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Original Article

ORIGINAL ARTICLE

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

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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 (TCO_2) 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 TCO_2 target range. As of the first month, every followed patient met the TCO_2 target range objective in pre-dialysis measurements and >95% met the post-dialysis TCO_2 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 TCO_2 values. With it, nearly every patient in our cohort reached the established range, potentially reducing their mortality risk.

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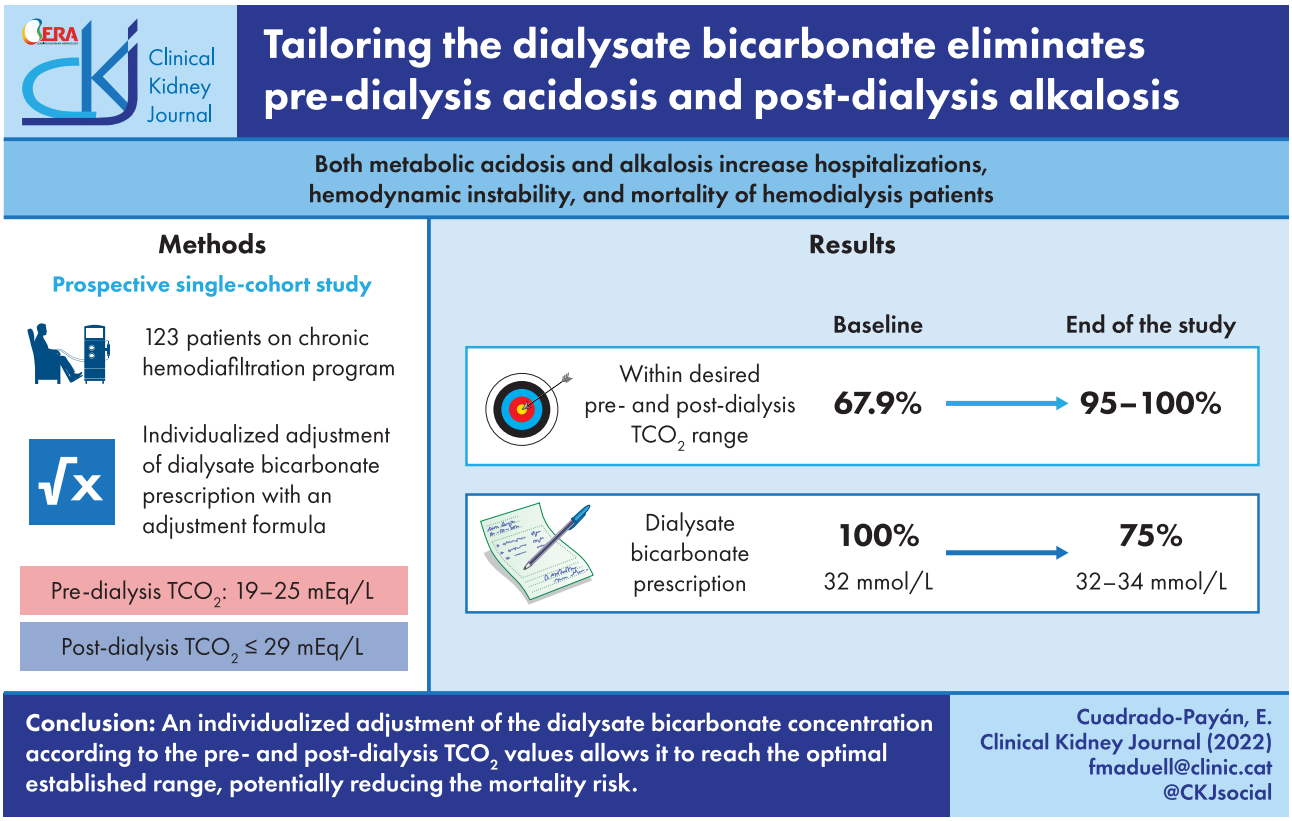
GRAPHICAL ABSTRACT



Keywords: acidosis, alkalosis, dialysate bicarbonate, haemodiafiltration, haemodialysis

