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 closely 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.](image)

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

$$
Ca_{ij} = \beta_0 + \beta_1 \text{Time}_j + \beta_2 \text{Bath}_1 + \beta_3 \text{Bath}_2 + \beta_4 \text{Age}_i + \beta_5 \text{Sex}_i + \\
\beta_6 (\text{Time}_j \times \text{Bath}_1) + \beta_7 (\text{Time}_j \times \text{Bath}_2) + \beta_8 (\text{Time}_j \times \text{Age}_i) + \\
b_{0i} + b_1 \text{Time}_j + b_2 \text{Bath}_1 + b_3 \text{Bath}_2 + \epsilon_{ij}
$$

(1)

where parameters $\beta_0$ through $\beta_8$ 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 $\epsilon_{ij}$ represents a residual. We considered Time and Age to be
a continuous predictor and Bath as a factor with Bath3 as the reference level. The correspondence between
the levels of Bath and the calcium concentration dialysis is as follows: Bath1 = 3.5 mEq/L; Bath2 = 3.0
mEq/L; and Bath3 = 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 $\beta_5$ and $\beta_8$. The estimated values and 95% confidence intervals for the fixed effects, the standard
deviations of the random effects, the parameter for the correlation structure, $\rho$, and the within-group standard
error, $\sigma$, are reported in Table 1.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LB</th>
<th>Estimate</th>
<th>UB</th>
<th>LB</th>
<th>Estimate</th>
<th>UB</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_0$</td>
<td>7.4276</td>
<td>7.9631</td>
<td>8.4986</td>
<td>$\sigma_{b_0}$</td>
<td>0.5628</td>
<td>0.6943</td>
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<tr>
<td>$\beta_1$</td>
<td>0.0091</td>
<td>0.0293</td>
<td>0.0495</td>
<td>$\sigma_{b_2}$</td>
<td>0.6652</td>
<td>0.8746</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>0.9629</td>
<td>1.3451</td>
<td>1.7274</td>
<td>$\sigma_{b_3}$</td>
<td>0.6428</td>
<td>0.8261</td>
</tr>
<tr>
<td>$\beta_3$</td>
<td>0.2653</td>
<td>0.5923</td>
<td>0.9192</td>
<td>$\sigma_{b_0,b_2}$</td>
<td>-0.7174</td>
<td>-0.4993</td>
</tr>
<tr>
<td>$\beta_4$</td>
<td>0.0003</td>
<td>0.0101</td>
<td>0.0199</td>
<td>$\sigma_{b_0,b_3}$</td>
<td>-0.7879</td>
<td>-0.6212</td>
</tr>
<tr>
<td>$\beta_6$</td>
<td>-0.1198</td>
<td>-0.0833</td>
<td>-0.0468</td>
<td>$\sigma_{b_2,b_3}$</td>
<td>0.6870</td>
<td>0.9517</td>
</tr>
<tr>
<td>$\beta_7$</td>
<td>-0.1366</td>
<td>-0.1044</td>
<td>-0.0723</td>
<td>$\rho$</td>
<td>0.0956</td>
<td>0.1579</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>1.0916</td>
<td>1.2711</td>
<td>1.4800</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Because the effect of month and its interaction with Bath1 and Bath2 are statistically significant, the slope
of the line between serum calcium concentration and month is different for each bath. Parameters $\beta_6$ and $\beta_7$
indicate how different the slopes for Bath1 and Bath2 are from the slope for Bath3 (given by $\beta_1$), while
parameters $\beta_2$ and $\beta_3$ are the effects of Bath1 and Bath2 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
Bath1 or Bath2 is essentially the difference between its corresponding line and the line for Bath3). It can be
seen that the effect of Bath2 is inferior to the effect of Bath3 for most of the year, and the effect of Bath1 is
always superior to the others.

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

<table>
<thead>
<tr>
<th>Bath</th>
<th>Month 1</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bath 1</td>
<td>1.2618</td>
<td>0.8453</td>
<td>0.3455</td>
</tr>
<tr>
<td>Bath 2</td>
<td>0.4879</td>
<td>-0.0341</td>
<td>-0.6605</td>
</tr>
<tr>
<td>Bath 3</td>
<td>0.0293</td>
<td>0.1758</td>
<td>0.3516</td>
</tr>
</tbody>
</table>

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 Bath1 (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 Bath3 (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 Bath2 (3.0%), there was no significant increase in PTH level and the use of calcitriol was similar to Bath3, 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.

References


