ORIGINAL ARTICLE

The difference between delivered and prescribed dialysate sodium in haemodialysis machines

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ABSTRACT

Background. The choice of dialysate sodium (DNa) for haemodialysis (HD) patients remains controversial, with some studies reporting that a lower DNa improves blood pressure control and reduces intradialytic weight gain. Studies on DNa depend on the alignment of programmed to delivered DNa. We wished to determine whether there were differences between programmed and delivered DNa.

Methods. Dialysate samples were obtained from three dialysis machines: Fresenius 4008H (F4008H) and 5008S (F5008S) and B-Braun hemodiafiltration (HDF) Dialog+(BB). DNa was measured by indirect ion-selective electrode (ISE), flame photometry (FP) and ion chromatography (IC) at different DNa concentrations.

Results. We tested 18 F5008S, 18 F4008H and 31 BB machines over 153 HD treatments. The median measured minus programmed DNa was significantly greater with the BB machine [ISE, 7 (6–8); FP, 7 (6–8); IC, 6 (5–7)], followed by the F4008H [ISE, 5.5 (5–7); FP, 4 (2.25–5.75); IC, 4 (2–5)]and F5008S [ISE, 4 (2–5); FP, 1 (−1–1.75); IC, 1 (−0.5 to 2)] mEq/L (P < 0.05). At higher programmed DNa (140–145 mEq/L), measured DNa was greater for the BB and F4008 machines by all methods (P < 0.05), but only by ISE for the F5008 (P < 0.05).

Conclusions. We noted a systematic bias in DNa delivery with measured DNa being greater than that programmed by our HD machines. The magnitude of the bias varied between machines and with DNa. Our results may help explain the diverse results reported in studies of DNa.

Keywords: dialysate, flame photometry, haemodialysis, ion chromatography, sodium

INTRODUCTION

There is no current consensus for the optimal dialysate sodium (DNa) concentration for haemodialysis (HD) patients. Most dialysis patients gain sodium between HD sessions. Sodium removal is predominantly achieved by convection through ultrafiltration, although diffusion down a concentration gradient between serum and dialysate can additionally increase

sodium losses. This diffusive clearance, due to the 'sodium gradient', determines the change in serum sodium concentration at the end of the HD session and falls in plasma osmolality [1]. Choosing a DNa concentration lower than serum sodium should result in a reduction in the prevalence of hypertension and interdialytic weight gain (IDWG), but with a potential increased risk of intradialytic hypotension and cramps, whereas the

opposite effects may accompany the choice of a DNa concentration greater than the serum concentration [2–10].

Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) reported that higher DNa prescriptions were associated with increased IDWG on the order of 0.17% of post-dialysis weight (or 0.12 kg for a 70-kg patient) per 2 mEq/L (mmol/L) higher DNa [11]. In addition, the DOPPS also reported that the average pre-dialysis systolic blood pressure was lower in dialysis facilities that individualized DNa compared with those dialysis centres using a standard DNa for all patients [11]. Individualized DNa prescription using a patient's pre-dialysis serum sodium as a reference is thus considered by many as the ideal standard [2, 12–14]. However, the standard laboratory method of measuring serum sodium, using an indirect ion-selective electrode (ISE), can be affected by high glucose, lipid and protein concentrations [15].

What is more concerning is whether actually delivered DNa by HD machines matches the prescribed concentrations [12, 16]. Previous studies have suggested that prescribed and delivered DNa concentrations may differ significantly, with reports of an overall positive bias [10, 16, 17]. In the study by Ekbal et al. [17], setting individual dialysis machines to deliver a sodium concentration of 136 mmol/L resulted in a DNa in excess of the 136 mmol/L programmed, with a mean bias of 7.0 ± 2.1 mmol/L for one manufacturer's dialysis machine and 3.7 ± 2.6 mmol/L for a different dialysis machine using the flame photometer method [17]. Another study tested 333 HD treatments in four facilities, which produced a central dialysate supply for all dialysis patients and reported that the greatest differences between prescribed and measured DNa concentrations were in two clinics that used one particular manufacturer's dialysis machines compared with two clinics that used dialysis machines from a different manufacturer (least squares mean differences −3.27 and −3.77 mEq/L versus −1.44 and −1.78 mEq/L, respectively) [16].

