Dialysate calcium concentrations in hemodialysis - a linear mixed effects model

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Abstract

We investigated the longitudinal changes the serum calcium concentration due to changes in the calcium concentration in the dialysis bath. Over three years, 98 hemodialysis patients received three different calcium concentration dialysis bath, 3.5 mEq/L; 2.5 mEq/L; and 3.0 mEq/L. Both serum calcium concentration and parathyroid hormone (PTH) were recorded over time. Linear mixed effects model was fitted to longitudinal data of serum calcium concentration. It showed that serum calcium are clossely associated with calcium concentration in dialysate. The bath with calcium at 3.0% seems to be the most suitable.
Keywords: Serum calcium; dialysate calcium; chronic kidney disease.

1. Introduction

Chronic kidney disease (CKD) is a growing public health problem worldwide, called the epidemic of the 21st century, being determined or associated with health disorders like obesity, *diabetes mellitus* and hypertension.

CKD patients has hemodialysis as therapy what remove blood toxic substances by diffusion process, giving them a survival. Through semipermeable membrane, the patient's blood is brought into contact with a solution called dialysate, also known as dialysis bath. By differences in concentration, blood toxic substances diffuse into the dialysate which is then discarded.

Current management of mineral metabolism in CKD patients involves the use of active vitamin D (calcitriol), what suppress PTH (parathyroid hormone), to normalized of serum calcium e phosphate. Calcium concentration in dialysate management is important for patient's hemodynamic stability (Toussaint et al., 2006). Low concentration, active vitamin D could be used, including the intravenous use (Slatopolsky et al., 1984). High concentration, it could increase serum calcium levels what be association higher mortality (Block et al., 2004).

The aim of the present study was measure the impact of changing the dialysate calcium concentration in serum calcium of CKD patients. The analysis was carried out with the R statistical software (R Core Team, 2015) with use of the **nlme** package (Pinheiro et al., 2015).

2. Materials and methods

Over three years, 98 hemodialysis patients received three treatments that consisted of different calcium concentration dialysis bath: 3.5 mEq/L; 2.5 mEq/L; and 3.0 mEq/L (in this order). Serum calcium concentrations (mg/dl) were recorded monthly (12 records by treatment) and PTH biannual. From the 98 patients, only these 8 had no missing values. Patients with more than 24 missing values were excluded from the analysis (a total of 36). In addition, factors as sex and age were also recorded.

Inclusion criteria for the study were patients with Intravenous Device (VD) or Arteriovenous Fistula (AVF) who underwent 3 weekly dialysis sessions of 4 hours, and had medical prescription of blood and bath flow greater than 300 mL/min and 500 mL/min, respectively.

The experimental protocol was approved by the ethics committee of the State University of Maringa (Brazil), report 152/2011, according to the Resolution 196/1996.

3. Model formulation

Serum calcium concentration curves, grouped by treatment and corresponding to 8 patients had no missing values, are displayed on Figure 1. We observe that in some patients, the serum calcium levels tend to increase or decrease slightly (with bath number 1 featuring the most erratic behavior), but for most of them, the calcium levels remain relatively constant over time (the curves for each treatment appear to be roughly parallel within each patient). This pattern suggests that an appropriate model for the data might include random components associated with both the intercept and slope, i.e., the effect of time and each bath for each patient.

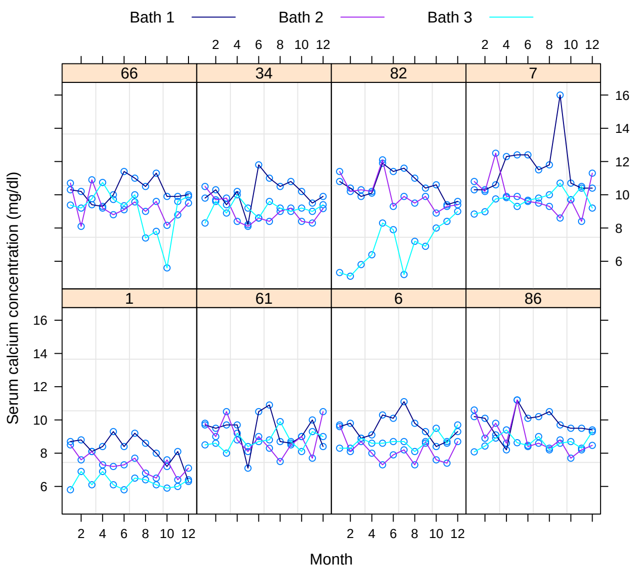

Figure 1: Serum calcium concentration curve for each treatment during 12 months.

