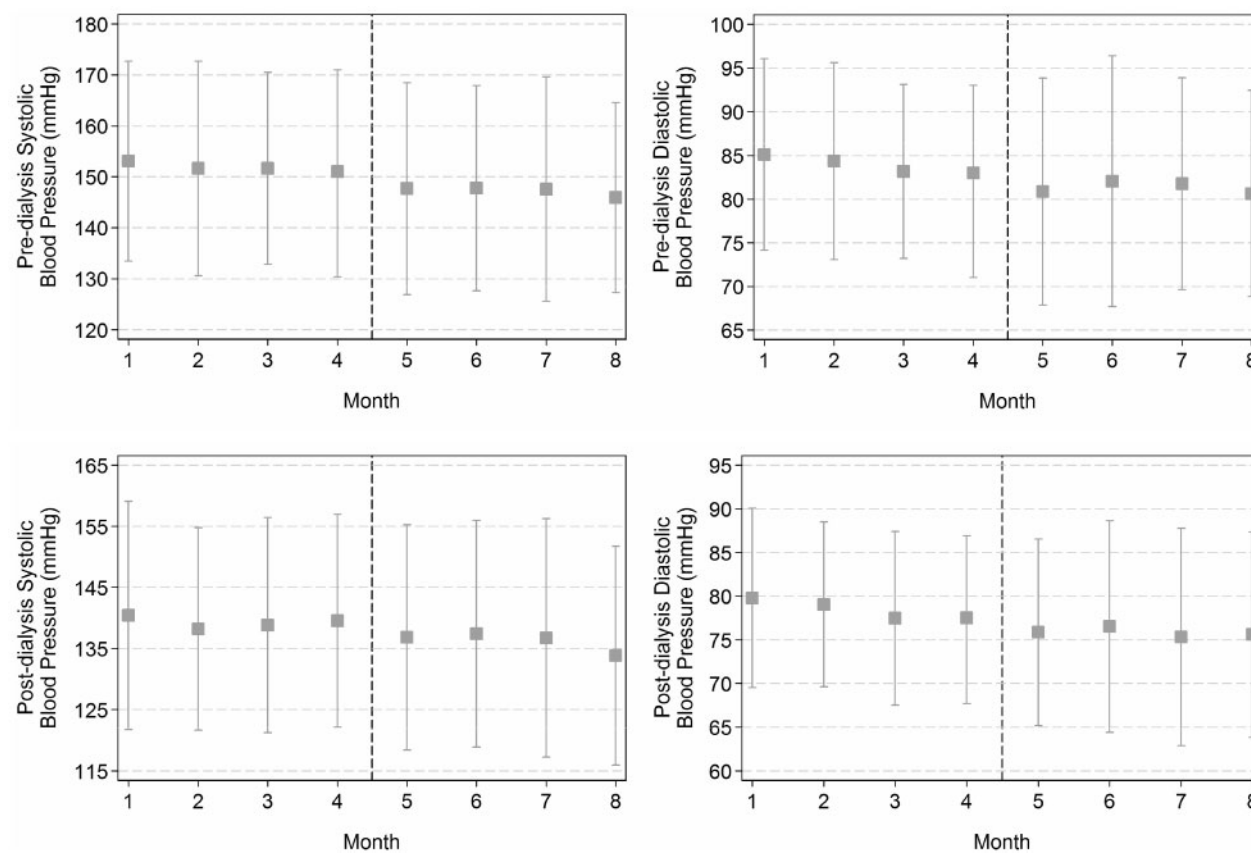


Fig. 2. Blood pressure by month of observation (markers represents means, error bars represent SDs, with change in dialysate [Na⁺] indicated by the dashed vertical lines).

to medium. There was no relationship between dialysate [Na⁺] and adverse events. There was a statistically significant association between female gender and more frequent normal saline infusions.

