Clinical Kidney Journal

Clinical Kidney Journal, 2023, vol. 16, no. 5, 859–867

https://doi.org/10.1093/ckj/sfad013
Advance Access Publication Date: 23 January 2023
Original Article

ORIGINAL ARTICLE

Practical implementation and clinical benefits of the new automated dialysate sodium control biosensor

Francisco Maduell, José J. Broseta, Diana Rodríguez-Espinosa, Joaquim Casals, Victor Escudero, Miquel Gomez, Lida M. Rodas, Marta Arias-Guillén, Manel Vera and Néstor Fontseré

Department of Nephrology, Hospital Clínic Barcelona, Barcelona, Spain

Correspondence to: Francisco Maduell; E-mail: fmaduell@clinic.cat; Twitter: @FMaduell

ABSTRACT

Background. A key feature of dialysis treatment is the prescription of dialysate sodium (Na). This study aimed to describe the practical implementation of a new automated dialysate Na control biosensor and to assess its tolerance and the beneficial clinical effects of isonatraemic dialysis.

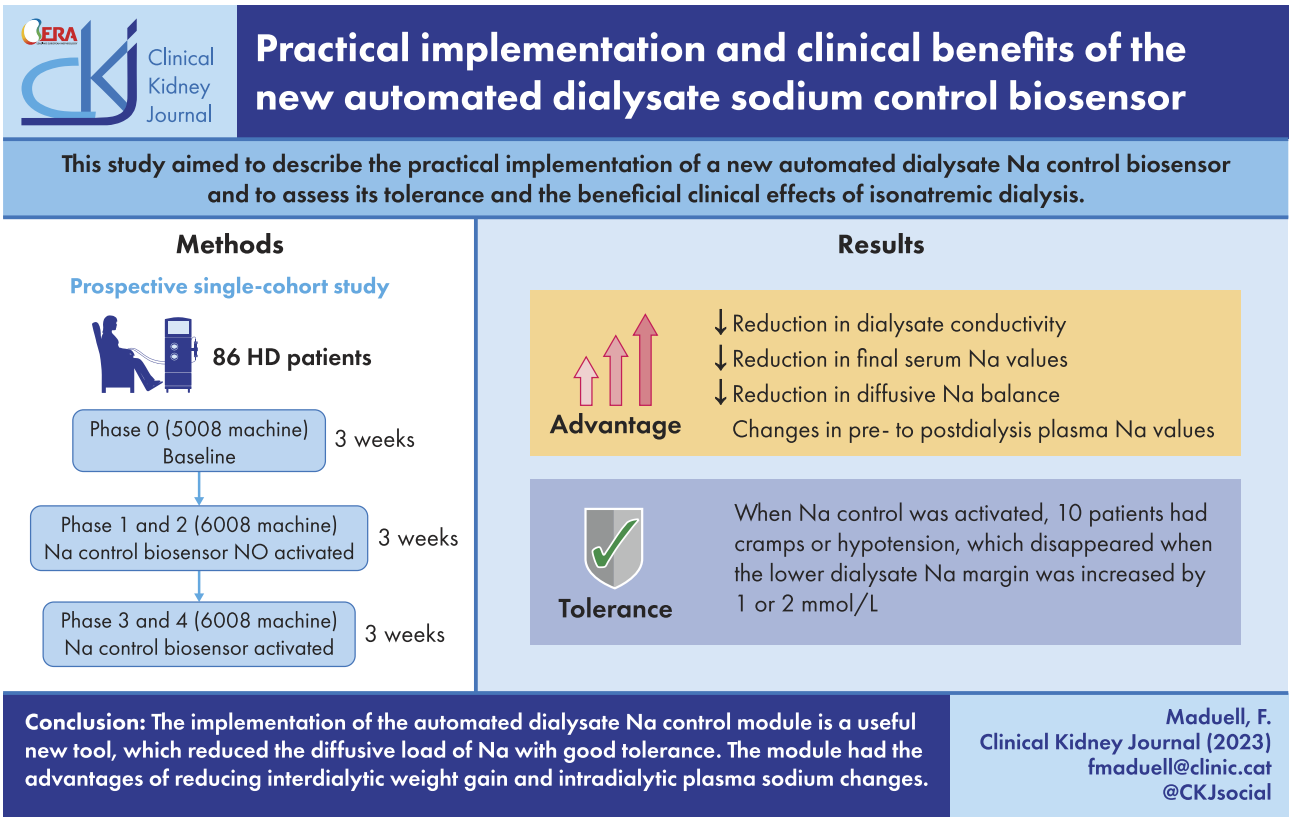
Methods. A prospective study was carried out in 86 patients who, along with their usual parameters, received the following five consecutive phases of treatment for 3 weeks each: phase 0: baseline 5008 machine; phases 1 and 2: 6008 machine without activation of the Na control biosensor and the same fixed individualized Na dialysate prescription or adjusted to obtain similar conductivity to phase 0; phases 3 and 4: activated Na control to isonatraemic dialysis (Na dialysate margins 135–141 or 134–142 mmol/L).

Results. When the Na control was activated, the few episodes of cramps or hypotension disappeared when the lower dialysate Na margin was increased by 1 or 2 mmol/L. The activated Na control module showed significant differences compared with baseline and the non-activated Na module in final serum Na values, diffusive Na balance, and changes in pre- to postdialysis plasma Na values. The mean predialysis systolic blood pressure value was significantly lower in phase 4 than in phase 1. There were no significant differences in total Na balance in the four 6008 phases evaluated.

Conclusions. The implementation of the automated dialysate Na control module is a useful new tool, which reduced the diffusive load of Na with good tolerance. The module had the advantages of reducing thirst, interdialytic weight gain and intradialytic plasma Na changes.

