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Full Length Research Paper

Comparing different sedation medications using generalized estimating equations approach

M. A. Cengiz[1]*, T. Şenel[1], Y. Terzi[1], N. Murat[1] and N. Savaş[2]

[1]Department of Statistics, Ondokuz Mayıs University, Samsun, Turkey.
[2]Department of Mathematics, Erzincan University, Erzincan, Turkey.

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Generalized estimating equations (GEE) provide an applicable approach to modelling repeated and clustered data that are often encountered in medical application. This approach is very useful especially when response variables are correlated and categorical, covariates are time-depended, there are a large number explanatory variables and missing data. In this study, using this approach we focus on modelling repeated sedation measurements obtained during magnetic resonance imaging (MRI) and computerized tomography (CT) for children.

Key words: Sedation, midazolam, generalized linear models.

INTRODUCTION

Magnetic resonance imaging (MRI) and computerized tomography (CT) require the patient to lie still for periods of up to 60 min. These two diagnostic procedures also require strict immobility and sedation for a successful result. If a child can not remain adequately still for examination, sedation may be necessary. Optimal sedation management of children before MRI and CT has received attention in the last decade (Pershad et al., 2007; Godambe et al., 2003). The sedation medications must be chosen carefully for children's safety and effectiveness. Many researches related to the comparison of different sedation medications have been performed successfully (Cravero and Blike, 2004; Heard et al., 2008). In these studies, for each medication group sedation level were obtained at different time points within the time up to 60 min. In addition to sedation level measurements, the other multiple assessment of the same patient were recorded and the within subject, such as sedation levels at different time point for a given patient, were correlated. This case is an example when a longitudinal study is made with responses being measured repeatedly on the same patient across time.

In medical studies, statistical analysis of the data set described above has been performed by many researchers, who use the known methods such as ANOVA, MANOVA and Linear Models, assuming the repeated observations from each patient are uncorrelated. Since repeated observations are made on the same patient, observed responses are generally correlated. For Robust analysis, this association must be accounted for. Weighted least squares model is used for repeated categorical data. This model works well for large sample size, no missing data, a small number of response variable and discrete independent variables. Recent years has witnessed a new statistical method of analysing for data do not meet these conditions.

Mathematical models for multiple regression, Linear Models and Time series are generally useful where random variables are approximately normal and can be explained by some linear structure. However, data can be clearly non-normal when they represent categorical or frequency observations. GLM offer convenient and highly applicable tools for these kinds of data. They allow for more general structures and more general distributions than linear regression and ANOVA. Nelder and Wedderburn; (1972) developed the concept of GLMs and an extensive treatment was given by (McCullagh and

*Corresponding author. E-mail: macengiz@omu.edu.tr.

Abbreviations: GEE, Generalized estimating equations; **MRI,** magnetic resonance imaging; **CT,** computerized tomography; **GLM,** generalized linear models.

Table 1. Descriptions of predictor values used in the analysis.

Predictor	Description
Group	M: Midazolam; D: Diazepam; L: Luminal; C: Cardiac Cocktail.
Age	Between 4 months old and 13 years old.
Weight	Between 6 and 46.
Test	CT and MRI.
Sex	Male and female.
Disease	Diseased with neurological damage. No diseased.
SBP	Systolic blood pressure.
PUL	Pulse.
NB	Number of breathes / a minute.
OSAT	Oxygen saturation.
Comp	Complication, none, nausea, vomiting, apnea and additional sedation.
Adopt	Adaptation level, very good, good, average and bad.

Nelder, 1989). With the introduction of GLM, a much more flexible instrument for statistical modelling was created. As special cases, they include multiple linear regression, logit and probit models for quanta responses and log linear response models for counts.

Introduced generalized estimating equations (GEE) (Liang and Zeger, 1986), which were developed to extend the generalized linear models (GLM) introduced by (Nelder and Wedderburn, 1972). In this study, we give brief review of GLM and GEE and use the both methods in comparing different sedation medications used during CT and MRI.

