Tailoring the dialysate bicarbonate eliminates pre-dialysis acidosis and post-dialysis alkalosis

Elena Cuadrado1, José Jesús Broseta1, Diana Rodríguez-Espinosa1, Enrique Montagud-Marrahi1, Lida Rodas1, Néstor Fontseré1, Marta Arias-Guillén1, Naira Rico2 and Francisco Maduell1

1Department of Nephrology and Renal Transplantation, Hospital Clinic of Barcelona, Barcelona, Spain and
2Department of Biochemistry, Hospital Clinic of Barcelona, Barcelona, Spain

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

ABSTRACT

Background. Both metabolic acidosis and alkalosis increase hospitalizations, haemodynamic instability and mortality in haemodialysis patients. Unfortunately, current practices opt for a one-size-fits-all approach, leaving many patients either acidotic before or alkalotic after dialysis sessions. Therefore an individualized adjustment of these patients’ dialysate bicarbonate prescriptions could reduce these acid–base imbalances.

Methods. This is a prospective single-cohort study of patients on a chronic haemodiafiltration programme. The dialysate bicarbonate prescription was modified according to the pre- and post-dialysis total carbon dioxide (TCO2) values of 19–25 mEq/L and ≤29 mEq/L, respectively, with an adjustment formula calculated with the data obtained from previously published work by our group. In addition, we analysed this adjustment’s effect on plasma sodium, potassium, phosphorus, parathyroid hormone (PTH) and calcium.

Results. At baseline, only 67.9% of patients were within the desired pre- and post-dialysis TCO2 target range. As of the first month, every followed patient met the TCO2 target range objective in pre-dialysis measurements and >95% met the post-dialysis TCO2 target. At the end of the study, 75% of the patients were on dialysate bicarbonate of 32–34 mEq/L. There were no clinically significant changes in calcium, phosphate, PTH, sodium or potassium levels. Also, we did not notice any increase in intradialytic adverse events.

Conclusions. We suggest an individualized adjustment of the dialysate bicarbonate concentration according to the pre- and post-dialysis TCO2 values. With it, nearly every patient in our cohort reached the established range, potentially reducing their mortality risk.
INTRODUCTION

End-stage kidney disease alters body homeostasis and acid–base status due to the kidneys’ inability to excrete ammonium, primarily, and also to secrete organic and inorganic anions, such as sulphate and phosphorus, whose participation in this process is minor, leading to metabolic acidosis, which leads to an increased risk of hospitalization and mortality in this population. Thus renal replacement therapies must correct patients’ acidotic states to avoid these unwanted outcomes [1–3].

In haemodialysis (HD) the dialysate bicarbonate is the main driver responsible for correcting chronic metabolic acidosis [2]. Post-dialysis measured plasma bicarbonate is usually 2–5 units higher than the pre-dialysis concentration [4]. It is influenced by the prescribed dialysate bicarbonate concentration, the HD session duration and the amount of ultrafiltered and substituted plasma volume [5]. With online haemodiafiltration (OL-HDF), there is a higher bicarbonate delivery, achieving higher plasma levels and better acidosis control than with high-flux HD [6]. However, this increased delivery can often lead to bicarbonate overcorrection and post-dialysis metabolic alkalosis [7, 8].

Observational evidence shows a U-shaped correlation between pre-dialysis plasma bicarbonate levels and adverse effects such as haemodynamic instability [9] and all-cause mortality with both metabolic acidosis and alkalosis [5, 10]. Despite there not being high-quality evidence determining which are the optimal pre- and post-dialysis bicarbonate values that physicians should target in this population [11] and the lack of consensus on this subject across guidelines [2], the latest Kidney Disease: Improving Global Outcomes recommendation is to target a pre-dialysis plasma bicarbonate level >22 mEq/L [12–15]. This recommendation has led to bicarbonate overshooting, increasing the number of patients with metabolic alkalosis, which has been associated with increased mortality in cases with pre-dialysis bicarbonate levels >27 mEq/L [5, 16–18]. Given that the measurement of total carbon dioxide (TCO₂) in venous blood samples allows plasma bicarbonate to be accurately estimated (which is 1–2 mEq/L higher than the actual plasma bicarbonate level) [19] without the need to perform arterial blood gases, we used this method in a previous publication to evaluate the effects of reducing the bicarbonate dialysate concentration from 35 mEq/L to 32 mEq/L in every patient on maintenance HD from our unit [20]. With this intervention, we significantly and safely increased the number of patients within the desired pre- and post-dialysis TCO₂ target of 22 and 27 mEq/L, respectively. In addition, there was an improvement in secondary hyperparathyroidism without adverse effects on potassium, calcium or phosphorus metabolism.