Received: 17.10.2022; Editorial decision: 2.1.2023

GRAPHICAL ABSTRACT



Keywords: cardiovascular risk, dialysate sodium, diffusive sodium load, hemodiafiltration, interdialytic sodium changes, intradialysis tolerance

INTRODUCTION

Sodium (Na) is the major extracellular ion that defines osmolarity and extracellular volume. The prescription of Na in the dialysate is one of the key features of dialysis treatment [1]. Several studies have shown that a low predialysis serum sodium ($_S$Na) concentration is associated with higher mortality in patients undergoing haemodialysis (HD) [2–5]. Increased mortality associated with higher predialysis $_S$Na variability was observed by the MONDO (MONitoring Dialysis Outcome) initiative [6]. More recently, Fujisaki *et al.* [7] reported that higher mortality was associated with the difference between final and initial $_S$Na, also called delta $_S$Na (Δ_SNa), suggesting that the increase in Δ_SNa may be the cause of organ damage. The deleterious effect of intradialysis Δ_SNa may reflect cyclical changes in brain structure (swelling and contraction) with osmotic changes induced by dialysis [8].

Na balance in HD patients essentially depends on salt intake and its elimination during dialysis treatment. Na loss during HD is essentially at the expense of convection (ultrafiltration related to interdialytic weight gain) and, to a lesser extent, diffusion (the gradient between the patient's $_S$Na and dialysate Na) [9]. A positive Na gradient during HD favours haemodynamic stability, reduces the risk of intradialysis hypotension, and favours adequate perfusion of vital organs [10]; however, it also increases osmolarity, thirst and extracellular volume and, consequently, hypertension and left ventricular hypertrophy. It is also associated with adverse cardiovascular effects [1]. In contrast, a negative Na gradient, with low dialysate Na prescriptions, has been associated with a reduction in interdialytic weight gain at the expense of an increase in episodes of intradialysis hypotension and tissue hypoperfusion [10].

Dialysate Na prescription is usually based on a fixed concentration. Some nephrologists individualize dialysate Na prescription according to predialysis $_S$Na concentration. Manual dialysate Na alignment to predialysis $_S$Na concentration may then be reconsidered periodically, according to the results [11]. To personalize dialysis prescription, dialysate–plasma Na gradient prescription should be considered rather than dialysate Na concentration alone [12].

The recent incorporation of dialysis machines with Na control modules represents an innovative approach in dialysate Na prescription, relying on an automated Na balancing module that is able to align dialysate Na concentration to $_S$Na according to physician diffusive balance prescription [13–16]. Based on this new tool, clinicians have the opportunity to customize dialysate Na prescription according to patients' needs in an easy and timely manner without the cumbersome task of laboratory testing [16]. Kuhlmann *et al.* [13] propose a zero diffusive balance controller as a starting point because it provides an adequate option for most patients under HD. Ságová *et al.* [14] showed that automated dialysate Na control reduces intradialytic $_S$Na changes. Therefore, this new Na control biosensor is able to achieve approximate isonatraemic dialysis and to prevent

excessive thirst and weight gain and, at the same time, avoid the adverse effects of low dialysate Na.

The goal of the present study was to describe the change from the 5008 dialysis machine to the new-generation 6008 machine, which incorporates the Na module as standard, and to assess the practical implementation, tolerance and possible beneficial effects of the implementation of the automated Na module to obtain an isonatraemic dialysis close to zero diffusive balance.

MATERIALS AND METHODS

We performed a prospective single-centre study in patients in a chronic HD programme. The study included 86 patients, 53 men and 33 women, with a mean age of 66.96 ± 17 years (range 21–90) on a regular dialysis programme. The patients were dialysed through an autologous arteriovenous fistula in 71%, through a prosthetic fistula in 5% and through a tunnelled central catheter in the remaining 24%. The causes of end-stage kidney disease were vascular kidney disease (25 patients), diabetic kidney disease (17 patients), chronic glomerulonephritis (15 patients), interstitial nephritis (7 patients), autosomal dominant polycystic kidney disease (6 patients), systemic disease (2 patients), urological (5 patient) and aetiology unknown (9 patients). Net fluid removal was prescribed according to the patients' clinical needs. There were eight patients (9%) with a urine volume >50 mL/day; most were anuric. There were no special inclusion/exclusion criteria and every patient in our dialysis unit who gave informed consent was included. The study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki.

The dialysis parameters were kept constant in each of the sessions: dialysis time 334 ± 82 min (240–480 min); blood flow 413 ± 37 mL/min (300–450 mL/min); dialysate flow 400 mL/min. The postdilution haemodiafiltration modality was used in 95% of the patients and expanded HD in the remaining 5%. All patients, along with their usual parameters, received the following five consecutive treatment phases for 3 weeks each:

Phase 0: 5008 machine, current dialysis treatment with fixed individualized Na dialysate prescription.

Phase 1: 6008 machine, current dialysis treatment with the same fixed individualized Na dialysate prescription. The Na control biosensor was not activated.

Phase 2: 6008 machine, current dialysis treatment with the fixed individualized Na dialysate prescription but adjusted to obtain similar dialysate conductivity to phase 0. The Na control biosensor was not activated.

Phase 3: 6008 machine, current dialysis treatment with activated Na control. Isonatraemic dialysis: diffusive balance close to 0 mmol with an allowed margin of variability between 135 and 141 mmol/L. These margins were adjusted if the patient had cramps, hypotension or other related symptoms.

Phase 4: 6008 machine, current dialysis treatment with activated Na control. Isonatraemic dialysis: diffuse balance close to 0 mmol with an allowed margin of variability between 134 and 142 mmol. These margins were adjusted if the patient had cramps, hypotension or other related symptoms.

Four types of dialysis concentrate were used: 55% ACF3 A4 (Na 140, potassium 1.5, calcium 1.5, magnesium 0.5, chloride 106.5, bicarbonate 35; acetate 4 mmol/L and glucose 1 g/L), 13% ACF3 A2 (same composition but calcium 1.25 mmol/L), 28% Smartbag 211.5 (Na 138, potassium 2.0, calcium 1.5, magnesium 0.5, chloride 109, bicarbonate 32; acetate 3 mmol/L and glucose 1 g/L) and 5% Smartbag 211.25 (same composition but calcium 1.25 mmol/L).