These differences in delivered DNa and programmed DNa may potentially explain why the results, particularly of multi-centre trials, have been discordant [2] when centres use different dialysis machines [18]. More recently, automated adjustments of DNa have been introduced to achieve 'zero diffusive balance' using conductivity balance as a surrogate of sodium concentration [19]. As such, we wished to determine whether there were differences in delivered DNa and programmed DNa concentration in our dialysis centres with different dialysis machines.

MATERIALS AND METHODS

We conducted a quality improvement study in three dialysis facilities: Royal Free Hospital, Edgware Community Hospital and Tottenham Hale Kidney and Diabetes Centre under the care of University College London, Department of Renal Medicine. Fresh dialysate samples were obtained during priming of Fresenius HD 4008H (F4008H) and Fresenius haemodiafiltration 5008S (F5008S) machines (Fresenius Medical Care, Bad Homburg, Germany) and B-Braun haemodiafiltration machines Dialog+(BB; BBraun, Melsungen, Germany). Dialysate was formed by combining ultrapure dialysis water with sodium bicarbonate (Bibag, Fresenius Medical Care) and an acid electrolyte concentrate (Kimal, Uxbridge, UK) within the HD machine. The final dialysate composition was set to deliver different sodium concentrations (135, 136, 140 and 145 mmol/L) in combination with varying potassium concentrations (1, 2 or 3 mmol/L) and calcium (1.0, 1.25, 1.5 and 1.75 mmol/L), with fixed

concentrations of magnesium (0.5 mmol/L), bicarbonate (32 mmol/L), acetate (3 mmol/L) and glucose (5.5 mmol/L).

DNa was measured by three methods: flame photometry (FP), indirect ISE and ion chromatography (IC). FP (Flame Photometer IL 943, Instrumentation Laboratory, Warrington, UK) used the appropriate calibration standards and Roche aqueous controls and optical filters. Indirect ISE assessment used a standard multichannel biochemical analyser (Roche Modular Panalyser, Roche Diagnostics, Burgess Hill, UK). The coefficient of variation for the ISE method for measuring sodium in an aqueous solution was 1.01% for a sodium concentration of 120 mmol/L and 0.57% for a sodium concentration of 160 mmol/L and 0.4% for the flame photometer at both concentrations [17]. Ion chromatography (Dionex ICS-1000 Ion Chromatography System, Dionex, Sunnyvale, CA, USA) used a coefficient of variation of the assay of <2% and a coefficient of all standards of 0.42%.

HD machines were regularly serviced and retested every 6 months and conductivity testing was performed using a reference instrument attached directly to the dialysis machine blue and red dialyser couplings. The reference instrument was set to read dialysate conductivity (in mS/cm) and temperature (in °C) in real time. Should the conductivity measurement differ by ±0.2 mS/cm from its supposed value, a machine recalibration of the conductivity sensors was performed. If the temperature differed by −1.5/0.5°C, a temperature sensor recalibration was performed.

Statistical analysis

Results are expressed as mean ± standard deviation (SD) or median [interquartile range (IQR)] as appropriate. Data comparison was done by one-way analysis of variance with post hoc analysis using Fisher's least significant difference or independent samples t-test for parametric variables and Kruskal–Wallis test with Dunn's post hoc analysis or Mann–Whitney U test for non-parametric variables. A P-value <0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences software (version 22.0; IBM, Armonk, NY, USA).

Ethics

Our retrospective audit of service development complied with the UK National Health Service Health Research Authority guidelines for clinical audit and service development, with all patient data anonymized prior to analysis (https://www.hra.nhs.uk), complied with UK National Institute for Clinical Excellence best practices (www.nice.org.uk/media/796/23/best practiceclinicallaudit.pdf) and registered with the University College Department of Nephrology.

RESULTS

Thirty-six Fresenius machines (18 F5008S and 18 F4008H) and 31 BB machines were tested over a total of 153 HD treatments. Machine characteristics and main outcome measures are reported in Table 1.