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 (TCO_2) 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 TCO_2 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 TCO_2 to achieve

a pre-dialysis TCO_2 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/1.72 m^2). 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 TCO_2 values following the formula below, calculated with the data obtained from our previous article [20]:

$$HCO_3^- = (HCO_3^-)_i + \frac{\frac{[(TCO_2)_{pre}]_t - [(TCO_2)_{pre}]_m}{1.03} + \frac{[(TCO_2)_{post}]_t - [(TCO_2)_{post}]_m}{1.47}}{2},$$

where $(HCO_3^-)_i$ is the previous dialysate bicarbonate concentration used, $[(TCO_2)_{pre}]_m$ is the measured pre-dialysis TCO_2, $[(TCO_2)_{pre}]_t$ is the targeted pre-dialysis TCO_2 $[(TCO_2)_{post}]_m$ is the measured post-dialysis TCO_2 and $[(TCO_2)_{post}]_t$ is the targeted post-dialysis TCO_2. 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 HCO_3^- dialysate of 30 mmol/L who presents with a pre-dialysis measured TCO_2 of 19 mEq/L and a post-dialysis level of 25 mEq/L, the dialysate bicarbonate prescription would be

$$HCO_3^- = 30 + \frac{\frac{22-19}{1.03} + \frac{27-25}{1.47}}{2} \approx 30 + \frac{3+1}{2} = 32.$$

If the next month the same patient, now with a HCO_3^- dialysate of 32 mmol/L, has a pre-dialysis measured TCO_2 of 20 mEq/L and a post-dialysis level of 25 mEq/L, then the dialysate bicarbonate would be

$$HCO_3^- = 32 + \frac{\frac{22-20}{1.03} + \frac{27-25}{1.47}}{2} \approx 32 + \frac{2+1}{2} = 33,5 \rightarrow 34.$$

However, if the post-dialysis TCO_2 had been 22 mEq/L instead of 20 mEq/L, the dialysate bicarbonate would have been

$$HCO_3^- = 32 + \frac{\frac{22-20}{1.03} + \frac{27-22}{1.47}}{2} \approx 32 + \frac{2+3}{2} = 34,5 \rightarrow 34.$$

Other dialysis parameters

Patients were either on HDF or HDx. All of them used a 5008 CorDiax monitor (Fresenius Medical Care, Bad Homburg, Germany), with a 1.4–1.8 m^2 high-flux synthetic dialyzer (Theranova if HDx or FX CorDiax 60 if OL-HDF) and were prescribed sodium of 139 mEq/L to maintain a dialysate conductivity of 14.0 mS/cm, with blood (Qb) and dialysate flow (Qd) of ∼400 mL/min. The automated infusion system adjusted the infusion flow (Qi) in OL-HDF.

Measured variables

TCO_2 was measured by an Atellica Solution analyzer (Siemens Healthineers, Erlagen, Germany). TCO_2 in serum exists in two major chemical forms: dissolved CO_2 and bicarbonate anion. In the system, the enzymatic method converts all CO_2 to HCO_3^- to measure TCO_2. The targeted pre-dialysis TCO_2 value was set between 19 and 25 mEq/L. The baseline TCO_2 level was the mean TCO_2 obtained during the past 3 months before study initiation and was compared with the monthly measured TCO_2 levels during follow-up.

In addition, we analysed the effect of the tailored bicarbonate dialysate prescription approach on albumin, plasma potassium, phosphorus, alkaline phosphatase, magnesium and calcium. The mean of the past 3 months before the study initiation pre- and post-dialysis measurements of plasma potassium, calcium and pre-dialysis intact parathyroid hormone (PTH) levels was established as the baseline, which was then compared with the monthly measurements of the same parameters collected during the 6-month follow-up period. Throughout the follow-up, the patients received the standard-of-care treatment with calcimimetics, phosphate binders (including calcium- and non-calcium-based binders), and active vitamin D analogues, whose doses were titrated according to the analytical parameters and the criteria of the treating physician.

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 his/her 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).

Ethics

The local ethics committee approved the study, which was conducted according to the Declaration of Helsinki. All the patients gave their written informed consent to participate.

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 TCO_2 after tailoring the dialysate HCO_3^- prescription

Pre- and post-dialysis TCO_2 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).