For the comparison of the results, we calculated the average of the three sessions of the last week of each phase. Thirst and cramps were reported by nurses and doctors of the dialysis unit, as done routinely. The parameters collected were as follows: dialysate conductivity, replacement volume, interdialytic weight gain, pre- and postdialysis systolic and diastolic blood pressure, and initial and final plasma Na measured by the dialysis monitor itself using the ionic dialysance biosensor (intradialysis Δ_SNa was calculated). And finally, the new Na control module incorporated in the 6008 machine provides the diffusive Na balance and total Na balance both measured by the dialysis monitor itself in all four 6008 phases used. Diffusive Na balance is the gain or elimination of Na during dialysis treatment by diffusive mechanism, in relation to the difference in concentration between the patients' plasmatic Na and the dialysated Na concentration. Total Na balance is total amount of Na per dialysis session transferred into or out of the patient. Total Na balance can be split into two components: the diffusive component (depending on the dialysate to plasma Na gradient) and the net ultrafiltration component. The ultrafiltration component quantifies Na removed by ultrafiltration. Since Na does not undergo significant sieving across the dialyser membrane its concentration in dialysate can be considered close to those in plasma.

Sodium balances were calculated by 6008 dialysis machines based on dialysate conductivities pre- and post-dialyser measured by the built-in conductivity cells of the Online Clearance Monitor. Since the clearance of other electrolytes like potassium or bicarbonate modify the composition of spent dialysate and influence the relationship between conductivity and Na concentration, the 6008 machine use a patient kinetic model. This model approximates changes in plasma electrolyte concentrations during dialysis and allows the estimation of Na concentration based on dialysate conductivity. Full information about the model can be found in the Appendix 'Transition from conductivity to concentration balancing' in Ságová *et al.* [14]. Na control biosensor continuously monitors the dialysate side Na balance based on measurements of fresh and spent dialysate conductivities and the application of a kinetic model to account for the typical influence of other ions on dialysate conductivity. In activated Na control, as 'zero diffusive' mode, dialysate Na is then adjusted continuously in such a way as to minimize diffusive Na transfer [13–15].

Na intake was not calculated. Total Na balance estimated by the model in a single dialysis session only reflects Na removal during the dialysis session. However, with a longer follow-up in clinically stable HD patient without residual renal function and neglecting loss of Na in either stool or sweat, intradialytic Na removal must reflect Na intake. Otherwise, the patient would show a tendency to overhydration or dehydration. The only consideration that must be kept in mind is to assess a daily Na intake, a correction in accordance with the previous days without dialysis (i.e. the total Na balance on Mondays and Tuesdays must be divided by 3 days and the rest of the days by 2 days).

Quantitative variables are described as mean and standard deviation, while qualitative ones are reported as absolute and relative frequencies. Differences in qualitative variables were analysed with the χ^2 test. Quantitative parameters were analysed with Student's *t*-test for paired data. Parametric data were analysed with analysis of variance (ANOVA) for repeated data, followed by Bonferroni's *post hoc* test. $P < .05$ was considered statistically significant. A Pearson correlation

Table 1:. Comparison of conductivity, ultrafiltrate volume, replacement volume and pre/postdialysis blood pressure in the five study phases.

	Phase 0 5008 machine	Phase 1 6008 machine	Phase 2 6008 machine	Phase 3 6008 machine	Phase 4 6008 machine
Prescribed dialysate Na (mmol/L)	139.1 ± 0.52	139.1 ± 0.52	137.1 ± 0.45[b]	Automatic Na control (range 135–141)	Automatic Na control (range 134–142)
Conductivity (mS/cm)	13.95 ± 0.09	14.08 ± 0.08[a]	13.88 ± 0.08[b]	13.74 ± 0.11[c]	13.70 ± 0.13[c,d]
Interdialytic weight gain (mL)	2564 ± 796	2626 ± 828	2527 ± 714	2428 ± 732	2364 ± 824[e]
Dry body weight (kg)	68.95 ± 17.56	68.93 ± 17.58	68.86 ± 17.55	68.79 ± 17.58	68.78 ± 17.61
HDF replacement volume (L)	30.7 ± 12.1	33.9 ± 15.2	31.36 ± 12.5	31.0 ± 11.9	30.73 ± 12.8
Predialysis Na (mmol/L)	137.97 ± 1.81	138.49 ± 2.58[f]	137.93 ± 2.41	137.63 ± 2.62	137.93 ± 2.51
Postdialysis Na (mmol/L)	139.72 ± 1.11	140.35 ± 1.23[a]	138.91 ± 0.91[b]	137.81 ± 1.18[c]	137.58 ± 1.62[c]
Predialysis SBP (mmHg)	135.95 ± 24.0	136.58 ± 24.1	134.19 ± 22.0	133.53 ± 22.9	130.70 ± 21.5[e,g]
Predialysis DBP (mmHg)	65.14 ± 15.3	69.28 ± 13.5[h]	67.78 ± 13.2	66.78 ± 12.9	66.99 ± 13.0
Postdialysis SBP (mmHg)	138.91 ± 27.2	137.51 ± 25.6	135.29 ± 24.4	134.60 ± 23.9	135.00 ± 22.9
Postdialysis DBP (mmHg)	65.28 ± 15.1	69.33 ± 16.4	67.08 ± 13.8	66.83 ± 13.3	66.81 ± 13.0

Data are presented as mean ± standard deviation.
DBP: diastolic blood pressure; HDF: haemodiafiltration; SBP: systolic blood pressure.
[a]$P < .001$ vs phase 0.
[b]$P < .001$ vs phase 0 and phase 1.
[c]$P < .001$ vs phase 0, phase 1 and phase 2.
[d]$P < .05$ vs phase 3.
[e]$P < .05$ vs phase 1.
[f]$P < .05$ vs phase 2 and $P < .001$ vs phase 3.
[g]$P < .05$ vs phase 0.
[h]$P < .01$ vs phase 0.

coefficient was computed to assess the linear relationship between total Na balance and interdialytic weight gain. Analyses were performed using SPSS software version 23 (SPSS, Chicago, IL, USA) and graphics were prepared with GraphPad Prism version 8 (GraphPad Software).

RESULTS

More than 3000 sessions were carried out with the 6008 machines, and 1230 sessions were examined to collect the data and perform comparative analyses. Of the 86 patients initially included in the study, 4 did not complete it. The reasons for withdrawal before completing all phases required in the study were a kidney transplantation (two patients), change of centre (one patient) and withdrawal of consent (one patient). Thus, 82 patients were included in the statistical analysis.