Overall, measured DNa with the BB machines was higher than that prescribed when measured by ISE, FP and IC (P < 0.001; Table 1). Similarly, delivered DNa by the F4008S was significantly higher than that prescribed by all methods (P < 0.05), whereas measured DNa in the F5008S was higher than that prescribed only when assessed by ISE (P < 0.001; Table 1).

Table 1. Characteristics and main outcome measures of the tested machines

Dialysis machine characteristics	F4008H	F5008S	BB
Number of machines	18	18	31
Number of dialysis treatments	31	53	69
Conductivity (mS/cm)	14.29 ± 0.42	14.05 ± 0.35	14.25 ± 0.42
Programmed DNa (mEq/L)	140.3 ± 3.7	140.3 ± 3.8	139.9 ± 3.8
Measured DNa (mEq/L)			
ISE	145.75 ± 4.8	143.5 ± 3.05	146.5 ± 4.6
FP	143.9 ± 4.6	140.7 ± 2.9	146.7 ± 4.3
IC	143.6 ± 4	141.4 ± 3.5	145.4 ± 3.9
Measured minus programmed DNa (mEq/L), median (IQR)			
ISE	5.5 (5−7)	4 (2−5)	7 (6−8)
FP	4 (2.25−5.75)	1 (−1−1.75)	7 (6−8)
IC	4 (2−5)	1 (−0.5−2)	6 (5−7)
Measured potassium (mEq/L), median (IQR)	NA	2.2 (2.1−2.3)	1.4 (1.1–3.6)
Measured calcium (mmol/L), median (IQR)	NA	2.7 (1.7–3.7)	0.92 (0.36-1.52)
Measured magnesium (mmol/L), median (IQR)	NA	1.12 (1.06–1.26)	1.05 (0.98–1.14)

Results expressed as mean ± SD unless stated otherwise. 1.0 mEq/L sodium/potassium = 1.0 mmol/L, 2.0 mEq/L calcium/magnesium = 1.0 mmol/L.
NA, not available.

We then considered the difference between the measured and prescribed DNa and the different dialysis machines. When assessed by ISE, the difference was significantly lower with the F5008S than the F4008H or BB ($P < 0.05$), which were similar ($P = 0.19$; Table 1). When assessed by FP and IC, the difference between measured and prescribed DNa differed significantly between the three machines, with the highest difference observed with the BB machines, followed by the F4008H and F5008S machines ($P < 0.05$; Table 1).

At a prescribed DNa of 135 and 136 mEq/L

At a prescribed DNa of 135 mEq/L, the measured DNa by all methods was consistently higher than that prescribed for the F5008S (ISE: 141.1 ± 1.7; FP: 138.5 ± 1.7; IC: 139.1 ± 2.2) and BB machines (ISE: 142.6 ± 1.3; FP: 141.8 ± 0.9; IC: 141.2 ± 0.7) ($P < 0.001$). DNa delivered by the BB machines was significantly higher than that of the F5008S by all methods ($P < 0.05$; Figure 1A).

Similarly, at a prescribed DNa of 136 mEq/L, measured DNa by all methods was consistently higher than that prescribed for the F4008H (ISE: 142.8 ± 3.65; FP: 139.7 ± 2.58; IC: 140.4 ± 1.17) and BB machines (ISE: 142.2 ± 1.25; FP: 143.4 ± 1.9; IC: 141.1 ± 1.28) and by IC for the F5008S machines (139 ± 1.4) ($P < 0.05$) (DNa was measured for the F5008S by IC only). DNa delivery in the BB machines was significantly higher compared with that of the F4008H machines when assessed by FP ($P < 0.001$), whereas the two machines were similar when assessed by ISE and IC. Compared with the F5008S machines, both the BB and F4008H machines had higher DNa IC results ($P < 0.05$; Figure 1B).

When we considered the median difference, measured–prescribed DNa, at a prescribed DNa of 135 mEq/L, the BB machines had significantly higher values than the F5008S machines when assessed by all methods ($P < 0.05$). At a prescribed DNa of 136 mEq/L, the median measured–prescribed DNa was significantly higher in the BB machines compared with the F4008H machines when assessed by FP ($P = 0.004$) but not when assessed by ISE or by IC (Table 2).

