



Original article

Correlation of plasmatic sodium determined by the laboratory and that determined by the dialysis machine

Joaquim Casals^a, José Jesús Broseta^{a,*}, Rosa María Fernández^b,
Diana Rodríguez-Espinosa^a, Jimena del Risco^a, Miquel Gómez^a, Lida M. Rodas^a,
Marta Arias-Guillén^a, Manel Vera^a, Néstor Fontseré^a, Naira Rico^b, Francisco Maduell^a

^a Servicio de Nefrología y Trasplante Renal, Hospital Clínic, Barcelona, Spain

^b Centro de Diagnóstico Biomédico, Hospital Clínic, Barcelona, Spain

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ABSTRACT

Introduction: Changes in plasma sodium concentration (pNa , expressed in mEq/L) are common in hemodialysis (HD) patients. Hemodialysis monitors can estimate pNa by using an internal algorithm based on ion dialysance measurements. The present study studies the accuracy of the correlation between the pNa estimated by the dialysis monitor and that measured by the biochemistry laboratory at our center.

Material and methods: A single-centre prospective observational study in patients on a chronic HD program with the 6008 CAREsystem monitor and standard sodium (138 mmol/L) and bicarbonate (32 mmol/L) prescriptions. Venous blood samples were drawn from each patient before and after each HD session to ensure inter- and intra-individual validity. The pNa was measured in the biochemistry laboratory using indirect potentiometry and simultaneously the estimated pNa by the HD monitor was recorded at the beginning and at the end of the HD session. For statistical analysis, a scatterplot was made, and Spearman's correlation quotient was calculated. In addition, the differences between both methods were represented as Bland-Altman diagrams.

Results: The pre-dialysis pNa measured in the laboratory was 137.49 ± 3.3 , and that of the monitor, 137.96 ± 2.91 , with a correlation with R^2 value of 0.683 ($p < 0.001$). The post-dialysis pNa measured in the laboratory was 137.08 ± 2.23 , and that of the monitor was 138.87 ± 1.88 , with an R^2 of 0.442 ($p < 0.001$). On the Bland-Altman plots, the pre-dialysis pNa has a systematic error of 0.49, in favor of the monitor-estimated pNa , with a 95% confidence interval (CI) of (-3.24 to 4.22). In the post-dialysis pNa , a systematic error of 1.79 with a 95% CI of (-1.64 to 5.22) was obtained.

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* Corresponding author.

E-mail address: jjbroseta@clinic.cat (J.J. Broseta).

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Conclusion: The correlation between the pNa estimated by Fresenius 6008 CAREsystem HD monitor and that measured by the laboratory is good, especially pre-dialysis measurements. Further studies should verify the external validity of these results.

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Correlación entre el sodio plasmático determinado por el laboratorio y el determinado por el monitor de hemodiálisis

R E S U M E N

Palabras clave:

Dialisis iónica
Hemodiálisis
individualización
Sodio plasmático
Módulo de sodio

Introducción: Las alteraciones de la concentración plasmática de sodio (Na_p , expresado en mEq/L) son frecuentes en pacientes en hemodiálisis (HD). Los monitores de hemodiálisis tienen la capacidad de estimar la Na_p mediante un algoritmo interno a partir de las medidas de la dialisis iónica. En el presente estudio se estudia la correlación entre la Na_p estimada por el monitor de diálisis y la medida en el laboratorio de bioquímica de nuestro centro.

Material y métodos: Estudio observacional prospectivo y unicéntrico en pacientes en programa crónico de HD con el monitor 6008 CAREsystem y prescripción estándar de sodio (138 mEq/L) y bicarbonato (32 mmol/L). De cada paciente se extrajeron muestras de sangre venosa antes y después de la sesión para asegurar validez inter e intraindividual. Se analizó la Na_p en el laboratorio mediante potenciometría indirecta y simultáneamente se registraba la estimada por el monitor de HD al inicio y al terminar la sesión. Para el análisis estadístico se realizó un diagrama de dispersión y se calculó el cociente de correlación de Spearman. Además, se representaron las diferencias entre métodos mediante diagramas de Bland-Altman.

