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Original Article

Application of Multivariate Generalized Linear Mixed Model to Identify Effect of Dialysate Temperature on Physiologic Indicators among Hemodialysis Patients

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ABSTRACT

Introduction: One of the complications of hemodialysis treatment is hypotension, which can increase morbidity and mortality and compromise dialysis efficacy. Dialysate temperature is an important factor that contributes to hemodynamic stability during hemodialysis. This study investigated the effect of dialysate temperature on the patients' blood pressure and pulse rate. Model-based approaches were used to produce more reliable results compared with traditional methods.
Methods: A total of 30 patients were studied during 9 dialysis sessions. Dialysate temperatures were 37°C, 36°C and 35°C. A joint longitudinal model was used to analyze both responses of blood pressure and pulse rate, simultaneously.
Results: The results showed that low-dialysate temperature was not significantly associated with higher systolic blood pressure ($p>0.05$) or a higher pulse rate ($p>0.05$) either during or after dialysis. Pulse rate and blood pressure were higher for women during dialysate ($p<0.001$). However, increasing age was associated with higher blood pressure and a lower pulse rate ($p<0.001$).
Conclusion: Using several separate, repeated measure analysis of variances may produce misleading results, when there is more than one response variable measured over time, Multivariate statistical methods (including joint longitudinal models), should be used.

Introduction

Chronic kidney disease is associated with a range of pathological processes that lead to irreversible reduced kidney function.[1] To prevent uremia and its associated complications, patients need to undergo renal replacement therapies (hemodialysis, peritoneal dialysis or transplantation). Currently, hemodialysis is the most common treatment for patients worldwide and due to its wide availability, the life expectancy of these patients has been

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significantly increased.[2]
Despite its widespread use, hemodialysis is associated with several life threatening events. One of them is hypotension caused by the combination of low blood volume and loss of peripheral vascular resistance, with symptoms including nausea, vomiting, cramp, dizziness, weakness, and fatigue both during, and after dialysis sessions.[3] Cool dialysate has been shown to reduce hypotensive episodes during hemodialysis.[4] The effect blood cooling has upon blood pressure (BP) during very high efficiency hemodialysis with high ultrafiltration rate, is to stabilize BP without compromising the efficacy of hemodialysis.[3, 5] In addition, cooler dialysate improves left ventricular contractility, independently of preload and after-load.[6] In many studies examining renal replacement therapy and their effects upon BP and pulse rate, the data is typically collected at several time points. The usual statistical analysis for this kind of data is repeated measure analysis of variance, paired t-test as well as post hoc analysis. However, the sphericity assumption does not hold in many cases.[7] At the same time, most researchers use several separate models in case there is more than one response variable, which in turn increases a type I error and lowers statistical power of the tests.[7] A more efficient statistical method named "longitudinal analysis" can be more helpful and appropriate in these cases.
The variance, caused by repeated measurements over time, is a fundamental characteristic of longitudinal data. Moreover, assessing 2 or more correlated longitudinal response variables over time causes another type of variance which requires joint methods. Joint modeling of responses allows for evaluating response variables using several covariates and factors, these type of approaches also consider the interaction between the response variables. Joint modeling approaches results in smaller standard errors of coefficients and consequently more accurate estimating.[8] Several studies apply longitudinal univariate and joint methods to analyze medical data.[9-13]
We conducted this study to assess the effect of dialysate temperature and several risk factors, upon systolic blood pressure (SBP) and pulse rate, using a joint modelling approach based on generalized linear mixed effects models. We also compared the results from the original research that used usual repeated measure ANOVA for data analysis with the results in this study where multivariate longitudinal modeling was used.

Methods

1. The dataset

The present study utilized a data set corresponding to a clinical trial study (registry number: IRCT2012090810778N1 and Ethics Committee Approval number: D/P/16/35/9/1837) which was conducted in Hamadan, western Iran. Informed consent was obtained from all individual participants included in the study. There were 30 patients who underwent hemodialysis in 2018, with the following inclusion criteria: a history of hemodialysis for at least 3 months before beginning the study; not taking blood pressure lowering drugs on the day of dialysis; not suffering from cardiovascular disorders; not having severe anemia (hemoglobin <8); cancer and thyroid disorders; and desire to participate in the study. All the patients underwent hemodialysis 3 times a week, with each treatment lasting for 3 to 4 hours. Hemodialysis was conducted at 3 different temperatures (37°C (normal), 36°C and 35°C), each dialysate used 3 times, and BP and pulse rate were recorded before and after dialysis (for more information check the original study).[14]