At a prescribed DNa of 140 mEq/L

Measured DNa by all methods for the F4008H (ISE: 144.8 ± 1.78; FP: 143.4 ± 2.4; IC: 142.7 ± 1.19) and BB machines (ISE: 146.7 ± 2.6; FP: 145.9 ± 2.08; IC: 144.95 ± 2.0) was consistently higher than that prescribed ($P < 0.05$), while measured DNa in the F5008S (ISE: 142.8 ± 1.95; FP: 139.8 ± 1.67; IC: 140.1 ± 2.9) was significantly higher than that prescribed when assessed by the ISE method ($P \leq 0.001$). Compared with the F5008S, DNa delivery by the BB machines was significantly higher by all methods ($P < 0.001$) and was significantly higher by FP and IC ($P < 0.05$) for the F4008H; it was also higher by ISE, but did not achieve statistical significance ($P = 0.051$). DNa delivered by the BB machines was significantly higher than that of the F4008H by FP and IC ($P < 0.05$), and was also higher by ISE, yet was statistically insignificant ($P = 0.06$) (Figure 1C).

The median measured difference in prescribed DNa and delivered DNa was greatest for the BB machines, followed by the F4008H and the F5008S ($P < 0.001$), and on *post hoc* analysis, the difference was significant only between the BB and F5008S machines when assessed by all methods ($P < 0.001$; Table 3).

At a prescribed DNa of 145 mEq/L

Measured DNa in the F5008S machines (ISE: 147.4 ± 2.3; FP: 144.5 ± 1.9; IC: 145 ± 1.97) was significantly higher than that prescribed when assessed by ISE only ($P = 0.017$), while both the F4008H (ISE: 150.2 ± 5.26; FP: 149.4 ± 1.14; IC: 147.7 ± 4.42) and BB machines (ISE: 152.6 ± 1.36; FP: 152 ± 1.37; IC: 150.35 ± 1.53) were consistently higher than prescribed ($P \leq 0.05$). The BB machines delivered significantly higher DNa than both the F5008S and F4008H machines by all methods ($P < 0.05$), and similarly the differences with the F4008H machine was higher than that of the F5008S by all methods ($P < 0.05$) (Figure 1D).

The median measured–prescribed DNa was highest for the BB machines, followed by the F4008S and the F5008S ($P < 0.001$). On *post hoc* analysis, the difference was significant between the BB and F5008S machines when assessed by all methods ($P < 0.001$) and between the F4008H and F5008S machines when assessed by IC ($P = 0.045$; Table 3).
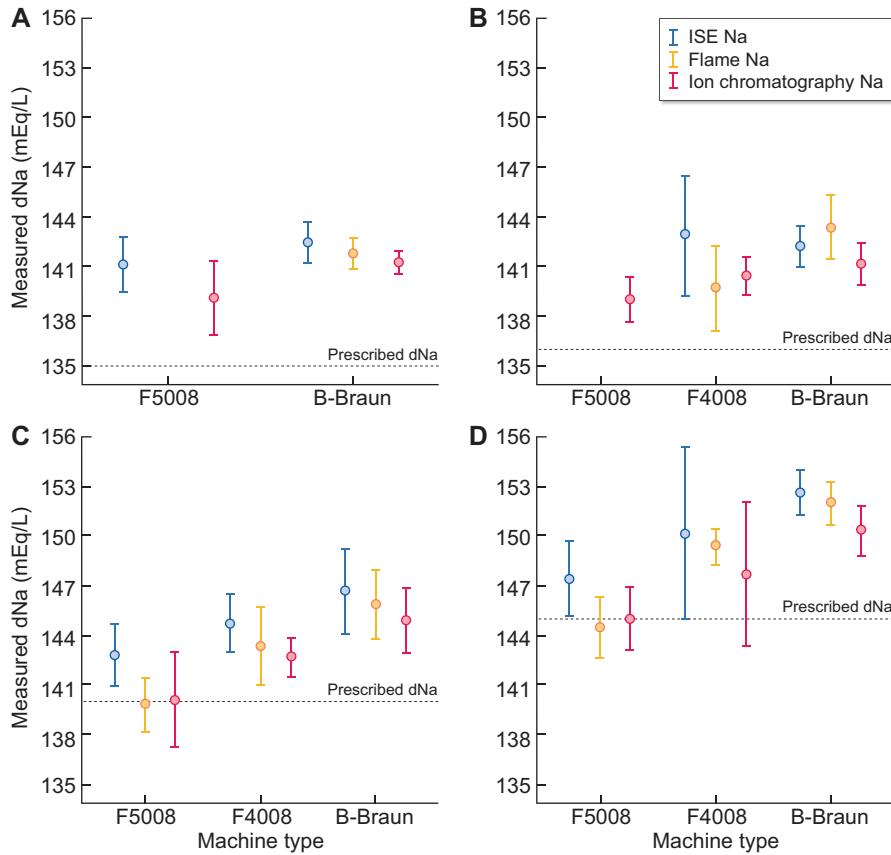
FIGURE 1: Measured DNa by machine type at different prescribed DNas: **(A)** 135 mEq/L, **(B)** 136 mEq/L, **(C)** 140 mEq/L and **(D)** 145 mEq/L. Results expressed as mean ± SD.