Resultados: La Na_p prediálisis medida en el laboratorio fue de $137,49 \pm 3,3$, y el del monitor $137,96 \pm 2,91$, con una correlación con valor de R^2 de 0,683 ($p < 0,001$). La Na_p postdiálisis medida en el laboratorio fue de $137,08 \pm 2,23$ y la del monitor de $138,87 \pm 1,88$, con una R^2 de 0,442 ($p < 0,001$). En los diagramas de Bland-Altman, la Na_p prediálisis obtuvo un error sistemático de 0,49 mEq/L a favor de la Na_p estimada por el monitor, con un intervalo de confianza (IC) al 95% de (-3,24-4,22). En cuanto a la Na_p postdiálisis, se obtuvo un error sistemático de 1,79 mEq/L con un IC al 95% de (-1,64-5,22).

Conclusión: La correlación entre la Na_p estimada por el monitor de HD 6008 CAREsystem de Fresenius y la medida por el laboratorio es buena, siendo mejor en las mediciones prediálisis. Nuevos estudios deberán comprobar la validez externa de estos resultados.

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Introduction

Sodium (Na) is the most abundant cation in the extracellular compartment and is the most important determinant of plasma volume and osmolarity.^{1,2} Na homeostasis is essential for maintaining water-electrolyte balance and, ultimately, proper cellular function.³ This depends on the intestinal absorption of Na and its excretion in the feces, sweat and, above all, urine.^{2,4} For this reason, dysnatremias are frequent in patients with chronic kidney disease and especially in those on hemodialysis (HD).⁵

Conductivity is considered a reliable and practical surrogate for monitoring the Na concentration of dialysis fluid, so this is used as a safety variable to ensure the mixture of acid concentrate, bicarbonate and treated water is correct.⁶ A variation of 1 mmol/l of Na causes a 0.1 mS/cm change in conductivity.

In HD patients, both predialysis hyponatremia ($Na < 135$ mmol/l)⁷⁻¹⁰ and a difference between final and initial Na of HD treatment (i.e., an Na delta) greater than 4 mmol/l¹¹ have been associated with increased mortality. So, it is of great interest to know the plasma sodium concentration (Na_p) of HD patients.

In routine clinical practice, monthly or bimonthly determination of Na_p , has been performed in the biochemistry laboratory using venous blood samples. However, differences have been observed that should be considered depending on the type of method used in the analysis,¹² in particular flame photometry and potentiometry, which includes both direct and indirect potentiometry.

Currently, HD monitors can estimate the patient's Na_p , at each session and in real time, by means of an internal algorithm from ionic dialysance measurements. In addition, a recent addition has been introduced in some monitors, an Na

module that, from the Na_p monitoring of the patient, is able to automatically adjust the Na concentration in the dialysis fluid to try to achieve a neutral diffusive balance, which would approach isonatremia.^{13–15}

Given the disparity of methods for determining Na_p in the laboratory and the new possibility of estimating it by ionic dialysance in the HD monitor, the aim of the present study was to evaluate the correlation between Na_p estimated by the HD monitor and that determined in the laboratory.

Material and methods

Prospective, single-center, observational study of patients in a chronic HD program. All patients were dialyzed with the 6008 CAREsystem monitor. The acid concentrate prescription and Na (138 mEq/l) and bicarbonate (32 mmol/l) concentrations were kept constant in each patient, according to the concentrates' technical data sheet, as well as the rest of the dialytic parameters.