The most complete linear mixed effects model considered for individual serum calcium concentration response at month j ($j = 1, \dots, 12$) on patient i ($i = 1, \dots, 98$), denoted by Ca_{ij}, was

$$\begin{aligned} Ca_{ij} = {} & \beta_0 + \beta_1 Time_j + \beta_2 Bath_1 + \beta_3 Bath_2 + \beta_4 Age_i + \beta_5 Sex_i + \\ & \beta_6 (Time_j \times Bath_1) + \beta_7 (Time_j \times Bath_2) + \beta_8 (Time_j \times Age_i) + \\ & b_{0i} + b_{1i} Time_j + b_{2i} Bath_1 + b_{3i} Bath_2 + \epsilon_{ij} \end{aligned} \quad (1)$$

where parameters β_0 through β_8 represent the fixed effects associated with the intercept, time, treatment, age, sex and some of their two-way interactions; b_{0i} through b_{3i} are random patient effects associated with the intercept, time and treatment covariates; and ϵ_{ij} represents a residual. We considered $Time$ and Age to be a continuous predictor and $Bath$ as a factor with $Bath_3$ as the reference level. The correspondence between the levels of $Bath$ and the calcium concentration dialysis is as follows: $Bath_1 = 3.5$ mEq/L; $Bath_2 = 3.0$ mEq/L; and $Bath_3 = 2.5$ mEq/L.

4. Results and Discussion

After fitting a model which excludes the random intercepts associated with the effect of time, and testing whether we need to keep these random effects in the model, we decided to omit them. Repeating this procedure for the random intercepts associated with each bath, we decided to retain these. As for the residual covariance structure, we selected the first-order autoregressive structure with heterogeneous residual variances. Finally, removing nonsignificant fixed effects, our preferred model omits the factors associated with parameters β_5 and β_8. The estimated values and 95% confidence intervals for the fixed effects, the standard deviations of the random effects, the parameter for the correlation structure, ρ, and the within-group standard error, σ, are reported in Table 1.

Table 1: Estimates, lower and upper bounds (LB and UB) for the model's parameters.

	LB	Estimate	UB		LB	Estimate	UB
β_0	7.4276	7.9631	8.4986	σ_{b_0}	0.5628	0.6943	0.8567
β_1	0.0091	0.0293	0.0495	σ_{b_2}	0.6652	0.8746	1.1498
β_2	0.9629	1.3451	1.7274	σ_{b_3}	0.6428	0.8261	1.0616
β_3	0.2653	0.5923	0.9192	σ_{b_0,b_2}	-0.7174	-0.4993	-0.1919
β_4	0.0003	0.0101	0.0199	σ_{b_0,b_3}	-0.7879	-0.6212	-0.3696
β_6	-0.1198	-0.0833	-0.0468	σ_{b_2,b_3}	0.6870	0.9517	0.9934
β_7	-0.1366	-0.1044	-0.0723	ρ	0.0956	0.1579	0.2189
				σ	1.0916	1.2711	1.4800

Because the effect of month and its interaction with $Bath_1$ and $Bath_2$ are statistically significant, the slope of the line between serum calcium concentration and month is different for each bath. Parameters β_6 and β_7 indicate how different the slopes for $Bath_1$ and $Bath_2$ are from the slope for $Bath_3$ (given by β_1), while parameters β_2 and β_3 are the effects of $Bath_1$ and $Bath_2$ when $Time$ is zero. Despite the low value to slope for age, $beta_4$, there are clinical evidence that older patient higher the serum calcium concentration. To ascertain the effect of each treatment, Table 2 shows their effects at some specific months (the effect of $Bath_1$ or $Bath_2$ is essentially the difference between its corresponding line and the line for $Bath_3$). It can be seen that the effect of $Bath_2$ is inferior to the effect of $Bath_3$ for most of the year, and the effect of $Bath_1$ is always superior to the others.

Table 2: Effects of each bath on months 1, 6 and 12.

	Month 1	Month 6	Month 12
Bath 1	1.2618	0.8453	0.3455
Bath 2	0.4879	-0.0341	-0.6605
Bath 3	0.0293	0.1758	0.3516

The two graphs in Figure 2 (of the standardized residuals versus the estimated values and the observed values versus the estimated values) are diagnostic graphs for the specification of the mean, showing no clear trend. Figure 3 shows two quantile-quantile (QQ) graphs for the assumption of normal distribution, one for the residuals and the other for the predicted random effects. Clearly, the empirical distribution of the residuals has heavier tails than those prescribed by the normal distribution. The QQ plots for the predicted random effects are reasonable, with no suggestion of any problem.