Table 2. The difference between measured and programmed DNa at 135 and 136 mEq/L

Na measurement method	At programmed DNa 135 mEq/L*			At programmed DNa 136 mEq/L**		
	F4008H	F5008S (n = 10)	BB (n = 10)	F4008H (n = 10)	F5008S (n = 4)	BB (n = 11)
ISE measured minus programmed DNa	NA	6 (4.75−7.25)	7.5 (7−9)	5.5 (4.75−8.75)	NA	6 (6−7)
FP measured minus programmed DNa	NA	4 (1.75−5)	7 (6−7)	4.5 (0.75−6)	NA	8 (7−8)
IC measured minus programmed DNa	NA	4.5 (1.75−5.25)	6 (6−7)	5 (3.75−5)	2.5 (2−4.5)	5 (4.75−5.25)

Results expressed as median (IQR).
*P < 0.05 between F5008S/BB when DNa measured by all methods.
**P = 0.004 between F4008H/BB when DNa measured by FP.
NA, not available.

Table 3. The difference between measured and programmed DNa at a programmed DNa of 140 or 145 mEq/L

Na measurement method	At prescribed DNa 140 mEq/L*			At prescribed DNa 145 mEq/L**		
	F4008H (n = 11)	F5008S (n = 21)	BB (n = 20)	F4008H (n = 10)	F5008S (n = 17)	BB (n = 20)
ISE measured minus programmed DNa	5 (3.5−6)	3 (1−4)	7 (6−8)	7 (1−8.5)	2.5 (0.75−4)	8 (6.5−9)
FP measured minus programmed DNa	4 (1−5.5)	0 (−1−1)	6 (5−7)	4 (3.5−5.5)	−0.5 (−2.25−1)	7 (6−8.5)
IC measured minus programmed DNa	2 (2−4)	1 (−1−2)	6 (3.25−6)	4.5 (0.25−5.25)	1 (−1.5−1.5)	6 (4−7)

Results expressed as median (IQR).
*P < 0.001 between F5008S/BB by ISE, FP and IC.
**P < 0.001 between F5008S/BB by ISE, FP and IC; P = 0.045 between F4008H/F5008S by IC.

DISCUSSION

Dialysis patients are at increased risk of cardiovascular disease and stroke. Sodium balance is an important determinant of blood pressure. As such, preventing sodium accumulation is a major objective for HD treatments. DNa is a key component of the dialysis prescription, as it determines the diffusive sodium clearance and consequently influences the net sodium balance during a dialysis session [1, 3]. Despite the variable sodium prescription policies among different dialysis centres, alignment of the DNa with the serum sodium concentration to achieve neutral sodium flux is considered the most appropriate practice [11, 13]. Although a higher DNa may reduce the risk of intradialytic hypotension [20], in the longer term this may lead to increased weight gain between dialysis sessions and hypertension [21].

To be able to provide a neutral sodium balance, the programmed and delivered DNa need to be in alignment, but a previous study reported that dialysis machines may potentially deliver more sodium than programmed [16]. In our study, we measured sodium concentration by three different methods in fresh dialysate samples obtained during priming of three different HD machines: Fresenius 4008H, Fresenius 5008S and BB. Overall, measured DNa was greater than that programmed by all dialysis machines, at all prescribed sodium concentrations. The magnitude of bias varied between the dialysis machines and by the programmed DNa.