Based on these results, we hypothesize that an individually tailored rather than a generalized dialysate bicarbonate prescription will increase the percentage of patients within a desired bicarbonate target range. This study aims to evaluate the effects of an individually adjusted dialysate bicarbonate prescription according to the pre- and post-dialysis TCO₂ to achieve
a pre-dialysis TCO₂ level between 19 and 25 mEq/L and a post-dialysis level ≤ 29 mEq/L.

**MATERIALS AND METHODS**

**Study design and population**

This prospective, single-centre study included a cohort of patients from a previously published study [20]. These were stable individuals on chronic post-dilution online haemodiafiltration (HDF) or an expanded HD (HDx) programme for at least 12 months under a regular prescription with dialysate bicarbonate concentration of 32 mEq/L. We excluded patients with temporary percutaneous catheters as vascular access, those awaiting a living donor kidney transplantation, those on immunosuppressive treatment, those on oral bicarbonate supplements and those with significant residual kidney function (defined as residual diuresis > 100 mL/24 h and urea clearance > 2.5 mL/min/1.73 m²). Included subjects were followed for 6 months.

**Individualized bicarbonate titration**

In the included patients, the dialysate bicarbonate prescription was modified according to the pre- and post-dialysis TCO₂ values following the formula below, calculated with the data obtained from our previous article [20]:

\[
\text{HCO}_3^- = (\text{HCO}_3^-)_p + \frac{[(\text{TCO}_2)_p] - [(\text{TCO}_2)_m]}{2} + \frac{[(\text{TCO}_2)_m] - [(\text{TCO}_2)_p]}{22}.
\]

where \((\text{HCO}_3^-)_p\) is the previous dialysate bicarbonate concentration used, \([(\text{TCO}_2)_p]_m\) is the measured pre-dialysis TCO₂, \([(\text{TCO}_2)_p]_m\) is the targeted pre-dialysis TCO₂, \([(\text{TCO}_2)_p]_p\) is the measured post-dialysis TCO₂ and \([(\text{TCO}_2)_p]_m\) is the targeted post-dialysis TCO₂. The result of this equation is rounded to whole numbers in the direction of the pre-dialysis result.

For instance, for a patient with a \(\text{HCO}_3^-\) dialysate of 30 mmol/L who presents with a pre-dialysis measured TCO₂ of 19 mEq/L and a post-dialysis level of 25 mEq/L, the dialysate bicarbonate prescription would be

\[
\text{HCO}_3^- = 30 + \frac{22-19}{2} + \frac{27-25}{14} \approx 30 + \frac{3 + 1}{2} = 32.5.
\]

If the next month the same patient, now with a \(\text{HCO}_3^-\) dialysate of 32 mmol/L has a pre-dialysis measured TCO₂ of 20 mEq/L and a post-dialysis level of 25 mEq/L, then the dialysate bicarbonate would be

\[
\text{HCO}_3^- = 32 + \frac{22-20}{2} + \frac{27-25}{14} \approx 32 + \frac{2 + 1}{2} = 33.5 \to 34.
\]

However, if the post-dialysis TCO₂ had been 22 mEq/L instead of 20 mEq/L, the dialysate bicarbonate would have been

\[
\text{HCO}_3^- = 32 + \frac{22-20}{2} + \frac{27-22}{14} \approx 32 + \frac{2 + 3}{2} = 34.5 \to 34.
\]

**Statistical analysis**

Quantitative variables are reported as mean and standard deviation (SD), while qualitative ones are reported with absolute and relative frequencies. Each patient served as her/his own control, so the repeated measures analysis of variance with a Bonferroni correction was used to compare quantitative data. A 2-sided P-value < .05 was considered statistically significant. Analyses were performed with SPSS Statistics version 26 (IBM, Armonk, NY, USA) and graphics were prepared with GraphPad Prism version 8 (GraphPad Software, San Diego, CA, USA).

