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Linear mixed models to evaluate if peritoneal protein excretion rates are influenced by the modality of peritoneal dialysis and other conditions of prescription

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SUMMARY

Peritoneal protein excretion (PPE) is a well-known, undesired consequence of peritoneal dialysis (PD). Following a prospective, observational design, we used a multilevel mixed model approach to analyze the effects of the modality of PD and other prescription characteristics on 24-hour PPE (main study variable) in a cohort of patients starting PD.

Key words: mixed model; peritoneal dialysis; peritoneal equilibration test;

1. INTRODUCTION AND OBJECTIVES

Peritoneal protein excretion (PPE) is a well-known, undesired consequence of Peritoneal Dialysis (PD), contributing to a variable extent to malnutrition (see Pollock, Cooper, Ibels and Kantzow, 2000) and other untoward complications of this modality of dialysis, including dyslipemia and hormonal disturbances (see Robey, Shreedhar and Batuman, 1989).
However, there is insufficient information on the factors which influence PPE during PD therapy. In particular, the effects of the modality of PD (Continous Ambulatory Peritoneal Dialysis (CAPD) or Automated Peritoneal Dialysis (APD)) and other conditions of prescription remain nuclear.

In general, attempts to disclose these questions have been hampered by imbalances between the scrutinized populations. We performed a multilevel mixed models approach to control for imbalances in the characteristics of patients managed on different schedules over time.

The following objectives were studied:

1. To analyzed the effects of the modality of PD and other prescription characteristics on 24-hour PPE (main study variable) in a cohort of patients starting PD.
2. To explore other potential predictors of 24-hour PPE in the whole study group, paying particular attention to the characteristics of PD prescription

2. METHODOLOGY

Type of study: Prospective, observational study on a cohort of patients starting PD in the University Hospital of A Coruña (Spain) between January 2000 and June 2010.
Setting: University Hospital of A Coruña (Spain)
Population: We included for analysis all patients starting PD during the above mentioned period, fulfilling two conditions, namely minimal follow-up of two months without peritonitis and baseline (second month after initiation of PD) estimation of PPE in both 24-hour and peritoneal equilibration test (PET) dialysate collections. We used traditional, lactate-buffered, GDP-rich solutions until May 2008, when all active patients were progressively switched to bicarbonate-lactate-buffered, low-GDP solutions.

Study variables: The main study variable was PPE in collected 24-hour spent dialysate. We compared the effects of the modality of dialysis, as also other general conditions of prescription, on 24-hour PPE. The main control variable was PPE during a standard 4-hour PET, using 2.27% glucose-based dialysate. We also used essential demographic, clinical and laboratory data as control variables.
The essential study and control variables were available in all patients (as demanded by inclusion criteria), while the secondary control variables were known in >95% of the cases, until the end of follow-up.

Statistics analysis:
We compared the time course of 24-hour PPE under both modalities of PD until the end of the second year, using both intention-to-treat and as-treated approaches. Numerical variables are presented as mean ± standard deviation (SD) or median values (range), as appropriate. Univariate comparisons between variables were produced according to Student's t test, ANOVA, Mann-Whitney and Wilcoxon tests (numerical), and χ^2 distribution (categorical). We also analyzed longitudinally different demographic, clinical, peritoneal functional, adequacy and prescription variables, scrutinizing for univariate correlations with 24-hour PPE using the Spearman's correlation.
Multivariate analysis was based on multilevel linear mixed models (see Brown and Prescott, 2006), with forward stepwise variable selection. Patient effect was adjusted as random effect, while the scrutinized covariates were adjusted as fixed effects. Serial estimations of PPE during PET, representing the individual characteristics of peritoneal protein transport over time, were systematically included in the different tested models.