Assessment of tolerance of dialysis treatment

In general, the dialysis sessions were carried out without notable clinical incidents and there were no serious adverse events. Of note, during the change from phase 0 to phase 1 through the 3 weeks of phase 1, five patients experienced more thirst. In phase 3, when Na control was activated, six patients had cramps or hypotension, which disappeared when the lower dialysate Na margin was increased by 1 or 2 mmol/L. During phase 4, cramps or hypotension were experienced by three patients but disappeared when the Na ranges were returned to the previous phase.

Dialysate conductivity

The results of conductivity in each of the phases are shown in Table 1. Significant differences were observed in practically all the study phases. These differences were maintained regardless of the concentrate used.

Interdialytic weight gain

The Na control module showed a tendency to decrease interdialytic weight gain (Table 1). Compared with phase 1, weight gain significantly decreased in phase 4, with the Na control module with the widest margins.

Blood pressure

The mean of the pre- and postdialysis systolic and diastolic blood pressures are shown in Table 1. The mean of predialysis systolic blood pressure was significantly lower in phase 4 than in phase 0 and phase 1.

Initial and final plasma Na

In the baseline phase, the mean initial $_{S}$Na value was 137.97 ± 1.81 mmo/L (range 131–142 mmo/L) with no significant changes in predialysis Na observed in any of the four study phases (Table 1). However, final $_{S}$Na values in the phases with the activated Na module (phases 3 and 4) were significantly lower than those in phases 0, 1 and 2 (Table 1).

Diffusive Na balance

Significant differences in diffusive Na balance were observed in the four phases in which the 6008 monitor was used. As expected, the values of diffusive Na balance were lowest in the two phases when the Na module was activated to achieve an isotonic dialysis (zero diffusive balance) (Fig. 1).

Once the Na control module was activated, 46% of dialysis sessions achieved a zero diffusive balance (0–30 mmol), 36% remained between 31 and 100 mmol, and 18% gained more than 100 mmol. The main differential factor in achieving zero diffusive balance was the initial plasma $_{S}$Na value. When patients were classified in quartiles according to their initial plasma $_{S}$Na value, only 9.3% of patients in the first quartile ($_{S}$Na 125.5–136.4 mmol/L) achieved zero diffusive balance, while

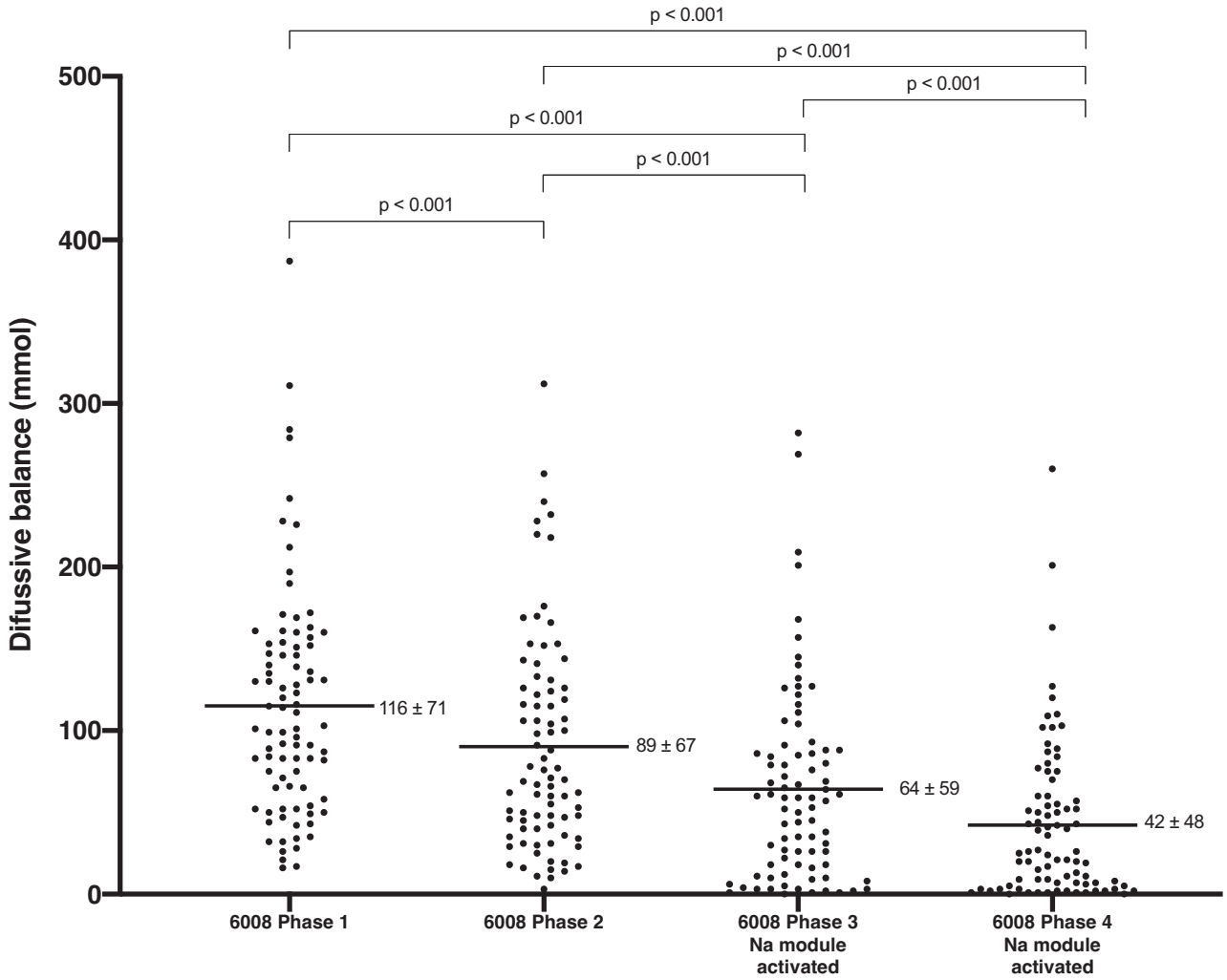


Figure 1: Comparison of diffusive Na balance in all study situations (ANOVA for repeated data).

it was achieved in 26.8% in quartile 2 ($_S$Na 136.5–138.1 mmol/L), 60.2% in quartile 3 ($_S$Na 138.2–139.6 mmol/L) and 93.3% in quartile 4 ($_S$Na 139.7–145.2 mmol/L). Other studied potential predisposing factors such as sex, age, dialysis vintage, vascular access, dialyser, heparin type, dialysis modality or the weekday did not show statistically significant differences.