2. Statistical analysis

2.1. Generalized Linear Mixed Effects Models (GLMMs)

Repeated measures over time for individuals cause a specific variance which must be analyzed through longitudinal analysis methods. Generalized Linear Mixed effects Models (GLMMs) are frequently used due to the possibility of modeling different types of response variable (continuous, binary, count, etc.). This approach used random effects to consider the variation of the repeated measurements for the same subject. This model provided subject specific interpretation as well as population average. The model presented the amount of Intra-Class Correlation (ICC) among the repeated measurements over time.[15]

3. Multivariate Analysis

In a multivariate approach, the impact of covariates on both the associated response variables were analyzed in a single model in which the inflation of type one error due to several statistical tests could be avoided.[7]
The bivariate model can be shown as,

$$E(Y_{1ij}|X_{ij}, w_i) = x_{\acute{\imath}j}\alpha + w_i \qquad (1)$$
$$E(Y_{2ij}|X_{ij}, b_i) = x_{\acute{\imath}j}\beta + b_i$$

in which

$$\begin{pmatrix} b_i \\ \mathrm{w_i} \end{pmatrix} \sim \mathrm{Normal}_2\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_b^2 & \rho\sigma_b\sigma_w \\ \rho\sigma_b\sigma_w & \sigma_w^2 \end{pmatrix}\right) \qquad (2)$$

In this multivariate linear mixed effect model, Y_{1ij} and Y_{2ij} are the continuous response variables for subject i at accession j. The covariates ($x_{ij'}$) are not necessarily the same for both sub-models. Moreover, α and β are the fixed effect coefficients. The random intercepts in each sub-model, b_i and w_i, follow a bivariate normal distribution with zero means, special variances and correlation term ρ, which takes the correlation between the 2 response variables into account.
The likelihood function is as below:

$$\prod_{i=1}^{N}\prod_{j=1}^{n_i} f_{y_{1ij|w_i,x_{ij}}}(Y_{1ij}|w_i, x_{ij})\, f_{y_{2ij|b_i,x_{ij}}}(Y_{2ij}|b_i, x_{ij}) f_{b_i,w_i}(b_i, w_i) \qquad (3)$$

in which the bivariate normal function ($f_{bi,wi}$) (b_i,w_i)) includes the correlation parameter which takes the association between the 2 response variables into account. Moreover,

$$f_{y1ij\mid wi,xij}) (Y_{1ij} \mid w_i, x_{ij}) \text{ and } f_{y2ij\mid bi,xij}) (Y_{2ij\mid bi,xij})$$

are normal density functions with identity link function.
The SAS version 9.2 and R version 3.1.3 (SAS North Carolina, USA) statistical software programs were then used to analyze the data. A significance level of 0.05 was considered. In the present study, we used SBP and pulse rate as response variables and time and temperature (and their interactions), age and gender of the patients as covariates.

Results

There were 30 patients (46.7% male) included in this study and the mean (standard deviation) age was 51.43±13.82 years, ranging from 21 to 74 years. The mean (standard deviation) SBP and pulse rate at several time points and across 3 groups is shown in Table 1. Moreover, Figures 1 and 2 show the development of response variables across the 3 groups. Patients' SBP became higher with the 35˚C cold dialysate, compared to the dialysates at 36˚C and 37˚C, while the 36˚C cold dialysate showed almost the lowest SBP along with the time. The patients' pulse rates were higher in the 37˚C dialysate group, compared with the other 2 groups of cooler dialysate. Moreover, the 35˚C cold dialysate gave the lowest pulse rate longitudinally.

The results of the joint model are presented in Table 2. The SBP and pulse rate were adjusted according to their interactions using multivariate generalized linear mixed-effects model. The following regression models are presented below:

$$\textit{Systolic blood pressure}_{ij} = 130.721 + 12.304 \times X_{ij1} + 0.446 \times X_{ij2} + \hat{w}_i$$

$$\textit{Pulse rate}_{ij} = 91.130 + 6.699 \times X_{ij1} - 0.277 \times X_{ij2} + \hat{b}_i$$

where, X_{ij1}, X_{ij2} stands for gender and age of subject i at occasion j, respectively. In addition, $\hat{w}_i$ and $\hat{b}_i$ are the estimated random intercepts for systolic blood pressure and pulse rate sub-models, respectively. Based on the resulting models, the mean SBP and pulse rate were 130.721 mmHg and 91.13 beats per minute (BPM), respectively, considering other fixed factors. The patients' SBP and pulse rate were not affected by different cold dialysate groups from pre-dialysis to post-dialysis. However, adjusted for the effect of cold dialysate and time of onset from the start of dialysis, female SBP was 12.304 mmHg significantly higher than males ($p<0.001$). In addition, a 1 year increase in age, resulted in a significant increase in the mean SBP by 0.466 mmHg ($p<0.001$). The average pulse rate for females was 6.699 BPM higher compared with males ($p<0.001$), and a 1 year increase in age caused a 0.277 BPM decrease in mean pulse rate ($p<0.001$). These results suggest