Each patient received between 2 and 5 HD sessions in which pre- and post-dialysis venous blood samples were drawn to ensure inter- and intra-individual validity. Na_p was determined in the laboratory using the Atellica™ Solution platform (Siemens), specifically on the LYTE® Integrated Multisensor module that uses indirect potentiometry (IP) in electrolyte measurement. The limit of quantification (LoQ) of Na in this analyzer is less than 50 mmol/l (50 mEq/l) with a total error $\leq 20\%$ in serum and plasma. This detection capability was determined in accordance with CLSI document EP17-A2.¹⁶

The results are expressed as mean \pm standard deviation when the variables are quantitative and as absolute and relative frequencies when they are qualitative. To evaluate statistical inference, we constructed scatter diagrams and calculated Spearman's correlation coefficient, and used a Bland-Altman diagram to quantify the mean difference between the 2 methods with a confidence interval that includes 95% of the differences between one technique and the other. Finally, we set the cut-off point for statistical significance at $p < 0.05$. Statistical analysis was performed with the SPSS program® version 25 (IBM Corp., Armonk, NY, USA).

Results

Eighty-one patients (49 males and 32 females) with a mean age of 68 ± 16 years were included. The etiology of renal failure was: chronic glomerulonephritis in 12 cases (14.6%), tubulointerstitial nephropathy in 7 cases (8.5%), vascular etiology in 25 cases (30.5%), polycystic in 6 cases (7.3%), diabetic nephropathy in 15 cases (18.3%), systemic disease in 1 case (1.2%), urological in 3 cases (3.7%), renal tumor in 2 cases (2.4%), cardiorenal in 1 case (1.2%) and cases of non-affiliated etiology in 9 cases (11%). The patients were dialyzed through an arteriovenous fistula in 70% of the cases, through a prosthetic fistula in 5% and the remaining 25% through a tunneled central venous catheter. The different parameters of the dialysis sessions were as follows: dialysis time, 319 ± 72 min (240–480 min); blood flow (Q_b) 411 ± 37 ml/min (300–450), dialysis bath flow (Q_d) 400 ml/min; hemodiafiltration modality in 95% and extended HD in the remaining 5%. Finally, anticoagulation was per-

formed with sodium heparin in 36.5% of cases, low molecular weight heparin in 51.5% of cases and no heparin in the remaining 12%.

A total of 277 dialysis sessions, performed with 15 different 6008 CAREsystem monitors, were analyzed, in which pre- and post-dialysis Na_p values, both those determined by the dialysis monitor and those obtained by indirect potentiometry in the laboratory, were collected for comparison.

The predialysis Na_p measured in the laboratory was 137.49 ± 3.3 (range: 126–146), while that of the monitor was 137.96 ± 2.91 (range: 128–144). As for post-dialysis, that determined by the laboratory was 137.08 ± 2.23 (131–145) and that of the monitor, 138.87 ± 1.88 (133–144). A correlation was obtained between predialysis Na_p measured by both methods, governed by the equation laboratory predialysis $\text{Na}_p = 0.938 \times \text{Na}_p$ monitor predialysis + 8.1, with an R^2 value of 0.683 and a $p < 0.001$ (Fig. 1A). As for post-dialysis Na_p , a correlation was obtained governed by the formula Na_p post-laboratory dialysis = $0.789 \times \text{Na}_p$ post-monitor dialysis + 27.6, with an R value² of 0.442 and a $p < 0.001$ (Fig. 1B). To rule out potential biases, we performed a sub-analysis by dialysis shift of the differences found between monitors and found no statistically significant differences.