Table 1. Baseline characteristics of the study population (N = 112)

Characteristics	Values
Age (years), mean ± SD	69.5 ± 15.9
Male, *n* (%)	75 (66.9)
Dialysis vintage (months), mean ± SD	53.4 ± 5.9
Dialysis modality, *n* (%)	
Post-dilution online HDF	109 (97.3)
HDx	3 (2.7)
HD access, *n* (%)	
Native arteriovenous fistula	83 (74)
Prothesic arteriovenous fistula	6 (5.4)
Tunnelled catheter	23 (20.5)
Dialysis prescribed time (minutes), mean ± SD	320.9 ± 82.4
HD parameters, mean ± SD	
Blood flow (mL/min)	409 ± 35
Dialysate flow (mL/min)	387 ± 39
Dialysis-related treatments, *n* (%)	
Phosphate binders	
Calcium-based	39 (32.3)
Non-calcium-based	16 (14.3)
Calcifediol	52 (46.4)
Active vitamin D	38 (33.9)
Calcimimetics	30 (26.8)

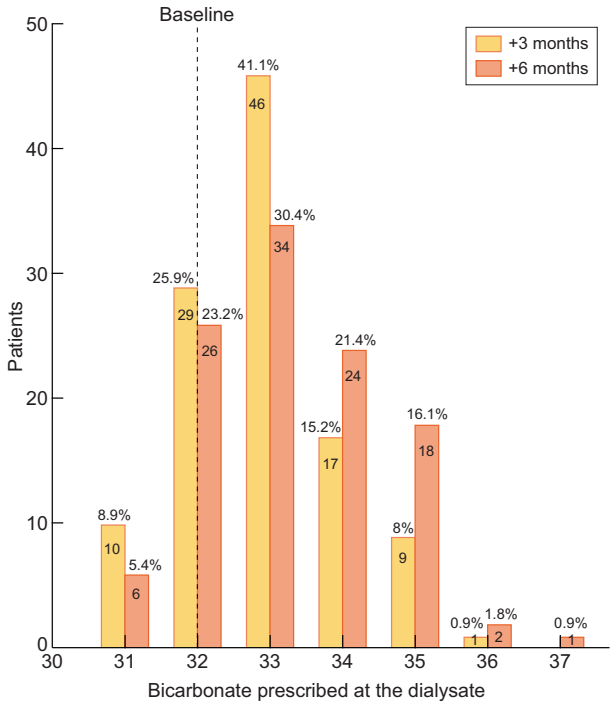


FIGURE 2: Distribution of HCO_3^- dialysate prescription among the study population at the end of the study.

At baseline, only 80 (71.4%) patients were within the desired pre-dialysis TCO_2 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 HCO_3^- prescription, we found a right-skewed distribution at 3 months, with most patients meeting the desired target TCO_2 with dialysate HCO_3^- concentrations between 32 and 34 mEq/L. At 6 months since follow-up, dialysate HCO_3^- concentrations became more normally distributed, with most patients requiring HCO_3^- concentrations between 32 and 35 mEq/L to meet the targeted TCO_2 (Figure 2). As of the first month, every followed patient met the TCO_2 target range objective in pre-dialysis measurements and >95% met the post-dialysis TCO_2 target (Figure 3).

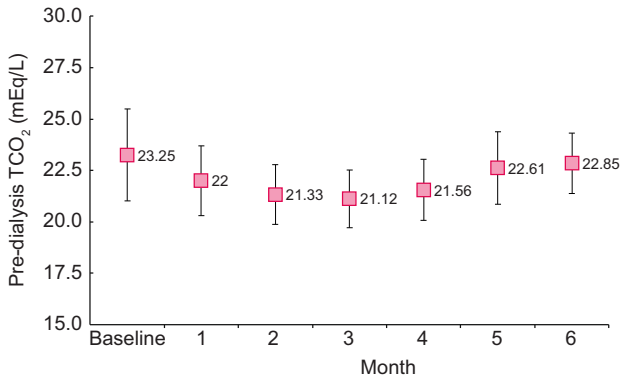
Changes in plasma sodium and potassium

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 ($P < 0.001$) at 3 months and 9.85 ± 0.8 mg/dL ($P = .145$) at 6 months, with a mean post-dialysis calcium of 9.91 ± 1.05 mg/dL. Regarding phosphorus, pre-dialysis