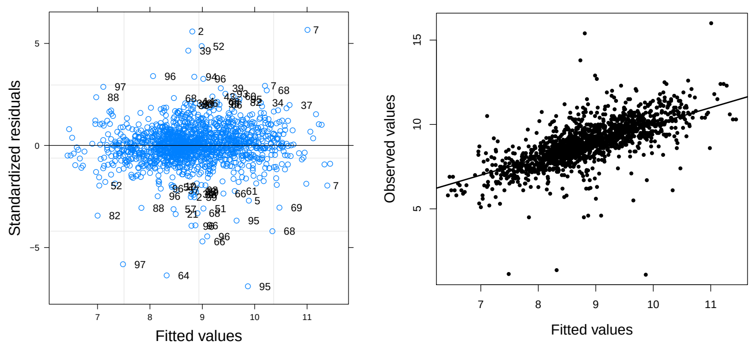

Figure 2: Diagnostic graphs.

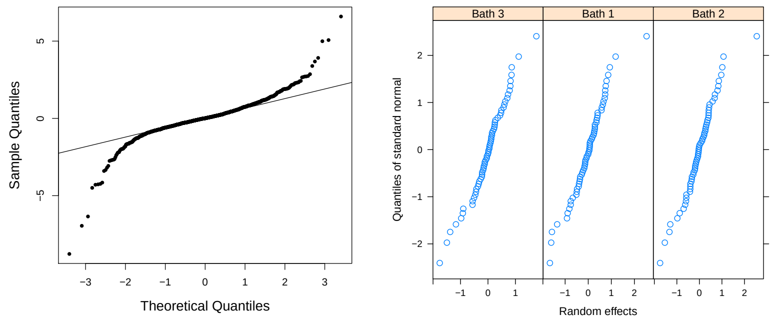

Figure 3: Further residual plots. The left plot is a normal QQ plot for the residuals, while the right panel shows normal QQ plots for the predicted random effects.

Another evaluation of the model's adequacy is provided by comparing the individual profiles (observed values) and the conditional profiles (obtained using the estimates of the random effects) and marginal profiles (corresponding to the fixed effects), as presented in Figure 4.

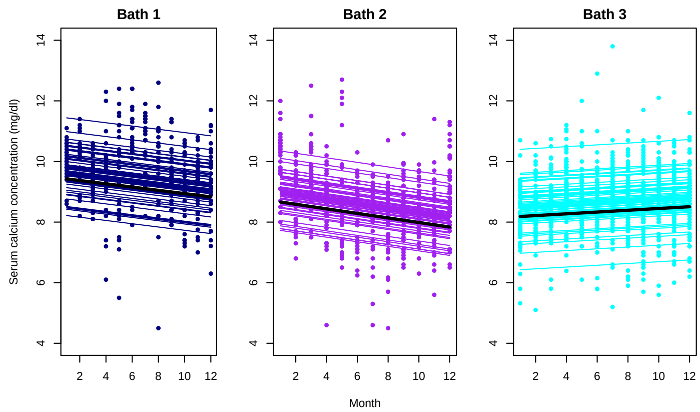

Figure 4: Model predictions at the individual and population levels, overlaid on observed data.

During $Bath_1$ (3.5%), it was observed the highest serum calcium concentration due to the positive balance determined by this concentration. The patients showed an upward trend for calcemia and lower PTH levels indicating low bone dynamics (Karohl et al., 2010). In this period, few patients used or needed Calcitriol to control PTH level, and bone biopsy and parathyroidectomy were not performed.

In $Bath_3$ (2.5%) had clear increase PTH level indicated higher bone dynamics. In this period it was increased in the administration of active vitamin D with an aim to obtain normalization of serum calcium and phosphate.

Considering the period of $Bath_2$ (3.0%), there was no significant increase in PTH level and the use of calcitriol was similar to $Bath_3$, indicating that this bath is most rational.

5. Conclusions

The mixed effects model can fit a profile for each patient that theoretically allows individualization of control of chronic diseases. However, in practice due to costs is adopted one or a few types of control, where every patient should suit. In this work, the proposed model points to the serum calcium concentration are closely associated with calcium concentration in the dialysate. Clinically, the bath with calcium at 3.0% seems to be the most suitable as overall treatment.

Since this is a preliminary study, the data used here is currently being re-analyzed to take into account the missing values.

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