Total Na balance

There were no significant differences in total Na balance (diffusive and convective balance) in which the 6008 monitor was used: 248 ± 95 mmol in phase 1, 257 ± 93 mmol in phase 2, 263 ± 95 mmol in phase 3 and 272 ± 109 mmol in phase 4. Calculated as daily Na intake, in 13 patients (15%) it was <85 mmol (<5 g), in 55 patients (67%) between 85 and 150 mmol, and in 14 patients (17%) >150 mmol. There was statistically significant correlation between total Na balance and interdialytic weight gain (Fig. 2).

Difference between the initial and final Na or Na delta (the Δ_SNa)

Significant differences in Δ_SNa were observed in the five phases (Fig. 3). In the two phases with activation of the Na module to achieve a zero diffusive balance, Δ_SNa values were significantly reduced. Changes of the intradialytic plasma Na concentration are showed in Table 2. There were 5 patients (6%) with Δ_SNa ≥4 mmol/L during phase 0, which increased to 11 patients (13%) in phase 1 and 7 patients (8.5%) during phase 2, but only 2 patients during activated Na module phases 3 and 4. A Δ_SNa value of >2 mmol/L was achieved in 29 patients (35%) in phase 0, 31 patients (38%) in phase 1, 25 patients (30%) in phase 2, but in only 10 patients and 9 patients (12% and 11%) during activated Na module phases 3 and 4, respectively (Table 2).

DISCUSSION

The present study shows that the implementation of automated dialysate Na control to obtain a zero diffusive balance was associated with a decrease diffusive Na balance and intradialytic $_S$Na changes, a trend in diminishing interdialytic weight gain and predialysis systolic blood pressure, all of which help to improve cardiovascular risk because they are all independent risk factors for mortality. This customized dialysate Na prescription according to patient needs was carried out with good tolerance and the few cases of cramps or hypotension episodes were easily resolved by adjusting the dialysate Na action margins of the Na control biosensor.

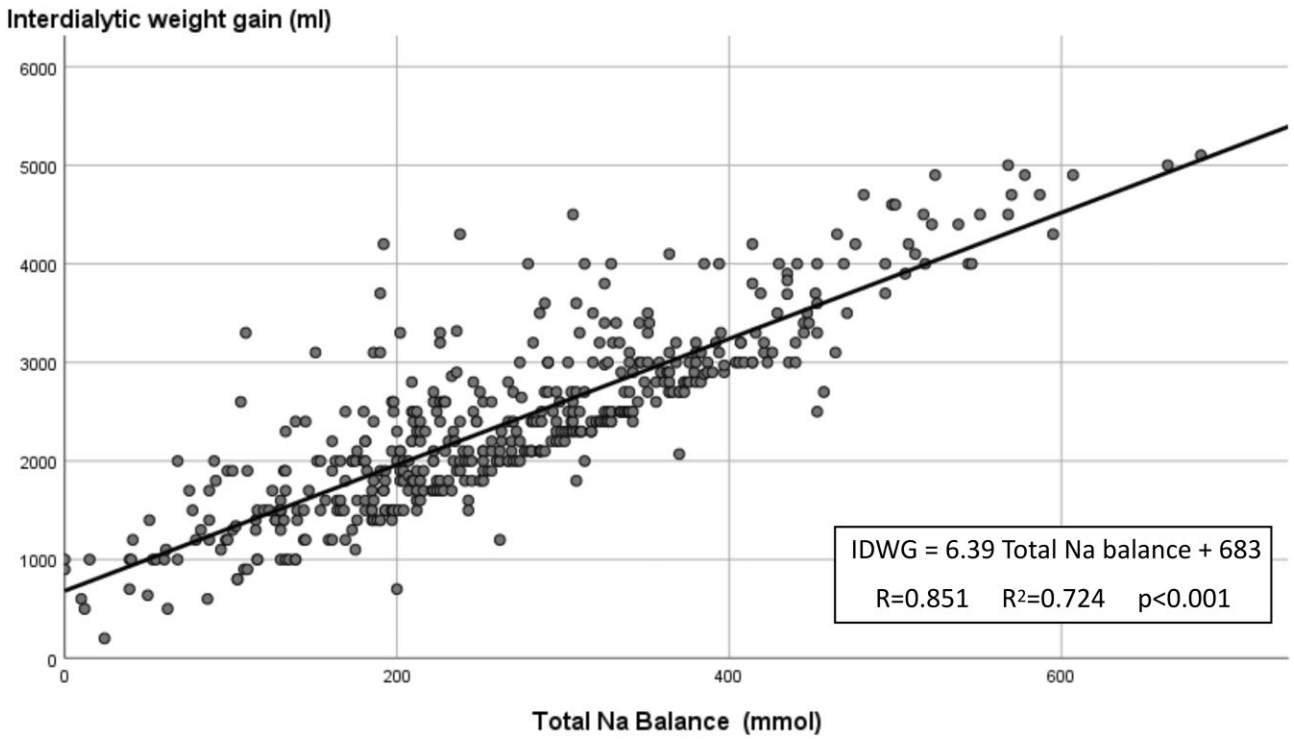


Figure 2: Correlation between total Na balance and interdialytic weight gain.

Adequate dialysis should allow complete elimination of interdialytic Na load and avoid intradialytic Na load with increased interdialytic weight gain [17]. Only the ionized proportion of Na is available for diffusion and therefore its movement is determined by the gradient between the concentrations of electrochemically active ions from the plasma to the dialysate, as well as by temperature and acidity. The Gibbs–Donnan effect refers to a phenomenon caused by anionic plasma proteins that are too large to pass through the dialysis membrane, creating an electric field that attracts cations and reduces the amount of diffusible Na in plasma [18]. This is the reason why $_S$Na values are corrected and approach those of the dialysate, and may even exceed them due to the negative potassium balance being compensated by a positive Na balance and to the Gibbs–Donnan effect [13]. That is why, to achieve a diffusive balance close to zero, the patients finished the dialytic treatment with a $_S$Na value higher than the dialysate Na value.