Using the Bland-Altman plot, in reference to pre-dialysis Na_p , a systematic error of +0.49 mEq/l (95% CI: –3.24 to 4.22) was observed in favor of the monitor with respect to the laboratory. In the case of post-dialysis Na_p , a systematic error of +1.79 mEq/l (95% CI: –1.64 to 5.22) in favor of the monitor over the laboratory was observed (Fig. 2). We subsequently performed another *post hoc* analysis to evaluate whether the differences between the Na_p measured by the monitor minus that obtained in the laboratory were consistent as a function of the patient's Na_p measured in the laboratory, which we analyzed at both times, finding that the difference is greater in the more hyponatremic patients and that, moreover, this difference gradually decreases until it is reversed in those with higher Na:

$$\begin{aligned} \Delta \text{Na}_p(\text{laboratory-monitor})_{\text{predialysis}} \\ = 37.773 - 0.271 \times \text{Na}_p(\text{laboratory})_{\text{predialysis}} \end{aligned}$$

$$\begin{aligned} \Delta \text{Na}_p(\text{laboratory-monitor})_{\text{predialysis}} \\ = 62.087 - 0.44 \times \text{Na}_p(\text{laboratory})_{\text{postdialysis}}, \text{ with } R^2 \\ \text{of } 0.23 \text{ and } 0.328, \text{ respectively.} \end{aligned}$$

Discussion

Intradialytic Na balance is a crucial point of treatment. A positive intradialytic Na gradient favors hemodynamic stability and adequate perfusion of vital organs,⁹ however, it increases plasma osmolality, thirst and extracellular volume, thus leading to increased blood pressure, greater left ventricular hypertrophy and favoring the development of

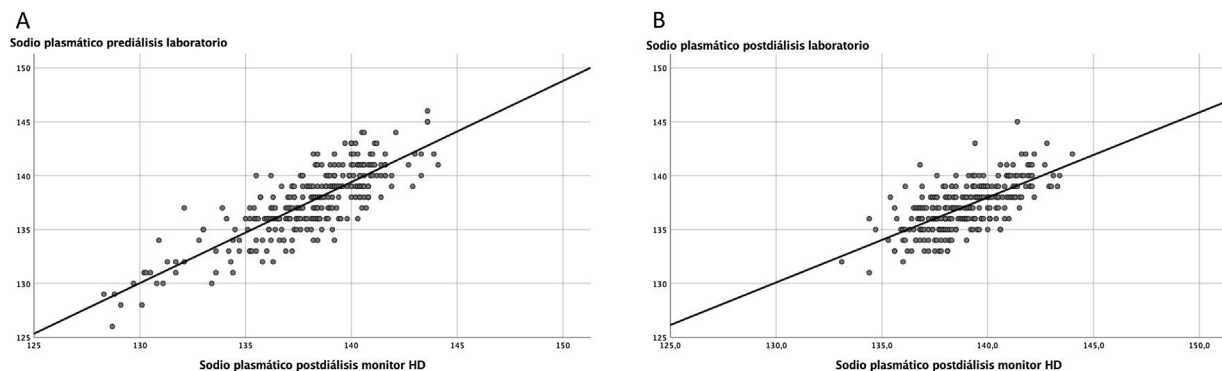


Figure 1 – Correlation of plasma sodium concentration measurement in the monitor versus the laboratory. A) In pre-dialysis samples. B) Post-dialysis.

