Clinical Evaluation of a Model for Prediction of End-Dialysis Systemic Ionized Calcium Concentration in Citrate Hemodialysis

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Key Words

Citrasate® • Citrate dialysis • Hemodialysis • Ionized calcium • Mathematical model

Abstract

Background/Aim: Citrate anticoagulation in hemodialysis (HD) is increasingly drawing attention in the nephrology community. One of the major deterrents to a more widespread use are the monitoring requirements for fear of systemic calcium derangements. Means of accurately predicting systemic ionized calcium (iCa) may help to overcome this challenge. We have previously presented a mathematical model of regional citrate anticoagulation (RCA) to address this need. Here, we present a refined model and show results in an independent validation cohort of maintenance HD patients on Citrasate®, a calcium- and citrate-containing dialysate. **Methods:** A hybrid RCA model was developed, comprising the previously published 'native' RCA model and a statistical correction based on levels of alkaline phosphatase as a marker of bone turnover. The model was validated in 120 patients on Citrasate, a dialysate containing 0.8 mmol/l citrate and 1.125 mmol/l calcium. Systemic iCa was measured at the beginning and end of one HD treatment in each subject. Serum iCa predictions were compared between our previously published model and the new hybrid model. **Results:** On average, the hybrid model predicted end-HD systemic iCa with an error (predicted – measured) of 0.028 mmol/l, compared to –0.051 mmol/l with the previously published model. There were only 4 subjects out of the 120 analyzed in whom the prediction error was ≤ -0.1 mmol/l, and only 6 in whom the error was $> +0.1$

mmol/l (max: +0.13 mmol/l). **Conclusion:** This study demonstrates that the novel hybrid model is an improvement over the previously published model and that it is capable of predicting end-dialysis systemic iCa levels with improved accuracy and precision even in a citrate dialysis setting which was much different from the original derivation cohort.

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Introduction

Regional citrate anticoagulation (RCA) in hemodialysis (HD) refers to the use of citrate for achieving anticoagulation that is strictly limited to the extracorporeal circuit. The concept is based on citrate chelating ionized calcium (iCa) in the plasma, thereby inhibiting the coagulation cascade. Citrate anticoagulation in renal replacement therapy has been described already in the early 1960s. While the traditional setup is composed of a pre-dialyzer citrate infusion, a calcium-free dialysate and a post-dialyzer calcium infusion, other forms of citrate dialysis are being explored, such as heparin-sparing dialysis using calcium- and citrate-containing dialysate without citrate or calcium infusion in combination with reduced heparin, or heparin-free dialysis using a calcium- and citrate-containing dialysate in combination with an arterial citrate infusion but no post-dialyzer calcium substitution.

Beyond the obvious advantage of eliminating the bleeding risk associated with heparin dialysis, RCA has been shown to confer several additional benefits, among

them a reduction in complement activation, degranulation of granulocytes and platelets, and a reduced release of interleukin-1 β , all of which reflect an improved biocompatibility of the extracorporeal circuit [1–3]. A key concern, however, with citrate dialysis is systemic calcium derangements, which can potentially be life threatening. This typically necessitates frequent intradialytic measurements of systemic iCa that contribute to the laboriousness of citrate dialysis. Means of accurately predicting systemic iCa in various settings of citrate HD may help reduce this burden and facilitate implementation of citrate dialysis on a broader scale. We have previously published a comprehensive citrate dialysis model [4]. Here, we present a refinement of this model and show results in an independent validation cohort of chronic HD patients on Citrasate[®], a calcium- and citrate-containing dialysate.

Methods

The ‘Native’ RCA Model

We recently developed a comprehensive model of calcium and citrate kinetics during RCA in HD based on physicochemical, biochemical, and physiologic principles [4]. In brief, calcium and citrate kinetics are modeled in the intravascular and interstitial compartments as well as along the entire extracorporeal circulation. The main solutes of interest are total calcium and iCa, free citrate, and the calcium-citrate complex, and the key components of the model comprise citrate generation, citrate metabolism, and the resulting solute equilibria; solute concentration changes caused by access recirculation; the required pre-dialyzer citrate concentration (if desired; otherwise, the pre-dialyzer citrate concentration can be pre-specified) and the resulting solute concentrations; calculation of the dialysate composition with respect to the above solutes; calculation of diffusive and convective dialyzer solute fluxes; calculation of post-dialyzer solute concentrations, and calculation of solute concentrations downstream of any calcium infusion (if applicable).