Predialysis plasma Na fluctuations in patients are normally small, supporting the hypothesis of an individual Na setpoint [9, 19]. However, variability in predialysis $_S$Na among patients is very high, showing differences in diet, lifestyle and comorbidities [20]. In the present study, there was variability between 125 and 145 mmol/L. Despite this wide variability in predialysis $_S$Na, the usual prescription for dialysate Na in most dialysis units is usually between 138 and 140 mmol/L. In our study, the initial dialysate Na prescription ranged from 138 to 140 mmol/L, reflecting this general fixed dialysate Na prescription. Indeed, there is no current medical rationale to prescribe dialysate Na on a fixed concentration basis except to facilitate practice [16]. Manual individualization of the dialysate Na prescription should be related to the predialysis $_S$Na concentration as the reference value, and manual dialysate Na alignment to predialysis $_S$Na concentration may then be reconsidered periodically according to the results. However, measuring the analytical values of predialysis $_S$Na is impractical since these values are not available in each session. Therefore, the incorporation of Na control modules allows—as tools embedded in HD machines, automatically and without additional cost—individualization of the Na in the dialysate to reduce the influence of Na in the dialysate on Na balance as much as possible during treatment [13–15].

Adherence to a low-salt diet is crucial in HD treatment [21]. Apart from cardiac health, dietary salt restriction has additional benefits in HD patients since it reduces thirst and interdialytic weight gain. It is currently recommended to restrict dietary salt intake to about <5 g (85 mmol) per day [22–24]. Although the support of a nutritionist is important, an additional advantage of using the Na module is that the total Na balance provides approximate information on patients' salt intake, which therefore allows dietary recommendations to be adjusted more precisely. In this study, we observed that 15% of the patients maintained a low-salt diet (<85 mmol/day) in all phases, 75% maintained a diet with salt intake between 85 and 150 mmol/day and the remaining 10% a diet without salt restriction (>150 mmol/day) in all phases.

The control of the final result obtained from the dialysate is carried out using conductivity (as an alternative to Na) and allows small adjustments to be made in the proportion of concentrates, alarms or leaving in a bypass situation, if advisable [25]. However, dialysis machines have a fairly wide safety window in conductivity, between 0.3 and 0.5 mS/cm, which is therefore a source of variability [26]. A previous study [27] reported that changing the monitor from 5008 to 6008, with the same dialysis prescription, was associated with an increase in dialysate conductivity and, consequently, higher postdialysis $_S$Na. These results were confirmed in the present study (phase 0 versus phase 1), which is why we added phase 2 to correct this deviation and to allow activation of the Na module in conditions similar to previous dialysis with the 5008 machine. In this regard, it is

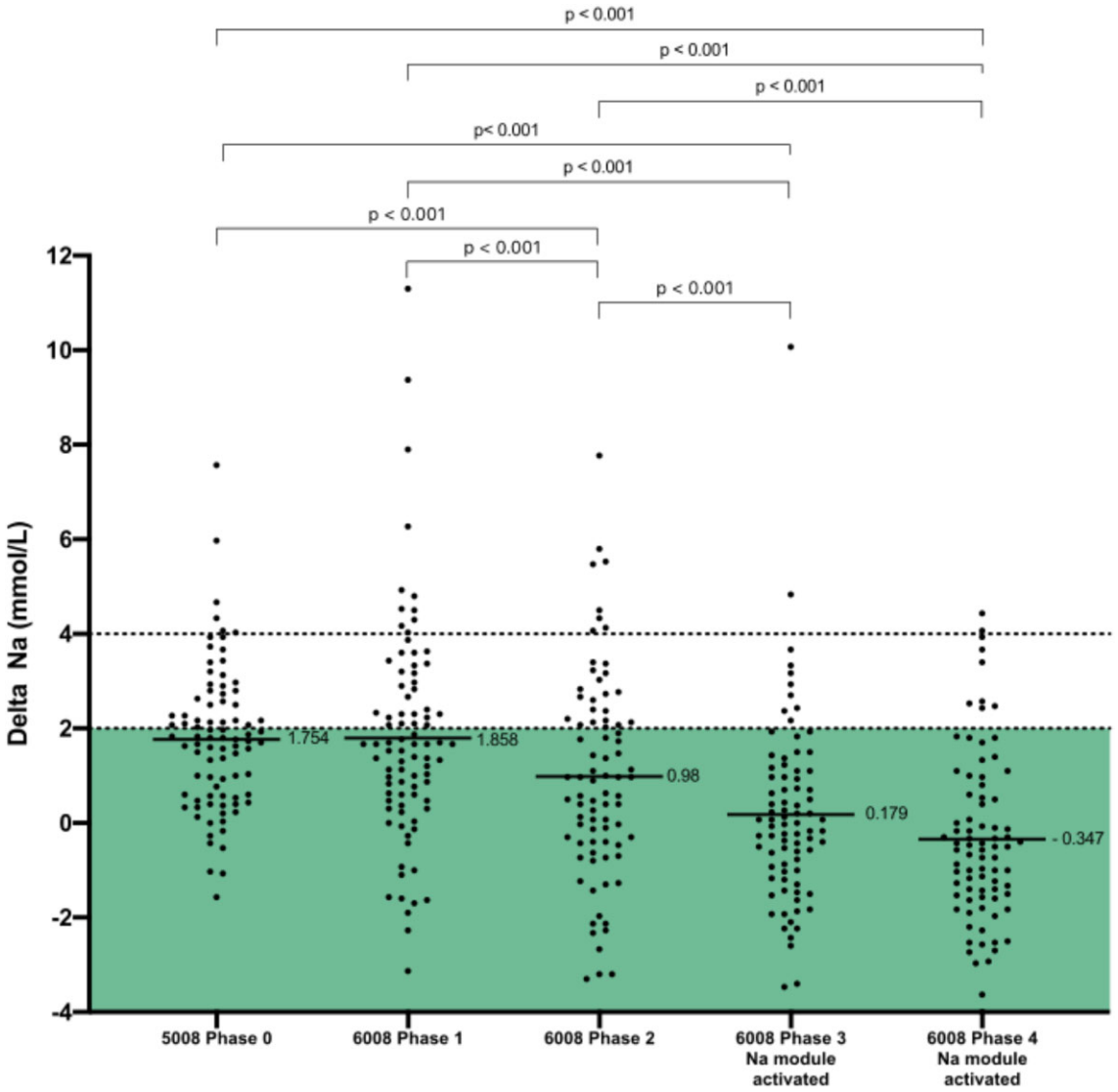


Figure 3: Comparison of difference between the initial and final plasma Na (Δ_SNa) in all study situations (ANOVA for repeated data).