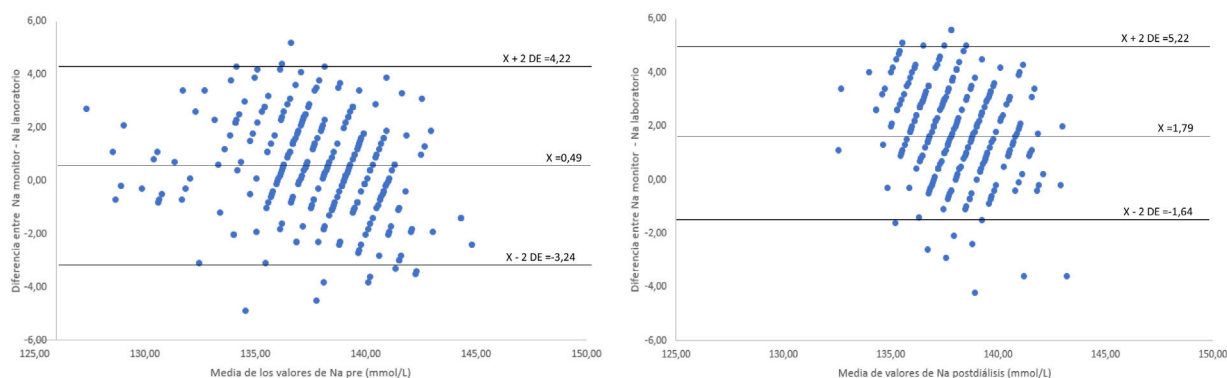


Figure 2 – Bland-Altman plot to quantify the mean difference between the two methods of measuring plasma sodium concentration.

cardiovascular events.¹⁷ In contrast, a negative gradient is associated with lower interdialytic weight gain and better blood pressure control at the expense of favoring intradialytic hypotension and tissue hypoperfusion.⁹ This is relevant when prescribing HD treatment, since different studies have been published, with consistent results among them, that correlate the Na prescribed on the monitor with the Na finally achieved in the dialysis fluid.¹⁸

This observational study has shown that there are no major differences, in our center, between Na measured by the HD machine by ionic dialysance and Na measured by indirect potentiometry in the laboratory from venous blood samples. As shown in Fig. 1, there is a good correlation between the Na_p measured by the machine and that measured in the laboratory, with the best fit in the case of predialysis Na_p . In general terms, what we observed is that the value of Na_p is overestimated by the dialysis machine, more in the high range of Na values and, above all, in the case of post-dialysis Na_p .

The Bland-Altman diagram in Fig. 2 shows how the predialysis Na_p has a systematic error of 0.49 mEq/l in favor of the monitor. That is, the monitor will give us a slightly higher Na_p than the laboratory Na. Assuming 0.5 mEq/l mean systematic error seems a good option, since the laboratory gives us the Na_p figures in whole numbers, without decimals, so we would be dealing with a negligible error. However, in the case of post-dialysis Na_p , the mean systematic error is 1.79 mEq/l in favor of the monitor. The fact that postdialysis Na_p in the

different analyses correlates worse than predialysis Na_p could be related to being an indirect measurement method based on ionic dialysance. Thus, there could be greater variation in the ionic composition of the plasma at the end of dialysis (other elements are added, such as chlorine or bicarbonate) which could alter the estimation of the Na value,¹³ in addition to other factors such as changes in glycemia,¹⁹ protein binding or the formation of complexes with anions such as sulfate and phosphate.²⁰ This means that the post-dialysis Na_p value should not be considered reliable in clinical situations that require an exact natremia value.

Both standard errors have a wide 95% confidence interval, which could have clinical implications, although this is lower in the case of post-dialysis Na_p . In fact, if we observe the range of Na_p values, predialysis, it falls between 127 and 144 mEq/l, whereas post-dialysis it narrows between 134 and 144 mEq/l, a finding that supports the effect of dialysis fluid in modifying Na_p values during HD treatment.

Subsequent *post hoc* analysis confirmed that pre-dialysis and post-dialysis Na_p remained without statistically significant differences between the different monitors and dialysis shifts. However, we did find that the differences between the Na_p measured by the monitor and that of the laboratory, both pre- and post-dialysis, depended on the patient's blood Na_p , with patients with a lower Na_p having a greater difference in favor of the monitor, while those with a higher Na_p had a smaller difference and in favor of the laboratory. These find-

ings, which become clinically relevant in extreme Na_p , should be considered. Perhaps this margin of error could be corrected by the formula suggested in this work, especially in hyponatremic patients, to correct the monitor's overestimate.