RCA with Pre-Dialyzer Citrate Infusion and Calcium- and Citrate-Containing Dialysate

RCA study treatments using pre-dialyzer sodium citrate infusion (136 mmol/l), calcium- and citrate-containing dialysate (calcium: 1.25 mmol/l in one treatment, 1.5 mmol/l in all others; citrate: 0.8 mmol/l) and no post-dialyzer calcium substitution were performed in chronic HD patients. Subjects with pre-dialysis serum bicarbonate levels >28 mmol/l, serum albumin <3 g/dl or aspartate aminotransferase or alanine aminotransferase levels greater than twice the upper limit of normal were excluded from the study. The project was approved by the Institutional Review Board of Beth Israel Medical Center (New York, N.Y., USA), and written informed consent was obtained from all subjects before enrollment.

The native RCA model was used to determine starting rates for the citrate infusion, so as to achieve desired pre-dialyzer iCa concentrations over a broad target range of 0.25–0.65 mmol/l. Blood samples (pre-dialyzer up- and downstream of the citrate

infusion, and post-dialyzer) were collected at the following time points: before dialysis, after 15, 30, 45, 90, 120, 150, and 180 min, and at the end of the treatment. The citrate infusion rate was adapted according to measured pre-dialyzer iCa levels, if needed, so as to attain the above targets. In two treatments, citrate profiling (intermittent reductions in citrate infusion rates) was applied.

Total calcium and total protein were measured at the start of HD by Spectra Laboratories (Rockleigh, N.J., USA). Hematocrit and plasma iCa were measured bedside at all time points using the Abbott iStat point-of-care analyzer (Abbott Point of Care Inc., Princeton, N.J., USA). All subjects were dialyzed using Fresenius F180NR high-flux dialyzers (Fresenius Medical Care, Waltham, Mass., USA). The subjects’ routine dialyzer blood flow rates were unchanged, and dialysate flow rate was fixed at 500 ml/min.

The ‘Hybrid’ RCA Model

The ‘hybrid RCA model’ for prediction of end-dialysis plasma iCa refers to a combination of our previously published native RCA model (see above) and a statistical correction derived from a regression equation. We use ΔiCa_{pred_RCA} to denote the difference between the end-dialysis iCa as predicted by the native RCA model and the actual (measured) end-dialysis iCa, according to

$$\Delta iCa_{pred_RCA} = iCa_{pred_RCA} - iCa_{measured} \quad (1)$$

For post-HD predictions using the native RCA model, starting systemic iCa levels were adapted to measured values, so as to be able to assess the intradialytic prediction quality of the model. The subjects’ alkaline phosphatase (AP) levels closest to the study date were grouped into tertiles (AP_tertile). Dialysis treatment time is denoted as t_d . Bivariate Pearson correlation analyses were performed to assess relationships between ΔiCa_{pred_RCA} on one hand and AP_tertile, t_d , and iCa_{pred_RCA} on the other hand. A multiple linear regression model was fitted with ΔiCa_{pred_RCA} as the dependent variable and AP_tertile, t_d , and iCa_{pred_RCA} as predictors. This regression model was used to estimate the difference (ΔiCa_{pred_MLR}) between the tentative systemic iCa prediction of the native RCA model (iCa_{pred_RCA}) and the actual (measured) end-dialysis iCa ($iCa_{measured}$). ΔiCa_{pred_MLR} was then used for simple additive correction of iCa_{pred_RCA} to yield the final end-dialysis systemic iCa prediction (iCa_{pred_hybrid}). The process of obtaining an end-dialysis systemic iCa prediction with the hybrid RCA model is depicted in figure 1.

Validation of the Hybrid RCA Model in an Independent Cohort

The study cohort comprised an entire HD facility with all patients using Citrasate, a dialysate containing 0.8 mmol/l citrate and 1.125 mmol/l calcium (Advanced Renal Technologies, Bellevue, Wash., USA). No citrate infusion was used. Serum iCa was measured cross sectionally in all patients at the beginning and end of dialysis on one occasion. Total calcium, AP and total protein were measured before dialysis. The prediction quality of the native RCA model for pre-dialysis serum iCa was assessed, and the prediction quality for end-dialysis serum iCa was assessed for both the native and the hybrid RCA models. For comparison, the average change in serum iCa from the start to the end of dialysis was calculated across all subjects and used for simple estimation of end-HD serum iCa by adding the average (‘typical’) change to each subject’s pre-HD serum iCa concentration. Laboratory measurements were performed by Spectra Laboratories (Milpitas, Calif., USA).

Fig. 1. Schematic overview of the process of obtaining an end-dialysis systemic iCa prediction with the hybrid RCA model.