Although not part of the core analyses, we repeated multivariate modelling restricting analyses to the sample of the cohort dialysing for the entire period of observation. These restricted analyses resulted in statistical estimates that were very similar to

those from the core analyses presented earlier (data not shown).

Discussion

Hypertension is thought to increase cardiovascular morbidity and mortality in patients with end-stage kidney failure [22–24]. One of the prime determinants

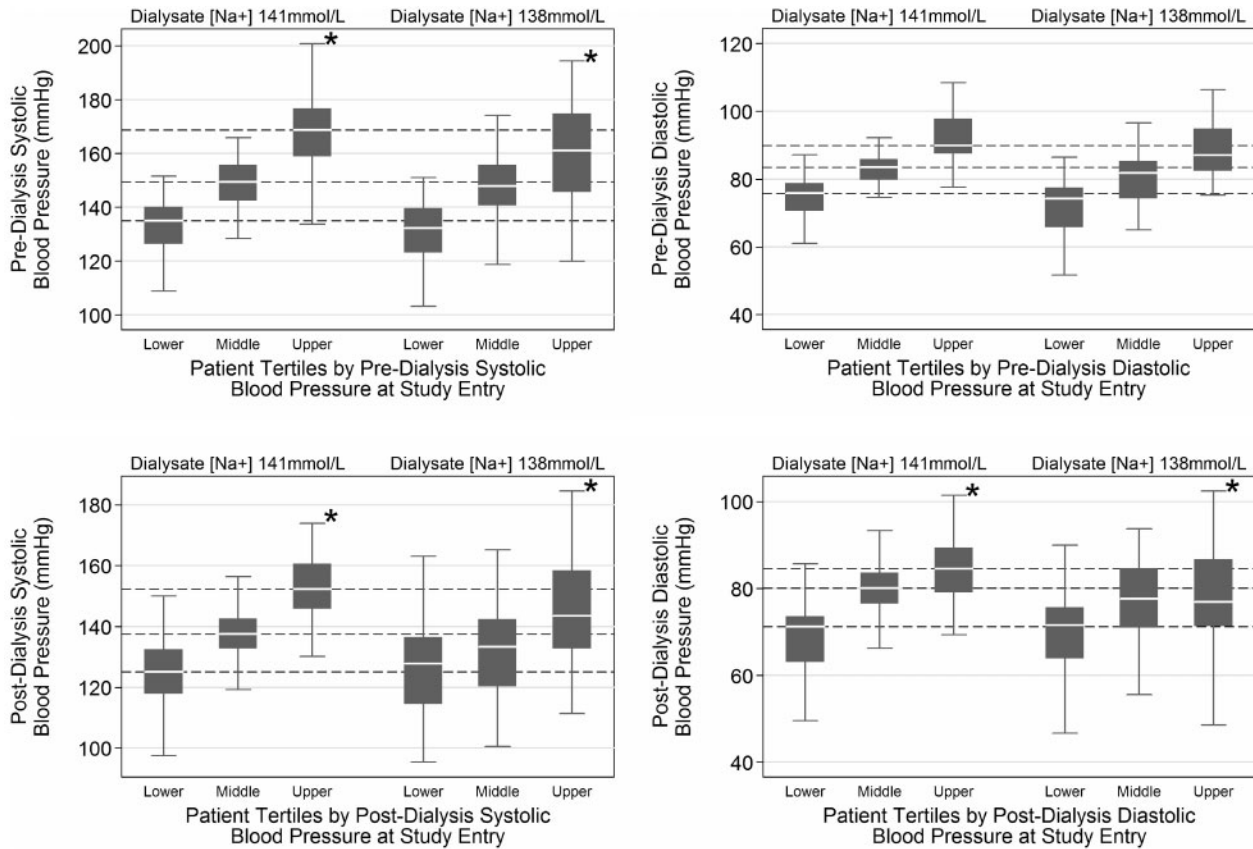


Fig. 3. Change in BP with change in dialysate [Na⁺], stratified by tertiles defined at study entry (boxplot, where the central line represents the median, the box the first and third quartile, the whiskers the upper and lower adjacent values). Significant differences exist by dialysate [Na⁺] status within tertiles of BP as indicated by * in graph. Pre-dialysis systolic BP expressed as median (interquartile range) 169 (159–177) mmHg for dialysate [Na⁺] 141 mmol/l vs 161 (146–174) mmHg for dialysate [Na⁺] 138 mmol/l, *P* = 0.038; post-dialysis systolic BP 152 (146–160) vs 143 (133–158), *P* = 0.014; post-dialysis diastolic BP 85 (79–89) vs 77 (71–87), *P* = 0.029.