**RESULTS**

**Baseline characteristics**

Of the 123 patients included in the study, 11 were lost during the follow-up. One patient was transferred to another centre, five patients received a kidney transplant, two had missing lab values and two died. The causes of death were severe acute respiratory syndrome coronavirus 2 pneumonia and amyloid light-chain amyloidosis. The population’s demographic data, specific dialysis parameters and clinical baseline characteristics are explained in detail in Table 1.

**Changes in TCO₂ after tailoring the dialysate HCO₃⁻ prescription**

Pre- and post-dialysis TCO₂ levels significantly decreased from 23.25 ± 2.24 mEq/L and 27.38 ± 1.77 mEq/L at baseline to 21.33 ± 1.46 and 25.35 ± 1.11 at 2 months, 21.56 ± 1.49 and 25.54 ± 1.11 at 4 months and 22.85 ± 1.48 mEq/L and 26.81 ± 1.27 at 6 months, respectively (Figure 1).
At baseline, only 80 (71.4%) patients were within the desired pre-dialysis TCO₂ target range of 19–25 mEq/L, 97 (86.6%) were within the wanted post-dialysis range of 27–29 mEq/L, and 76 (67.9%) were within both. After individually tailoring the dialysate HCO₃⁻ prescription, we found a right-skewed distribution at 3 months, with most patients meeting the desired target TCO₂ with dialysate HCO₃⁻ concentrations between 32 and 34 mEq/L. At 6 months since follow-up, dialysate HCO₃⁻ concentrations became more normally distributed, with most patients requiring HCO₃⁻ concentrations between 32 and 35 mEq/L to meet the targeted TCO₂ (Figure 2). As of the first month, every followed patient met the TCO₂ target range objective in predialysis measurements and >95% met the post-dialysis TCO₂ target (Figure 3).

Changes in plasma sodium and potassium

There were no significant changes between baseline (137.9 ± 2.48 mEq/L) and pre-dialysis plasma sodium levels at 3 (137.79 ± 2.95 mEq/L; \( P = 1 \)) and 6 months (137.64 ± 2.53 mEq/L; \( P = .95 \)) since the follow-up or between post-dialysis plasma sodium levels at baseline (138.26 ± 1.67 mEq/L), 3 months (138.66 ± 1.5 mEq/L; \( P = .1 \)) and 6 months (138.07 ± 1.68 mEq/L; \( P = 1 \)). With regards to potassium, there was a significant decrease between plasma potassium levels at baseline (4.7 ± 0.7 mEq/L) and 6 months (4.5 ± 0.65 mEq/L; \( P = .007 \)). Post-dialysis values also significantly increased from 3.01 ± 0.39 mEq/L at baseline to 3.42 ± 0.81 mEq/L at 6 months (\( P < .001 \)).

Calcium, phosphate and PTH changes

Pre-dialysis calcium ranged from 8.59 ± 0.52 mg/dL at baseline to 9.02 ± 0.55 mg/dL (\( P < .001 \)) at 3 months and 8.74 ± 0.91 mg/dL (\( P < .001 \)) at 6 months, with a mean pre-dialysis calcium of 8.83 ± 1.05 mg/dL. The post-dialysis calcium values ranged from 9.7 ± 0.6 to 10.1 ± 0.66 mg/dL (\( P < .001 \)) at 3 months and 9.85 ± 0.8 mg/dL (\( P = .145 \)) at 6 months, with a mean post-dialysis calcium of 9.91 ± 0.5 mg/dL. Regarding phosphorus, pre-dialysis...
values slightly increased from 3.97 ± 1.07 mg/dL at baseline to 4.35 ± 1.28 mg/dL (P = .004) at 3 months but decreased to 4.03 ± 1.23 mg/dL (P = 1) at 6 months, with a mean pre-dialysis phosphorus of 4.19 ± 1.97 mg/dL. In contrast, post-dialysis levels remained similar: 1.71 ± 0.38 mg/dL at baseline, 1.79 ± 0.39 mg/dL (P = .12) at 3 months and 1.73 ± 0.49 mg/dL (P = 1) at 6 months, with a mean of 1.8 ± 1.17 mg/dL. After the change of HCO$_3^-$ in the dialysate, PTH tended to increase, from 223.9 ± 185.5 pg/mL at baseline to 243.53 ± 147.32 pg/mL (P = .389) at month 3, although this was reversed by month 6 (207.72 ± 112.78 pg/mL; P = .919) and no statistical significance was achieved. The mean PTH value was 229.24 ± 151.21 pg/mL. More data can be found in the Supplementary data, Table 1.