Table 1. Bivariate Pearson correlations between the end-HD systemic iCa prediction error of ΔiCa_{pred_RCA} on the one hand and AP_tertile, t_d , and iCa_{pred_RCA} on the other hand

	AP_tertile	t_d	iCa_{pred_RCA}
ΔiCa_{pred_RCA}			
Pearson correlation	-0.514	-0.656	0.828
Sig. (2-tailed)	0.035	0.004	<0.001
n	17	17	17

Results

Hybrid RCA Model

Seventeen RCA treatments with pre-dialyzer citrate infusion and calcium- and citrate-containing dialysate but without post-dialyzer calcium substitution were performed in a total of 8 subjects. Pre-HD values were 2.2 ± 0.1 mmol/l for total Ca, 1.08 ± 0.06 mmol/l for iCa, 7.24

± 0.6 g/dl for total protein, and 34.4 ± 3.5 vol% for hematocrit. Average starting infusion rate for sodium citrate (136 mmol/l) was 397 ml/h (range, 245–480 ml/h).

The native RCA model underestimated the end-dialysis systemic iCa by 0.03–0.29 mmol/l (average, 0.15 mmol/l, 95% confidence interval, CI, 0.11–0.20). The prediction error was found to follow a near-linear trend over the course of HD and was related to the patients' levels of total AP, a surrogate marker of bone turnover (fig. 2). The prediction error for end-HD systemic iCa was further related to the dialysis treatment length and the end-HD systemic iCa prediction itself of the native RCA model (table 1).

The multiple linear regression model for prediction of the end-HD systemic iCa prediction error (ΔiCa_{pred_RCA}) using tertiles of AP was found to be

$$\Delta iCa_{pred_RCA} = -0.541 - 0.000314 \cdot t_d + 0.554 \cdot iCa_{pred_RCA} - 0.00876 \cdot AP_tertile \quad (2)$$

with ΔiCa_{pred_RCA} in mmol/l, t_d in minutes, iCa_{pred_RCA} (the end-HD systemic iCa prediction of the native RCA

Fig. 2. The prediction error for systemic iCa concentration of the native RCA model plotted against elapsed dialysis treatment time for 17 citrate HD treatments. The curves for patients with high AP levels can be seen to cluster towards the bottom of the plot, i.e., the native RCA model underestimates systemic iCa concentration the most in these subjects.

Table 2. Model statistics for multiple linear regression for prediction of end-HD systemic iCa prediction error (ΔiCa_{pred_RCA}) [mmol/l] as a function of t_d , iCa_{pred_RCA} , and AP_tertile

	Unstandardized coefficients		Standardized coefficients	t	Sig.
	B	SE	β		
Constant	-0.541	0.169		-3.195	0.007
t_d [min]	-0.0003	0.00025	-0.232	-1.260	0.223
iCa_{pred_RCA} [mmol/l]	0.554	0.156	0.647	3.538	0.004
AP_tertile	-0.0088	0.0167	-0.091	-0.523	0.610

Overall model ANOVA $p < 0.001$; adjusted $R^2 = 0.68$.

model) in mmol/l, and AP_tertile coded from 1 to 3, with 1 being the lower and 3 the upper tertile of AP. The tertile limits for AP were 85–108, 108–150 and 150–592 U/l.

Model statistics are shown in table 2. Tertile of AP was retained in the model despite not being a significant predictor because it was deemed biologically relevant.

Figure 1 shows the process of obtaining an end-HD systemic iCa prediction using the hybrid model, and figure 3 compares the prediction error for end-HD systemic iCa between the previously published native RCA model (-0.153 ± 0.084 mmol/l, range, -0.29 to -0.03 mmol/l) and the hybrid model described above (0 ± 0.043 mmol/l, range, -0.08 to 0.08 mmol/l). The hybrid model reduced the prediction error to zero on average and markedly reduced the scatter, with the caveat that the derivation and

validation cohorts are identical in this case for the statistical correction part of the hybrid model.

Validation of the Hybrid RCA Model in an Independent Cohort

The hybrid model was validated in an independent cohort, comprised of an entire HD facility ($n = 125$ subjects) on Citrasate dialysate. Data from a total of 120 subjects (age: 61.3 ± 16.1 years; 64% male; 77.5% white, 0.8% African-American, 14.2% American Indian or Alaskan native, 1.7% other, rest missing race information) were available for analysis (1 treatment/subject). Average HD treatment time was 243 ± 21 min. Pre- and end-HD systemic iCa concentrations were on average 1.18 ± 0.12 and 1.06 ± 0.07 mmol/l, respectively. The starting iCa was underestimated by our previously published native

Fig. 3. Comparison of the prediction error for end-HD systemic iCa concentration between the previously published RCA model and the new hybrid model in 17 citrate HD treatments. Note that the statistical correction component of the hybrid model was derived in this cohort.