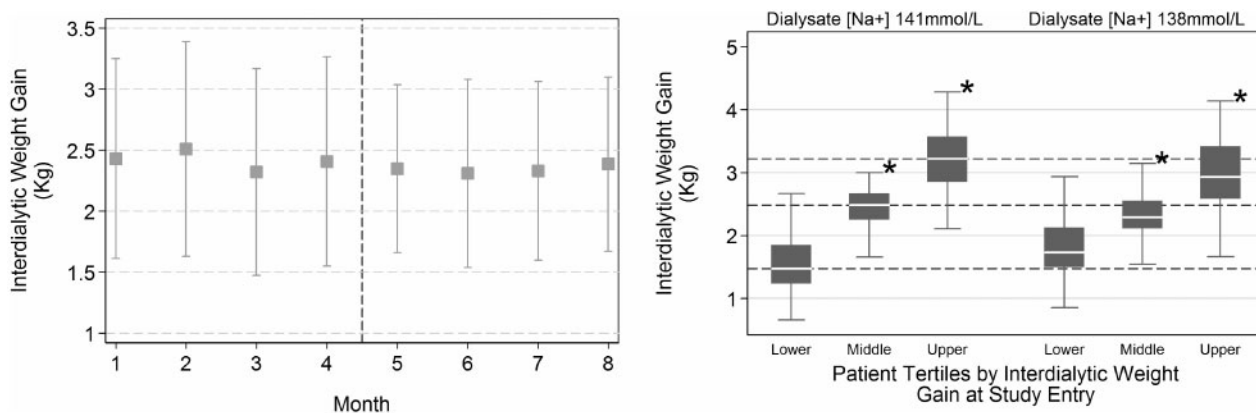


Fig. 4. IDWG by month of observation (markers represents means, error bars represent SDs, change in dialysate [Na⁺] indicated by the dashed vertical line), and according to dialysate [Na⁺] stratified by tertiles defined at study entry (boxplot, where the central line represents the median, the box the first and third quartile, the whiskers the upper and lower adjacent values). Significant differences exist by dialysate [Na⁺] status within tertiles of IDWG as indicated by * in graph. In the middle tertile, IDWG expressed as median (interquartile range) 2.5 (2.3–2.7) l for dialysate [Na⁺] 141 mmol/l vs 2.3 (2.1–2.5) l for dialysate [Na⁺] 138 mmol/l, *P* = 0.005). In the upper tertile, IDWG 3.2 (2.9–3.6) vs 2.9 (2.6–3.4), *P* = 0.031.

of hypertension is thought to be sodium loading [25,26]. This can occur via salts of chloride or bicarbonate, and can arise from either excessive oral intake [27,28] or excessive diffusion via dialysate

[29,30]. Our study suggests that a facility level decrease in dialysate [Na⁺] from 141 mmol/l to 138 mmol/l is associated with a modest overall reduction in BP of up to 5 mmHg, and a greater reduction in those with