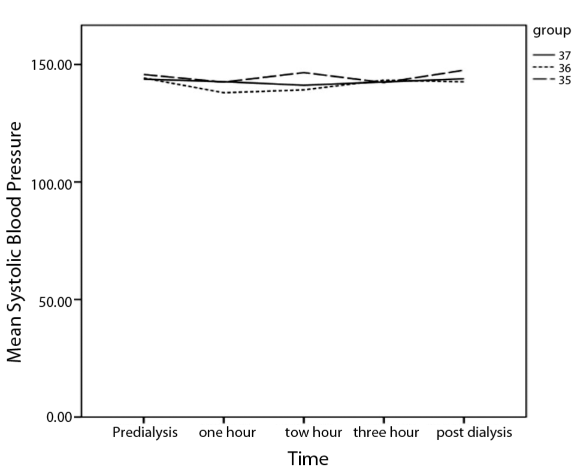

Figure 1. Mean systolic blood pressure over time for dialysate temperatures of 35˚C, 36˚C and 37˚C

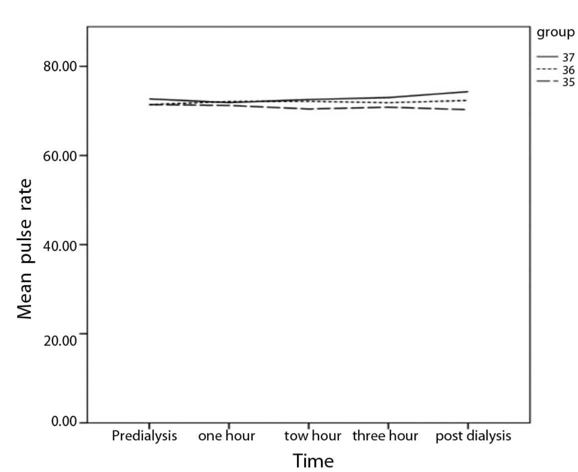

Figure 2. Mean pulse rate over time for dialysate temperatures of 35˚C, 36˚C and 37˚C

Table 1. Mean (Standard Deviation) of systolic blood pressure and pulse rate in patients receiving dialysate at different temperatures.

Response Variable	Group (Temp)°C	Pre-dialysis	1 hour	2 hour	3 hour	Post Dialysis
SBP						
	37	143.74 (22.37)	142.62 (21.07)	141.14 (22.65)	142.53 (18.52)	143.88 (21.68)
	36	144.21 (22.89)	137.95 (21.14)	139.17 (21.22)	143.29 (16.34)	142.61 (21.03)
	35	145.71 (24.82)	142.46 (24.77)	146.52 (33.01)	142.27 (18.16)	147.53 (24.84)
Pulse Rate						
	37	72.68 (12.57)	71.85 (13.69)	72.54 (13.57)	72.98 (12.81)	74.31 (13.69)
	36	71.42 (14.04)	72.11 (13.42)	72.14 (11.71)	71.84 (8.71)	72.34 (11.13)
	35	71.41 (13.38)	71.22 (12.08)	70.42 (11.62)	70.83 (8.48)	70.26 (10.21)

SBP, Systolic Blood Pressure; Temp, Temperature

Table 2. The results and formulas of multivariate generalized linear mixed-effects model assessing the development of systolic blood pressure and pulse rate

Parameter	Estimate	Standard Error	p-value	95% Confidence Interval	
				Lower	Upper
SBP					
Intercept	130.721	44.838	0.006	38.868	222.561
Time*	6.113	18.173	0.739	-31.114	43.340
Group†	-0.973	1.243	0.440	-3.520	1.572
Time*Group‡	-0.164	0.504	0.746	-1.198	0.869
Sex	12.304	1.348	< 0.001	9.542	15.065
Age	0.446	0.050	< 0.001	0.342	0.549
RI§	17.918	0.579	< 0.001	16.731	19.105
ICC‖	0.677	0.020	< 0.001	0.635	0.719
Pulse Rate					
Intercept	91.130	20.368	< 0.001	49.407	132.850
Time	-12.515	8.251	0.140	-29.418	4.387
Group	0.117	0.564	0.837	-1.039	1.273
Time*Group	0.350	0.229	0.137	-0.118	0.820
Sex	6.699	0.671	< 0.001	5.324	8.074
Age	-0.277	0.024	< 0.001	-0.327	-0.227
RI	13.024	0.421	< 0.001	12.162	13.887
ICC	0.843	0.012	< 0.001	0.817	0.869
Correlation between random intercepts	-0.245	0.021	< 0.001	-0.289	-0.202
Correlation between response variables	-0.185	0.016	< 0.001	-0.218	-0.152

*The continuous independent variable shows time development from pre-dialysis to post dialysis

†group, the cold dialysate indicating 35°C, 36°C and 37°Cc

‡The interaction between time and group which compares the development of response variable over time in the cold dialysate groups

§The variance of random Intercept

‖The intra-class correlation (ICC) due to repeated measures over time

ICC, Intra-class correlation; RI, Random intercept; SBP, Systolic blood pressure that patients' pulse rate response to cold dialysis was related to sex and age.