Safety

Among the 8636 sessions, there were 24 hypotensive episodes (0.3%) and 10 muscle cramp episodes (0.1%), which were attributed to dry-weight adjustments. There were no symptomatic arrhythmias.

DISCUSSION

The present study is, to our knowledge, the first to propose a formula to individualize the dialysate HCO$_3^-$ prescription. The implementation of this adjustment formula succeeded in improving the percentage of patients attaining pre- and post-dialysis HCO$_3^-$ levels within the desired target range.

In a previously published study [20], we managed to significantly increase the number of HD patients within a desired pre- and post-dialysis target range, avoiding excessive alkalosis and acidosis by reducing the dialysate HCO$_3^-$ concentration from 35 mEq/L to 32 mEq/L in every patient. However, ~20% of pre-dialysis and 11% of post-dialysis TCO$_2$ remained above the target range.

Among the factors determining HCO$_3^-$ pre-dialysis levels are acid generation (endogenous acid production, largely determined by dietary protein intake), interdialysis weight gain, time since the last dialysis, phosphorus binder use and post-dialysis serum HCO$_3^-$. The main determinants of post-dialysis serum HCO$_3^-$ are high-HCO$_3^-$ dialysate, the dialysate non-HCO$_3^-$ anion concentration, determinants of dialysis adequacy, dialysance of HCO$_3^-$ and non-HCO$_3^-$ anions, ultrafiltration rate, organic anion generation during dialysis and pre-dialysis serum HCO$_3^-$ [17, 18].

Pre-dialysis HCO$_3^-$ levels < 22 mEq/L [12] are associated with higher mortality rates; however, its correction can lead to overshooting, thus driving post-dialysis metabolic alkalosis, which can also lead to calcium phosphate precipitation in soft tissues and therefore increased mortality [5]. Although an interpretation of the international guidelines suggests a pre-dialysis TCO$_2$ target range between 19 and 25 mEq/L and a post-dialysis TCO$_2$ target ≤29 mEq/L, there are few recommendations in the literature to individualize the HCO$_3^-$ prescription, much less, a suggestion that encompasses both pre- and post-dialysis. To cover this gap, and based on those results and the available scientific evidence and using TCO$_2$ as a HCO$_3^-$ estimate, our study group determined the proposed formula to individualize the dialysate HCO$_3^-$ prescribed to each patient to a pre-dialysis TCO$_2$ target range between 19 and 25 mEq/L and a post-dialysis target ≤29 mEq/L.
As expected, most subjects achieved the target TCO2 with dialysate HCO3− concentrations between 32 and 35 mEq/L. However, using this formula, we identified 7–9% of patients who required HCO3− concentrations beyond these typical values. Changes in plasma HCO3− can affect the plasma concentration of other ions. HCO3− levels and accompanying modifications in blood pH are inversely correlated with ionized calcium, potassium, PTH and phosphate levels, whereas sodium levels are directly correlated. Despite achieving better pre- and post-dialysis plasma TCO2 in range rates, this outcome was obtained without significant changes in calcium, phosphate, PTH, sodium or potassium levels. Also, we did not notice any increase in adverse events derived from the mean slight decrease in TCO2 levels.

Our study has several limitations, as it was performed in a single centre with a short follow-up of 6 months. Although patients acted as their own controls and homogeneous dietary habits were assumed, the participants’ diet was not registered. In addition, and because of these limitations, we could not determine if these adjustments will affect hospitalization rates or mortality events.

In conclusion, the proposed formula succeeded in attaining pre- and post-dialysis HCO3− levels within the desired target range, with nearly every patient in our cohort reaching it. The development of more broad studies to improve the external validity of our results and produce practice-changing knowledge on this topic is necessary.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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AUTHORS’ CONTRIBUTIONS

E.C., J.B., D.R.-E. and E.M.-M. collected, analysed and interpreted the data and prepared the article. J.B., L.R., M.A.-G. and N.F. proportioned, collected the data and prepared the article. Statistical analysis was performed by J.B. and F.M. Each author contributed important intellectual content during article drafting or revision, accepts personal accountability for the author’s own contributions and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

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

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