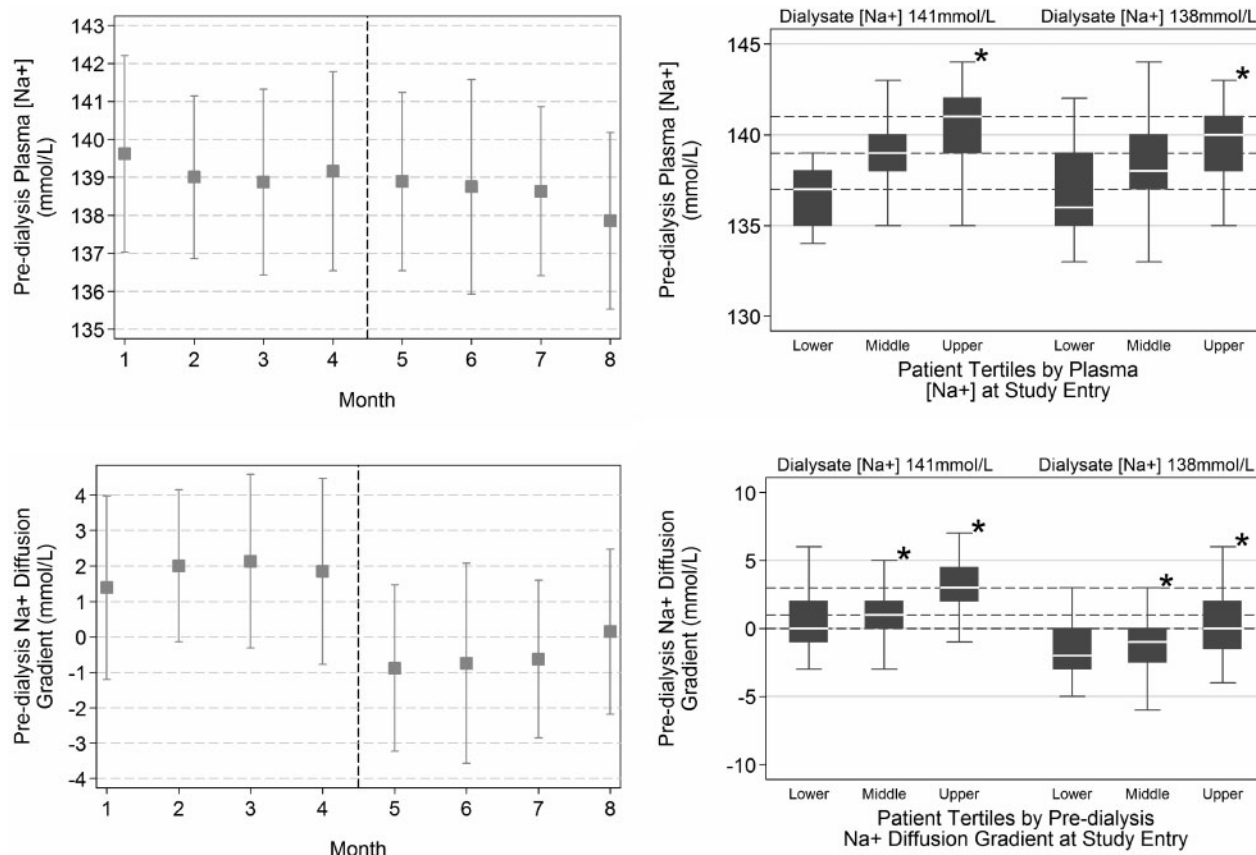


Fig. 5. Pre-dialysis plasma [Na⁺] and pre-dialysis Na⁺ diffusion gradient (ΔNa^+) by month of observation (markers represents means, error bars represent SD, change in dialysate [Na⁺] indicated by the dashed vertical lines), and according to dialysate [Na⁺] exposure stratified by tertiles defined at study entry (boxplot, where the central line represents the median, the box the first and third quartile, the whiskers the upper and lower adjacent values). Significant differences exist by dialysate [Na⁺] status within tertiles of plasma [Na⁺] and ΔNa^+ as indicated by * in graph. In the upper tertile, plasma [Na⁺] expressed as median (interquartile range) 141 (139–142) mmol/l for dialysate [Na⁺] 141 mmol/l vs 140 (138–141) mmol/l for dialysate [Na⁺] 138 mmol/l, $P = 0.003$. In the upper tertile, ΔNa^+ expressed as median (interquartile range) 3 (2–4.5) mmol/l for dialysate [Na⁺] 141 mmol/l versus 0 (–0.5–2.0), $P < 0.001$. In the middle tertile, ΔNa^+ 1 (0–2) mmol/l for dialysate [Na⁺] 141 mmol/l vs –1 (–2.5–0) mmol/l for dialysate [Na⁺] 138 mmol/l, $P < 0.001$.