Based on Table 2, the random intercepts were statistically significant which indicated that the mixed-effect approach was the appropriate choice. In other words, the variation caused by repeated measurements, along with time and across with the cold dialysate groups, was significantly related to the random intercepts ($p<0.001$). The degree of association of repeated measurement was calculated by the intra-class correlation. The intra class correlation of SBP and pulse rate was 0.677 and 0.843, showing a significant association ($p<0.001$).

The correlation between SBP and pulse rate is demonstrated by the correlation between random intercepts ($p=-0.245$ and $p<0.001$). Using the formula presented in the previous section, the correlation between SBP and pulse rate is -0.185 ($p<0.001$). The 2 response variables were statistically associated in a reverse direction.

Discussion

In this study, a multivariate approach was utilized to investigate the effect of temperature of dialysate solution on physiological variables of SBP and pulse rate in dialysate patients. The results in this study suggest that age and gender of the patients have a significant effect on the cardiovascular response to a cooler dialysate used for hemodialysis. The effects of these 2 covariates on SBP and pulse rate have not been previously investigated. According to the results, females showed higher SBP and pulse rate compared to males. Studies assessing the effect of age and sex on dialysis outcomes, like mortality rate, also reported a lower mortality rate in women on dialysis compared with men.[16]

In the used joint model, the effect of dialysate temperature was also shown to be associated with decreasing SBP, although this was not statistically significant. Although this result is consistent with the results of the previously published study,[14] it is inconsistent with the results of other studies. This might be due to the fact that other studies recruit patients with frequent hypotension episodes during dialysis, however, in this study, the patient cohort was not selected on these criteria. Taking into account the non-significant trend toward increasing SBP with reduced dialysate temperature, further studies should be conducted with larger sample sizes.

The results of the present study showed that, according to the joint longitudinal model, the effect of dialysate temperature on physiologic indicators of SBP and pulse rate were not significant. Borzou et al[14] reported that pulse rate changed significantly by dialysate temperature as determined by repeated measure ANOVA ($p<0.05$) which was inconsistent with the results of the present study. In their study,[14] however, there were no significant effects on SBP ($p=0.055$) which was consistent with the results of the present study. This inconsistency was also observed in other studies.[3-5] This is likely a result of all these studies neglecting the correlation between pulse rate and SBP. Moreover, the analysis in the present study is model-based, where in addition to the correlation between responses, the effects of other covariates were taken into account. This may lead to different results compared to non-model based analysis like ANOVA. Overall, the model-based approaches may provide a more statistically accurate analysis considering the adjusted effects of the parameters.[17]

In the present study a joint longitudinal model was applied instead of traditional repeated measure ANOVA. The association of response variables from a multivariate point of view leads to smaller standard errors for estimated coefficients, resulting in a true significance.[18, 19] Multivariate analyses result in more valid estimations compared with univariate approaches.[20] In a comparison of computational surveys of various univariate and multivariate learning curve models, Badiru showed that the bivariate model provided a slightly better fit than the univariate model. Moreover, the bivariate model provided more detailed information about the data.[21] Comparing multivariate and univariate GARCH models to forecast portfolio value-at-risk, Santos et al. concluded that the multivariate approach performed better than the univariate analysis.[22] McGuire et al. compared univariate and multivariate linkage analysis of traits related to hypertension and showed that multivariate linkage analysis was better able to detect chromosomal regions, while univariate linkage analysis only detected one gene.[23] Thorp used longitudinal joint and univariate mixed-effects models for metabolic syndrome data where multiple outcome variables were assesses using several predictors. The multivariate model was able to resolve the same questions as the univariate model. This model answered important additional questions about the association in the evolution of the response variables, as well as the evolution of the associations. By taking the association between the responses into account, the standard errors in estimation were reduced.[24]

Conclusion

The univariate repeated measure analysis of variance does not take into account the correlation of the response variable with other responses as well as covariates, thus using several separate repeated measure analysis of variances, may be misleading. Therefore, where there are more than one response variable, measured over time, multivariate statistical methods including joint longitudinal models, should be used.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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