Table 2:. Comparison of differences between the initial and final plasma Na (Δ_SNa) in the five study phases.

Δ_SNa (mmol/L)	Phase 0 5008 machine	Phase 1 6008 machine	Phase 2 6008 machine	Phase 3 6008 machine	Phase 4 6008 machine
<2 mmol/L	53 (64.6)	51 (62.2)	57 (69.5)	72 (87.8)	73 (89.0)
2–4 mmol/L	24 (29.3)	20 (24.4)	18 (22.0)	8 (9.8)	7 (8.5)
≥4 mmol/L	5 (6.1)	11 (13.4)	7 (8.5)	2 (2.4)	2 (2.4)

χ^2 test $P < .001$.
Data are presented as *n* (%).

recommended to monitor dialysate conductivity during the daily clinical visit and perform individualized adjustments of dialysate Na to correct and obtain the prescribed and desired conductivity. However, this monitoring is not necessary when using the Na module since it adjusts dialysate Na automatically and consequently dialysate conductivity.

The current distribution of body Na considers three main components: the best known osmotically active Na presenting in the total extracellular space, implicated in the control of extracellular fluid volume and haemodynamic responses; a slowly exchangeable pool of Na located in the bones; and the recently described Na component stored in skin and muscle interstitial tissues, representing so-called 'water-free tissue' storage, which induces homeostatic-regulatory activity in resident immune cells, which control lymphangiogenesis and blood pressure [28–30]. Tissue Na content is higher in patients with chronic kidney disease, diabetes and the dialysis population [31], and HD can mobilize Na tissue stores [32]. In this study, we

observed that isonatraemic dialysis treatment using the Na control module reduced the diffusive load, and consequently it should contribute to reducing tissue Na stores. Long-term studies are needed to assess the effect of sustained zero diffusive balance dialysis over time and to determine whether it reduces tissue Na stores and cardiovascular complications.

Although our goal was to achieve a zero diffusive balance, this could not be achieved in all patients, especially in those patients with lower predialysis $_S$Na. Two possible reasons are that the operating range of the Na module was limited to 134 mmol/L to preserve clinical tolerance, while the presence of cramps did not allow adequate adjustment to achieve this isotonic dialysis in other patients.

Changes in $_S$Na concentration from pre- to postdialysis may lead to organ damage and has been associated with independent risk factors for all-cause, cardiovascular and infectious disease–related mortality [7]. The deleterious effect of intradialysis Δ_SNa may reflect cyclical changes in brain structure (swelling and contraction) with osmotic changes induced by dialysis [8]. In a randomized trial of 31 patients, Ságová *et al.* [14] reported that Δ_SNa was −0.53 mmol/L for Na control treatments. In a study of 77 patients, Ponce *et al.* [15] observed that the Δ_SNa was −0.60 mmol/L with the Na control module. In the present study, Δ_SNa was 0.18 in phase 3 and −0.35 mmol/L in phase 4 with activated Na control treatments versus 1.53 mmol/L for standard fixed 138–140 mmol/L Na treatments. Therefore, to achieve no Na gradient, the new HD machine reduces pre- to postdialysis intradialysis changes in $_S$Na. Consequently, the automated Na and tonicity management tool embedded in the HD machine could potentially improve this problem and reduce the risk of mortality.

A limitation of the study is that there was no long-term clinical follow-up with the activated Na module (6 weeks); therefore, a randomized clinical trial with a primary outcome of mortality would be insightful in this subject. Another limitation is that we used the Na module in isonatraemic dialysis mode in all patients because it represents the default basic prescription for most patients. However, a few patients might need a hypertonic (hypotensive prone or hypovolaemic patients) or hypotonic (resistant hypertension, fluid overload or tissue Na excess) dialysis mode. And finally, another aspect to consider is the 9% of patients who had significant residual renal function and the contribution of this Na mass balance was not quantified.

In conclusion, the implementation of the automated dialysate Na control module is a highly useful new tool that allows automatic individualized prescription of dialysate Na, in real time and in each session, and reduces the diffusive load of Na with good tolerance. The module is potentially advantageous in reducing thirst and interdialytic weight gain, improving blood pressure control, and decreasing intradialytic $_S$Na changes. Therefore, this new biosensor will likely help to reduce the cardiovascular risk factors associated with increased mortality. Given the scarce literature on the management of this new tool, this study may help in the implementation of this biosensor. The initial benefits observed should be confirmed in long-term studies.

ACKNOWLEDGEMENTS

We would like to express our gratitude to all participating patients, as well as to all the staff of the Dialysis Section of Hospital Clínic of Barcelona for their collaboration in this study and their enthusiasm.

AUTHORS' CONTRIBUTIONS

F.M. conceived the study. J.J.B., LM.R., M.G, J.C., V.E., M.A.-G., M.V. and N.F. acquired the data. F.M. and J.J.B. analysed the data, created the figures and drafted the paper. All authors have revised the drafts and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no financial support for the project. F.M. has received consultancy fees and lecture fees from Baxter, Fresenius Medical Care, Medtronic, Nipro, Toray and Vifor. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author, F.M., upon reasonable request.