model on average by 0.1 ± 0.078 mmol/l. The end-HD systemic iCa was predicted by the hybrid model with an error (iCa predicted – iCa measured) of on average 0.028 mmol/l (95% CI, 0.016–0.04; range, –0.31 to 0.13 mmol/l), compared to –0.051 mmol/l (95% CI, –0.068 to –0.035; range, –0.44 to 0.14 mmol/l) with the previously published RCA model not taking AP into account (fig. 4, left and middle scatterplot). The mean of the absolute prediction errors was 0.068 mmol/l for the native and 0.052 mmol/l for the hybrid model. Using the average (‘typical’) change in serum iCa over the course of HD across all subjects for prediction of the end-HD serum iCa yielded clearly inferior results, as evidenced by a nearly twofold higher standard deviation in the prediction error compared to the hybrid model (standard deviation 0.124 vs. 0.065 mmol/l; see also fig. 4, right scatterplot).

Discussion

HD treatments involving the use of citrate administration (via infusion into the arterial line, addition to the dialysate, or both) can lead to changes in plasma iCa con-

centration, among others, which is one of the primary safety concerns in citrate dialysis, necessitating intermittent measurements of plasma iCa. We have previously published a model of calcium and citrate kinetics during RCA in HD based on physicochemical, biochemical, and physiologic principles [4]. Here we show in data on 17 treatments in 8 patients on citrate HD that the prediction error of this native model for systemic plasma iCa can progressively increase over the course of HD. We further show that this prediction error follows a near-linear time course and its slope is related to levels of AP as a marker of bone turnover and, presumably, calcium-buffering capacity of the bone (fig. 2). The native model underestimates the actual systemic iCa concentration most in those subjects in the highest tertile of AP. We believe that this is due to the fact that these patients buffer challenges to plasma iCa stability significantly better than anticipated.

Using the presented hybrid model, which incorporates a statistical correction to the previously published RCA model, practically eliminated the average prediction error for end-HD systemic iCa, as would be expected. More importantly, however, it substantially reduced the variability in the prediction error. In order to cross-validate these results, the hybrid model was applied to an independent cohort of chronic HD patients on a citrate-enriched dialysate (Citrasate). In this cohort, too, the hybrid model performed better than the native RCA model in predicting end-HD systemic iCa levels, yielding both a smaller average prediction error and a narrower range of prediction errors (average, 0.028 mmol/l; range, –0.31 to 0.13 mmol/l; fig. 4). Of note, the prediction errors extending into the negative range down to –0.31 mmol/l represent underestimations of the actual systemic iCa, i.e., the model erred on the safe side. In fact, the 4 subjects in whom the model underestimated end-HD serum iCa by >0.1 mmol/l (fig. 4) all presented unusual calcium kinetics: 3 subjects showed unexpected rises in iCa from 1.025 to 1.325, 1.05 to 1.225 and 1.025 to 1.325 mmol/l, and 1 subject maintained an unchanged serum iCa of 1.325 mmol/l. One might speculate that these findings may have been caused by gastrointestinal calcium administration (e.g., in the form of calcium-containing phosphate binders) during dialysis, but we were unable to definitively clarify the ultimate causes in these subjects.

Implementation of citrate dialysis on a larger scale, with its several benefits over standard heparin HD [1–3], remains a worthwhile goal. Models such as the one presented in this study are one step towards making citrate HD less laborious and, thereby, more feasible by seeking to eliminate the need for frequent intradialytic serum iCa

Fig. 4. Left and middle scatterplot: comparison of the prediction error for end-HD systemic iCa concentration between the previously published RCA model and the new hybrid model in an independent cohort of 120 chronic HD subjects switched to a citrate-enriched dialysate (Citrasate). Right scatterplot: for comparison, the prediction error is shown for an approach using the average intradialytic change in serum iCa across all subjects to estimate post-HD serum iCa.

measurements while maintaining safety. The results are promising, particularly when considering the heterogeneous nature of the citrate dialysis administration in the model derivation cohort, comprising different pre-dialyzer iCa targets, different treatment times and even citrate infusion rate profiling, which attests to the robustness of the underlying mathematical model. Additional efforts are required, however, to further improve the prediction accuracy and reduce the scatter in the prediction errors (i.e., improve precision). Steps in this direction might include an individualized representation of citrate

metabolism and pre-dialysis systemic citrate levels, as well as an improved handle on individual calcium-buffering capacity [5].

Disclosure Statement

Peter Kotanko holds stock in Fresenius Medical Care. Robert J. Kossmann is a member of the Renal Physicians Association Board of Directors (President elect); the Advanced Renal Technologies Board of Directors and the Fresenius Medical Care Physician Technology Leadership Group.

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