Model:

$$Y_{ij} = \alpha_{00} + \beta x_{ij} + \gamma t_j + u_{0j} + \varepsilon_{ij},$$

$$E\left(u_{0j}\middle|x_{ij}\right) = E\left(\varepsilon_{ij}\middle|x_{ij}\right) = 0$$
$$Var\left(u_{0j}\middle|x_{ij}\right) = \sigma_0^2; Var\left(\varepsilon_{ij}\middle|x_{ij}\right) = \sigma_\varepsilon^2 \quad u \text{ and } \varepsilon \text{ are independent}$$

$$Var\left(Y_{ij}\middle|x_{ij}\right) = \sigma_0^2 + \sigma_\varepsilon^2,\ \rho_1\left(Y\middle|x\right) = \frac{\sigma_0^2}{\sigma_0^2 + \sigma_\varepsilon^2}$$

where i=patient; j=observation

Y_{ij} dependent variable

x_{ij} independent variable

t_j time variable

We also tested potential interaction terms. We used the Akaike (AIC) and Bayesian (BIC) Information Criteria to compare maximum likelihood models.
We used the SPSS v.18.0 and Stata v.11 softwares for data processing.

Ethical and legal aspects: This ensures the anonymous of the data by data protection law (R.D 15/1999) and fulfilled the Helsinki Declaration

3. RESULTS

We scrutinized 284 patients, 197 on CAPD and 87 on automated PD (APD) at baseline. Sixty-eight patients who started on CAPD (34.5%) and 22 patients who started on APD (25.3%) suffered at least one episode of peritonitis during the first year (p=0.15).
Univariate, serial estimations of 24-hour PPE were marginally higher in CAPD patients, and remained essentially stable over time in both groups.
Multilevel mixed model analysis (Table 1) confirmed that PPE during PET is an accurate predictor of 24-hour PPE. The best model also identified CAPD (vs APD) therapy, total dialysate volume instilled per day and daily ultrafiltration (UF) as independent predictors of 24-hour PPE. Total volume drained performed as a surrogate of total volume instilled per day and UF (B=297.9, 95% CI 203.6/292.3, p<0,005). None of the remaining clinical, adequacy or prescription-related variables showed an independent correlation with 24-hour PPE. Neither we detected significant interaction terms among the best model variables, except for a minor interaction between PPE during PET and dialysate volume instilled (B=-0.18, 95% CI -0.36/-0.1, p=0.039).

Multivariate analysis disclosed a trend to a decrease in PPE during follow-up, although the effect was statistically significant only at 12 months. We explored the possibility that this effect could be the result of an earlier drop-out of patients with higher 24-hour PPE rates, which was not the case, although we detected a trend to higher late drop-out rates in patients at both the lower and higher quartiles of PET-related PPE rates.

Table 1: Predictors of 24-hour PPE. Multilevel mixed model analysis. Best model

	B	**SE**	**p**	**95% CI**
PPE during PET (per mg)	1.11	0.16	0.0005	0.80/1.42
Modality of PD (Ref. CAPD)	-888.5	286.0	0.002	-1448.6/-327.5
Total volume instilled (per L)	275.9	62.3	0.0005	153.9/397.9
Daily ultrafiltration (per mL)	0.41	0.20	0.041	0.02/0.80
Time on PD				
6 months	39.2	191.3	0.84	-335.8/414.1
12 months	-477.2	228.4	0.037	-924.9/-29.6
24 months	-486.3	268.0	0.070	-1011.5/38.9
Constant	2436.6	413.9	0.0005	1625.4/3247.8

Random effects	**Estimator**	**SE**	**P**	**95% CI**
Patients			<0.001	
Var (constant)	1220910	286626		770641/1934261
Var (residual)	4638165	295940		4092907/5255995

Akaike Information Criterion (AIC) 14556.7; Bayesian Information Criterion 14603.5
SE: Standard error; CI: Confidence interval; PPE: Peritoneal protein excretion; PET: Peritoneal equilibration test.

4. CONCLUSIONS

The individual characteristics of peritoneal protein transport are the major determinant of 24-hour PPE. The CAPD schedule associates higher PPE rates than the APD schedule. but this difference may be masked by the direct correlation between PPE and the total amount of dialysate instilled per day. Daily ultrafiltration and time on dialysis perform also as minor independent correlates of PPE during PD therapy.

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