REFERENCES

1. Cook NR, Cutler JA, Obarzanek E *et al.* Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ* 2007;**334**:885–8.
2. Hecking M, Karaboyas A, Saran R *et al.* Predialysis serum sodium level, dialysate sodium, and mortality in maintenance hemodialysis patients: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2012;**59**:238–48.
3. Sato N, Gheorghiade M, Kajimoto K *et al.* Hyponatremia and in-hospital mortality in patients admitted for heart failure (from the ATTEND registry). *Am J Cardiol* 2013;**111**:1019–25.
4. Rhee CM, Ravel VA, Ayus JC *et al.* Pre-dialysis serum sodium and mortality in a national incident hemodialysis cohort. *Nephrol Dial Transplant* 2016;**31**:992–1001.
5. Pérez-García R, Palomares I, Merello JI *et al.* Hyponatraemia, mortality and haemodialysis: an unexplained association. *Nefrología* 2016;**36**:42–50.
6. Ye X, Kooman JP, van der Sande FM *et al.* Increased mortality associated with higher pre-dialysis serum sodium variability: results of the international MONitoring Dialysis Outcome initiative. *Am J Nephrol* 2019;**49**:1–10.
7. Fujisaki K, Joki N, Tanaka S *et al.* Pre-dialysis hyponatremia and change in serum sodium concentration during a dialysis session are significant predictors of mortality in patients undergoing hemodialysis. *Kidney Int Rep* 2021;**6**:342–50.
8. Canaud B, van der Sande F, Kooman J. Predialysis hyponatremia and positive change of natremia within hemodialysis sessions are strong indicators of poor cardiovascular outcome in hemodialysis patients. *Kidney Int Rep* 2021;**6**:248–51.
9. Basile C, Libutti P, Lisi P *et al.* Sodium setpoint and gradient in bicarbonate hemodialysis. *J Nephrol* 2013;**26**:1136–42.
10. MacEwen C, Sutherland S, Daly J *et al.* Relationship between hypotension and cerebral ischemia during hemodialysis. *J Am Soc Nephrol* 2017;**28**:2511–20.
11. Raimann JG, Ficociello LH, Usvyat LA *et al.* Effects of dialysate to serum sodium (Na(+)) alignment in chronic hemodialysis (HD) patients: retrospective cohort study from a quality improvement project. *BMC Nephrol* 2018;**19**:75.
12. Canaud B. A personal and practical answer from a clinical perspective. *Kidney Dial* 2021;**1**:149–51.
13. Kuhlmann U, Maierhofer A, Canaud B *et al.* Zero diffusive sodium balance in hemodialysis provided by an

algorithm-based electrolyte balancing controller: a proof of principle clinical study. *Artif Organs* 2019;**43**:150–8.
14. Ságová M, Wojke R, Maierhofer A *et al*. Automated individualization of dialysate sodium concentration reduces intradialytic plasma sodium changes in hemodialysis. *Artif Organs* 2019;**43**:1002–13.
15. Ponce P, Pinto B, Wojke R *et al*. Evaluation of intradialytic sodium shifts during sodium controlled hemodialysis. *Int J Artif Organs* 2020;**43**:620–4.
16. Canaud B, Kooman J, Maierhofer A *et al*. Sodium first approach, to reset our mind for improving management of sodium, water, volume and pressure in hemodialysis patients, and to reduce cardiovascular burden and improve outcomes. *Front Nephrol* 2022;**2**:935388. doi: 10.3389/fneph.2022.935388.
17. Davenport A. Audit of the effect of dialysate sodium concentration on inter-dialytic weight gains and blood pressure control in chronic haemodialysis patients. *Nephron Clin Pract* 2006;**104**:c120–5.
18. Nguyen MK, Kurtz I. Quantitative interrelationship between Gibbs-Donnan equilibrium, osmolality of body fluid compartments, and plasma water sodium concentration. *J Appl Physiol* 2006;**100**:1293–300.
19. Keen ML, Gotch FA. The association of the sodium "setpoint" to interdialytic weight gain and blood pressure in hemodialysis patients. *Int J Artif Organs* 2007;**30**:971–9.
20. Odudu A, Lambie S, Taal MW *et al*. Use of online conductivity monitoring to study sodium mass balance in chronic haemodialysis patients: prospects for treatment individualisation. *Kidney Blood Press Res* 2011;**34**:439–46.
21. Cole NI, Swift PA, He FJ *et al*. The effect of dietary salt on blood pressure in individuals receiving chronic dialysis: a systematic review and meta-analysis of randomised controlled trials. *J Hum Hypertens* 2019;**33**:319–26.
22. Flythe JE, Chang TI, Gallagher MP *et al*. Blood pressure and volume management in dialysis: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. *Kidney Int* 2020;**97**:861–76.
23. Lindley EJ. Reducing sodium intake in hemodialysis patients. *Semin Dial* 2009;**22**:260–3.
24. Garofalo C, Borrelli S, Provenzano M *et al*. Dietary salt restriction in chronic kidney disease: a meta-analysis of randomized clinical trials. *Nutrients* 2018;**10**:732–47.
25. Marcelli D, Basile C. Does the relationship between measured and prescribed dialysate sodium matter in the nephrology community? *Nephrol Dial Transplant* 2021;**36**:577–80.
26. Stragier A, Lopot F, Švára F *et al*. Fallacies and pitfalls of dialysis sodium prescription and control. *Blood Purif* 2018;**46**:27–33.
27. Maduell F, Broseta JJ, Casals J *et al*. Variaciones de la conductividad y cambios en el sodio plasmático durante hemodiálisis relacionado con el cambio de monitor. *Nefrología* 2022; (In press). doi: 10.1016/j.nefro.2022.08.001.
28. Canaud B, Kooman J, Selby NM *et al*. Sodium and water handling during hemodialysis: new pathophysiologic insights and management approaches for improving outcomes in end-stage kidney disease. *Kidney Int* 2019;**95**:296–309.
29. Yi B, Titze J, Rykova M *et al*. Effects of dietary salt levels on monocytic cells and immune responses in healthy human subjects: a longitudinal study. *Transl Res* 2015;**166**:103–10.
30. Binger KJ, Heinig M *et al*. High salt reduces the activation of IL-4- and IL-13-stimulated macrophages. *J Clin Invest* 2015;**125**:4223–38.
31. Kopp C, Linz P, Maier C *et al*. Elevated tissue sodium deposition in patients with type 2 diabetes on hemodialysis detected by (23)Na magnetic resonance imaging. *Kidney Int* 2018;**93**:1191–7.
32. Dahlmann A, Dörfelt K, Eicher F *et al*. Magnetic resonance-determined sodium removal from tissue stores in hemodialysis patients. *Kidney Int* 2015;**87**:434–41.