A factor to consider when externally validating this study is the method used for Na measurement in each laboratory. Currently the main methods used for Na_p measurement or serum are flame atomic emission spectrometry and ion selective electrode potentiometry, the former being the reference method so far. In this method, the sample in solution is nebulized and introduced into the flame, where it is atomized. As the excited atoms decay to the basal electronic state, radiation is emitted which passes through a monochromator that isolates the characteristic wavelength for the desired ion. The intensity of light emitted will be proportional to the concentration of the ion present in the solution. Although the reference method for measuring Na_p or serum has always been atomic emission spectrometry, this is a laborious method that does not allow rapid sample throughput. For this reason, most laboratories use potentiometry as the main method, since the technology used is much simpler and allows automation of the samples. It consists of measuring the electrical potential between a reference electrode and an indicator electrode in an electrochemical cell when no current is flowing. The reference electrode is immersed in a solution of known concentration that generates a constant potential, while the indicator electrode, immersed in the test solution, is a membrane electrode selective to the ion to be determined. The potential generated at this electrode will vary according to the concentration of the ion present in the solution.²¹ The potentiometer of the electrochemical cell is then responsible for determining the potential difference between the two electrodes and then, by applying the Nernst equation,²² it is possible to calculate the concentration of the ion in question.

This method in turn is classified into two types, direct potentiometry (DP) and indirect potentiometry (IP). In the first case, it is not necessary to dilute the sample, and it is the method used in gas analyzers located, mainly, in the place of patient care.²³ In the case of IP, as in flame photometry, the sample is diluted, which allows the measured ion activity to be closer to the ion concentration and, for this reason, its use is more standardized than that of PD.¹⁶

The PI and PD methods measure the electrolyte activities in the aqueous phase of the plasma, which represents about 93%, but assume this result as if it were the concentration of electrolyte present in the total plasma, assuming a normal solid phase of about 7% which is basically composed of proteins and lipids. They differ only in that in the IP the percentage of solid phase component is considered for the calculation of the Na concentration, as long as the water content in the aqueous phase of the plasma remains constant, this difference between the Na ion concentration in the total plasma and the Na ion concentration in the aqueous phase of the plasma is predictable and can be ignored. However, the problem arises in some clinical conditions, such as hyperlipidemia or hyperproteinemia, in which the water content is replaced by protein or lipid. In these situations, the aqueous phase of plasma decreases and the solid phase increases and causes a phenomenon known as pseudohyponatremia.²⁴ This is even more pronounced with sample dilution, because a smaller volume

of plasma may be aspirated than expected. This phenomenon, however, is not expected in PD because it neglects the solid phase component. For this reason, the European Society of Endocrinology (ESE), the European Society of Intensive Care Medicine (ESICM) and the European Renal Association (ERA) recommend using PD test results to diagnose dysnatremias.

In subsequent studies it would be important to determine the Na concentration by PD in those HD patients with a high concentration of proteins and/or lipids to assess whether these differences are still observed with the Na_p measured by ionic dialysance or whether, on the contrary, the discrepancies are smaller. Furthermore, it is important to point out that dialysis monitors of different brands, with identical conductivity prescription, obtain different Na concentrations, with a range exceeding 4 mmol/l. This is due to the temperature coefficient chosen to correct conductivity to the ISO standard of 25 °C.²⁵ Another limitation of this work is that we did not correct natremia for glycemia.

In any case, our results agree with those obtained by Maierhofer et al. who, in a study including 384 dialysis sessions performed in 75 different patients, demonstrated a good correlation between pre-dialysis Na_p concentration determined by the monitor compared to blood samples analyzed by direct potentiometry.²⁶

In conclusion, the present study is a proof of concept indicating a good correlation between Na_p measured by the Fresenius CAREsystem 6008 HD monitor versus the laboratory. However, this is a proof of concept, and caution should be exercised in its interpretation, especially in cases where the result is above normal values and in post-dialysis samples. Further studies evaluating Na_p measured by the monitor against the diagnostic gold standard are needed.

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This study has not received financial support.

Conflict of interest

FM has received fees from Amgen, Baxter, Fresenius Medical Care, Medtronic, Nipro and Vifor. JJB has received honoraria from Fresenius Medical Care. The rest of the authors declare no conflicts of interest.

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