Overall, measured DNa by both the F4008H and BB machines was significantly higher than that programmed measured by ISE, FP and IC, whereas measured DNa in the F5008S was only higher than that programmed when assessed by the ISE method. The choice of programmed DNa influenced the magnitude of the difference between delivered and programmed dNa. At lower prescribed dNa concentrations (135 and 136 mEq/L), all three dialysis machines delivered significantly more sodium than was programmed, with the difference being greater for the BB and F4008H machines compared with the F5008S. With the higher programmed DNa (140 and 145 mmol/l), the BB and F4008H machines again delivered significantly more sodium than was programmed, while the F5008S machines only delivered a higher DNa when measured using the ISE method but not by IC or FP. These variances reflect the differences in the design of dialysis machines by manufacturers. Dialysis machines check the conductivity and pH after mixing ultrapure water, bicarbonate and acid concentrates of the final dialysate. Some machines then have a positive feedback loop designed to adjust the final conductivity by altering the proportion of water, bicarbonate or acid concentrate. Although the sodium concentration of the acid concentrate is entered into the dialysis machine, manufacturers are allowed a margin in error of ~2.5% in the sodium concentration. Errors in manufacture and inputting the acid concentrate sodium into the dialysis machine can lead to sodium gains during HD [10]. The F5008S was introduced to the market later than the other two dialysis machines, with software designed to automatically adjust DNa to achieve 'zero diffusive balance' by using conductivity balance [19]. However, a neutral conductivity balance may lead to sodium gains, depending on potassium losses and the changes in other cations and anions, with studies reporting an increase in plasma sodium in 15 of 16 patients [19].

Our findings are in contrast to the report by Gul *et al.* [16], who noted that the difference between prescribed and programmed DNa was greater with increasing DNa concentrations. However, they tested different dialysis machines than our study, using different bicarbonate and acid concentrates and

only measured DNa by ISE. We measured DNa by three different methods and found that the results using the ISE method were consistently higher than those measured by both FP and IC. This lends support to the previous finding that the standard ISE method used in everyday practice may overestimate sodium concentrations compared with other methods [15, 22].

Individualizing DNa has been proposed to achieve a neutral sodium balance and minimize the risk of intradialytic hypotension [13]. A diffusive sodium gradient from dialysate to blood can potentially be avoided using isonatric dialysis, in which sodium is only removed by convection, while avoiding any alteration in plasma osmolarity [20]. The adjustment in DNa can be manual, aligning the DNa to the pre-dialytic plasma sodium [23] or automatically using a control algorithm integrated into the dialysis machine [19]. However, the concept of isonatric dialysis depends upon the accurate measurement of plasma sodium and delivering the programmed DNa. Putting to one side the difficulties in accurately measuring plasma sodium [15], our results raise concerns about a potential positive sodium balance even when individualizing DNa prescriptions to be the same as pre-dialysis serum sodium. The net transfer of sodium from dialysate to the patient likely exceeds that which would have been expected based on the dialysis prescription [16].

Our study has some limitations. We measured DNa at the start of dialysis sessions and not sodium balance during HD. Thus the effects of a higher DNa than that programmed could be overcome by sodium losses achieved by ultrafiltration and does not necessarily imply patients would have had a positive sodium balance. However, our study may help explain why single-centre studies of reducing DNa report a reduction in interdialytic weight gains, whereas no overall effect is reported with multicentre studies using different dialysis machines and concentrates [2]. As such, further studies are warranted to assess the net Na balance during isonatric dialysis while correlating with the difference between measured and programmed DNa.

In conclusion, our study suggests that there is a systematic error (bias) in DNa delivery by our HD machines. The magnitude of error varied between machines and with the DNa concentration chosen.

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AUTHORS' CONTRIBUTIONS

A.M.S. and A.D. contributed to the study design, sample collection, drafting the paper, its critical revision and approved the final version.

CONFLICT OF INTEREST STATEMENT

None declared.

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