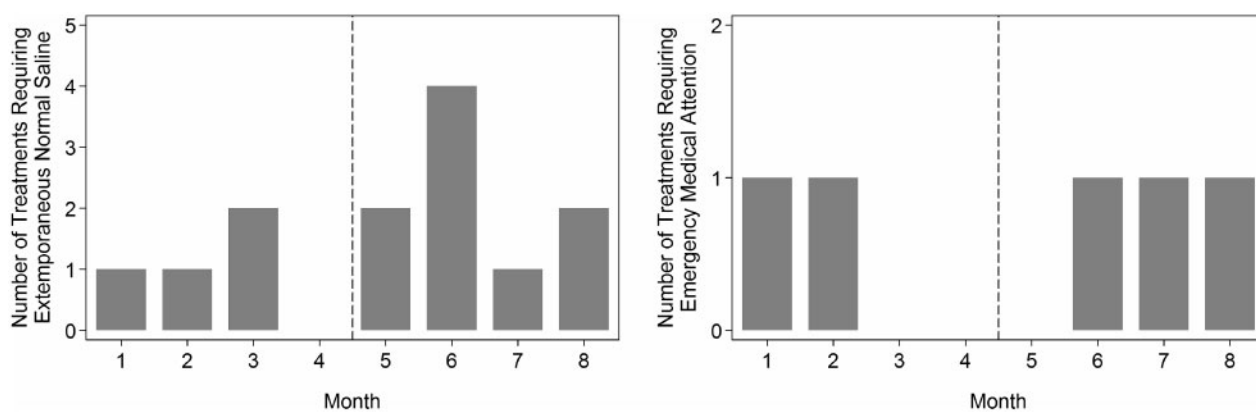


Fig. 6. Number of treatments requiring extemporaneous normal saline and emergency medical attention by month of observation (change in dialysate [Na⁺] indicated by the dashed vertical lines).

higher BP of up to 10 mmHg. There has been previous concern that such an improvement may be at the expense of increased intradialytic morbidity in hypotensive patients with predisposing cardiovascular

disease [31]. Our study, however, suggests that lower dialysate [Na⁺] is well tolerated by patients with pre-existing hypotension, and does not result in more saline infusions or emergency medical attention.

Table 2. Effects of a change in exposure on primary and secondary outcomes, presented as point estimates (95% confidence intervals)

| | Change in parameter associated with change in dialysate [Na ⁺] exposure from 141 to 138 mmol/l | Cohen's <i>d</i> | Change in parameter associated with each mmol/l increase in pre-dialysis ΔNa ⁺ | Cohen's <i>d</i> |
|---|--|------------------|---|------------------|
| IDWG (kg) | -0.04 (-0.11-0.03) | - | 0.02 (0.00-0.04)* | 0.08 |
| Pre-dialysis SBP (mmHg) | -4.32 (-6.23 to -2.41)* | 0.21 | 0.45 (-0.08-0.98) | - |
| Pre-dialysis DBP (mmHg) | -2.35 (-3.58 to -1.22)* ^a | 0.20 | 0.13 (-0.18-0.44) ^b | - |
| Post-dialysis SBP (mmHg) | -3.23 (-5.21 to -1.25)* | 0.17 | 0.19 (-0.35-0.73) | - |
| Post-dialysis DBP (mmHg) | -2.57 (-3.78 to -1.36)* | 0.25 | 0.25 (-0.08-0.58) | - |
| Pre-dialysis plasma [Na ⁺] (mmol/l) | -0.65 (-1.03 to -0.26)* | 0.26 | NA ^c | NA ^e |
| | Incident rate ratio with decrease in dialysate [Na ⁺] exposure | | Incident rate ratio with each mmol/l increase in pre-dialysis [Na ⁺]-gradient | |
| Extemporaneous saline infusions per month | 2.57 (0.78-8.49) ^c | - | 1.03 (0.79-1.35) ^d | - |
| Emergency medical attention per month | 1.35 (0.22-8.24) | - | 0.91 (0.58-1.44) | - |