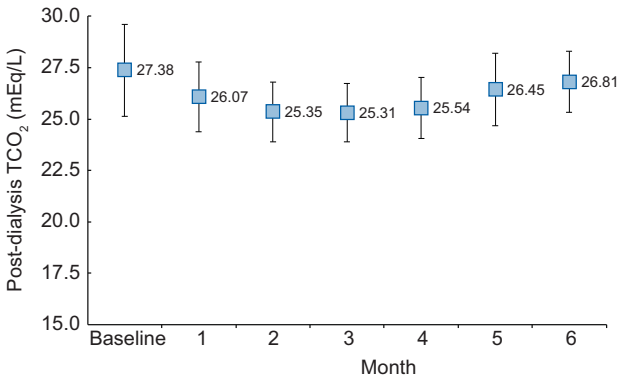


FIGURE 1: Mean ± SD monthly pre- and post-dialysis TCO_2 in venous blood samples.

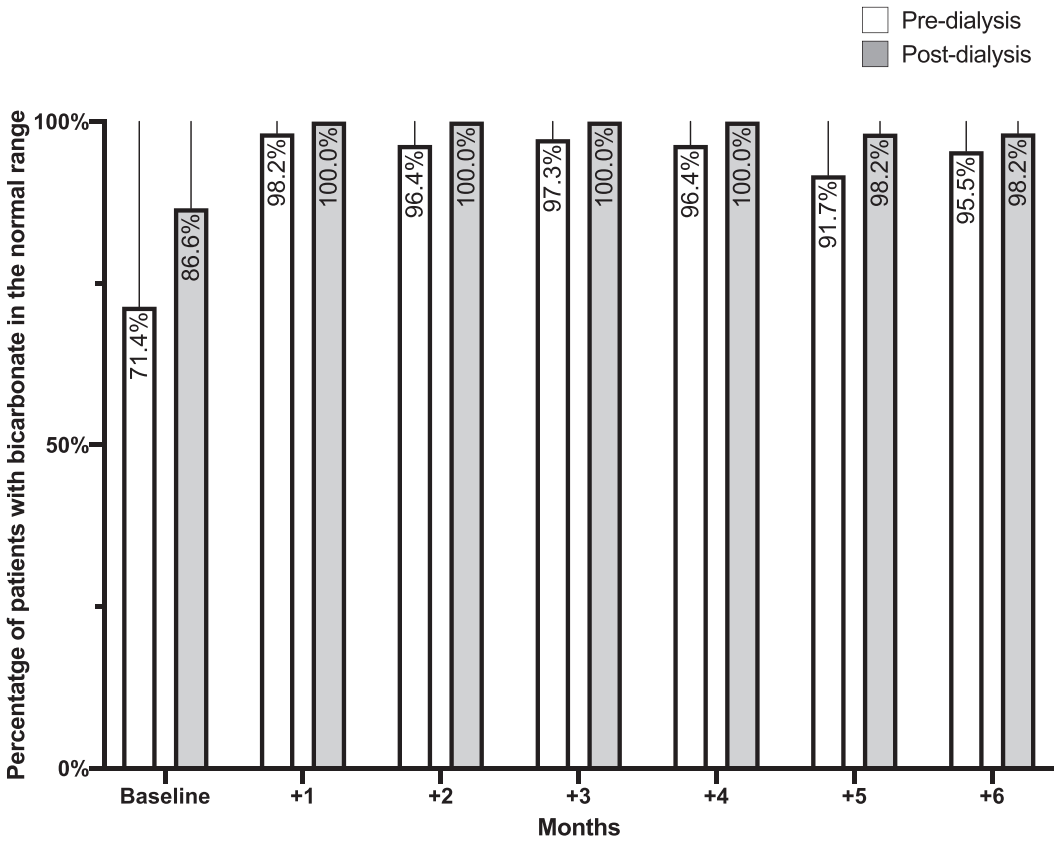


FIGURE 3: Percentage of patients on TCO_2 target range either at pre- or post-dialysis.

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 TCO_2 with dialysate HCO_3^- concentrations between 32 and 35 mEq/L. However, using this formula, we identified 7–9% of patients who required HCO_3^- concentrations beyond these typical values. Changes in plasma HCO_3^- can affect the plasma concentration of other ions. HCO_3^- 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 TCO_2 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 TCO_2 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 dietetic 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 HCO_3^- 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. analysed and interpreted the data. N.R. proportioned, collected and analysed the data. F.M. collected, analysed and interpreted 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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