^aOther covariates in the multivariate model: age -0.33 (-0.56 to -0.08).

^bOther covariates in the multivariate model: age -0.32 (-0.56 to -0.77).

^cOther covariates in the multivariate model: male sex 0.17 (0.04-0.77).

^dOther covariates in the multivariate model: male sex 0.18 (0.04-0.79).

^eNot available: direct calculation of independent from dependent variable in model.

IDWG, interdialytic weight gain; SBP, systolic blood pressure; DBP, diastolic blood pressure.

**P*-value < 0.05.

There is consistent support in the literature for the benefit of sodium restriction to patient outcomes. Proponents point to excellent survival in centres that espouse the technique [10,32]. Studies of sodium restriction can be grouped into those with interventions involving dialysate [Na⁺] or dietary sodium intake alone, or involving the combination. Those involving isolated changes to dialysate have tended to be underpowered and of short duration: this is of particular importance given the 'lag time' of several months between interventions on IDWG and the subsequent change in BP [12]. Notwithstanding, the large majority of studies have shown that higher time-averaged dialysate [Na⁺] relative to plasma [Na⁺] results in significantly either increased IDWG [3,6,33-43] or pre-dialysis BP [5,36,37,41,43,44]. Fewer studies have been completely negative [45-51]. It has been estimated that a high sodium dialysate for most HD populations would be characterized by [Na⁺] of ~141 mmol/l, and a low sodium dialysate by [Na⁺] of ~135 mmol/l [52].

The customary paradigm is that individual patients have a preferred plasma [Na⁺] set point, about which their pre-dialysis plasma [Na⁺] may only vary by -2 to +2 mmol/l [37,52-54]. According to this paradigm, sodium loading will increase plasma [Na⁺], thereby activating thirst and fluid intake and increasing IDWG and pre-dialysis BP [36,55-58]. Our study suggests that the purported individual fixed [Na⁺] set point may have been overstated [37,59,60]. Our study population clearly responded to reduced dialysate [Na⁺] exposure with an adaptation of natriuretic regulatory mechanisms, with progressively lower plasma [Na⁺], and therefore, reduced exchangeable sodium. Such adaptation has been reported in a minority of studies [5,36,42,61,62], but based on the findings of our study

may only occur over the medium-term, and for this reason may not have been observed in the many short-term studies reporting negative results.

It is axiomatic that individualized dialysate [Na⁺] prescription is more physiological than facility level prescription [53,63-65]. Unfortunately, sodium kinetic models are complex and difficult to apply. Notwithstanding, elegant studies from more than 20 years ago did show clinical improvements with the successful implementation of such models [66,67]. Simplified algorithms have also been used, based upon cumulative evidence showing the time-averaged dialysate [Na⁺] for isotonic HD to be between 0.1 and 3.0 mmol/l below that of pre-dialysis plasma [Na⁺], depending on laboratory methods used [16,36,47,68]. The most recent study of this nature (manually setting dialysate [Na⁺] to equal patient pre-dialysis [Na⁺] × 0.95) demonstrated both decreased IDWG and improved control of pre-dialysis BP [60]. The future of individualized dialysate [Na⁺] prescription may lie in the use of conductivity kinetic models, which take advantage of the linear relationship between the sodium content and total conductivity of dialysate and plasma water. The resulting tools are simpler and cheaper than sodium kinetic models [69,70]. There are still only limited reports of such systems in biofeedback algorithms, although results at this early stage do show that they can be used to modify sodium mass balance, although studies need to extend these findings to assess impact on IDWG and BP control [31].

A notable feature in our study was the lack of dramatic change in IDWG in our population over the period of observation. This was almost certainly due to the lack of dietary salt restriction and the continued steady ingestion of salt in the interdialytic period.

Maximal benefit from sodium restriction does require both dietary salt regulation (daily intake to <5–6 g) and reduction in dialysate [Na⁺] (<135–138 mmol/l), and is effective in the setting of both conventional and longer HD session lengths [71–73]. The dissociation between IDWG and BP in our study raises the issue of volume-independent effects of sodium exposure on BP [74]. Sodium exposure has been shown to increase peripheral vascular resistance by increases in intracellular calcium and sympathetic drive [75]. Further discussion of this topic is unlikely to impart further understanding of the results of this study, since we did not collect appropriate data to allow concurrent evaluation of these hypotheses.

The results of this study are not invalidated by the well-recognized seasonal variation in BP and IDWG that occurs in HD patients [76,77]. It is important to recall the seasons in New Zealand are reversed from those of the northern hemisphere, with the summer solstice at the time of this study taking place on 22 December 2004. Under normal circumstances, BP and IDWG in our study population, would therefore, be lower in the first half of our study (summer) than the second (autumn to winter). Given the opposite pattern in our results, we would suggest that the effect of dialysate [Na⁺] on BP and IDWG may be greater than we observed.

Finally, one other feature of the final multivariate models in our study warrants comment. Female sex was associated with more extemporaneous normal saline infusions for intradialytic hypotension. This possibly relates to the size of ultrafiltrate in females, which in this study was smaller compared with males but trending to be greater in relative terms as proportion of body water (4.2% in males assuming total body water equal to 0.6 × body weight, 4.9% in females assuming total body water equal to 0.55 × body weight, $P=0.14$). Similar observations have also been made in other studies (M. Keen, personal communication, 8 October, 2005 [37]).

There are obvious limitations to this study. It is a retrospective observational uncontrolled cohort study, and of course cannot be used to determine causality. The major variable in the study, BP, was assessed using recorded measurements in HD run-sheets, and the lack of ambulatory BP measurements is a drawback. Moreover, there are several potential sources of residual confounding that could conceivably contribute to the observed variation in outcomes. Firstly, dietary salt intake was not formally assessed by any means other than in *post-hoc* fashion using the proxy of IDWG. Second, target dry weight was also not formally assessed by any means other than prosaic clinical fashion. Third, the effect of antihypertensive medication was modelled very crudely by number of individual medications, not taking into account the type or dose. Undoubtedly these are potentially important confounders, although the lack of change in all three of the parameters over time (IDWG, target dry weight, number of antihypertensive medications) means that confounding will be mainly limited to

between-patient rather than within-patient effects, which, given the nature of the panel data, is of less significance. A strength of this study lies with the use of hierarchical linear mixed modeling, allowing for powerful statistical inference making full and effective use of the data at hand.

The results of this study suggest a suitably powered randomized clinical trial to determine whether dialysate [Na⁺] can be utilized to improve patient cardiovascular morbidity and mortality. The data allow key assumptions and sample sizes to be calculated. The primary outcome for such a study may be mortality, or a surrogate measures such as LVH [78,79]. Such a clinical trial would probably need to target a lower dialysate [Na⁺] than 138 mmol/l to achieve a larger clinical effect than was documented in this study, and might also explore the use of non-sodium containing fluids for extracorporeal circuit priming, and also for treatment of intradialytic hypotension [80,81]. Findings from such a study would potentially influence HD practice widely.

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Conflict of interest statement. None declared.

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