MATERIALS AND METHODS

In this study, Midazolam, Diazepam, Luminal and Cardiac Cocktail were compared in terms of sedation level. 127 children who received MRI and CT were included in this study. Group M (n=30) received Midazolam, Group D (n=31) received Diazepam, Group L (n=32) received Luminal and Group C (n=34) received Cardiac Cocktail. Sedation levels were maintained in the range of Ramsey Scale from 1 - 5 for each 15 min. Systolic Blood pressures, Pulse rates, the number of breathe, oxygen saturation were monitored. The other measurements, which may affect the sedation level, such as weight, disease status, test status, complication status, age and adaptation status, were also recorded. Descriptions of predictor values used in the analysis are given in Table 1. GEE approach is used to compare the different sedation medication. Then GEE is briefly described as follows.

For GLMs, repeated observations of the response variable Y are assumed conditionally exchangeable given observable covariates x. Their conditional probability distributions are assumed to be natural members of the exponential family, with conditional expectation $E(Y|x,\beta) = \mu$. This mean is related to the linear predictor $\eta = x^T\beta$ b

$$\eta = g(\mu) \quad (1)$$

Where, g is the link function, β is a vector of unknown parameters (the regression coefficients) and x is a design vector containing observable covariates and indicator variables. Y is density, its function may be expressed in the form of

$$f(y|\theta,\phi) = \exp\left\{\frac{y\theta - b(\theta)}{\phi} w + c(y,\phi)\right\} \quad (2)$$

Where, θ is the natural parameter, ϕ is an additional scale or dispersion parameter, b and c are specific functions corresponding to the type of exponential family distribution concerned and w is a known weighting constant.

It is possible to fit models where the underlying data are normal, gamma, Poisson and Binomial by suitable choice of the link function. The GLMs assumes that observations are uncorrelated. GEEs are used to account for the correlation between, observations, to characterize the marginal expectation of a set of outcomes and to estimate the parameters of the marginal model (Diggle et al., 1994). We now give GEE terminology briefly in GLM terms.

Let Y_{ij} ($i = 1,2,...,n$ and $j = 1,2,...,m$) be the jth outcome for ith patient (such as sedation level value at jth time in ith patient) where observations on different patients were assumed independent. Marginal regression models can be constructed as follow:

$$g(E(Y_{ij})) = x_{ij}\beta \quad (3)$$

Where, x_{ij} is px1 vector of covariates for the jth outcome is for ith patient, β is unknown parameter vector and g is link function.

Table 2. SAS GENMOD statements.

1	m	5	1	15	2	1	5	1	90	24	104	99	1	2	5	4	3
2	c	4	1	12	1	1	6	2	100	36	105	97	1	3	4	5	5
3	c	6	2	25	2	1	6	2	100	27	97	97	1	2	4	4	5
125	c	1	1	10	2	1	1	1	80	36	120	98	1	3	4	5	5
126	c	2.5	2	15	1	1	1	1	85	32	104	99	2	3	4	5	5
127	c	3	1	15	1	2	5	2	85	30	96	98	1	2	3	3	5;

```
Data sedation;
Input case group$ @;
Input age sex weight test comp adopts disease sbp nb pul osat@;
Do i=1- 5;
Input SED @@;
Output; end; datalines;
Proc genmod data=sedation;
Class case group;
Model sed=group age sex disease weight comp test adopt sbp pul osat nb /dist=mult;
Repeated subject=case / type=ind covb corrw;
Contrast 'c-d' group 1 -1 0 0; Contrast 'c-l' group 1 0 -1 0;
Contrast 'c-m' group 1 0 0 -1; Contrast'd-l' group 0 1 -1 0;
Contrast'd-m' group 0 1 0 -1; Contrast 'l-m' group 0 0 1 -1;
Run;
```

We need to model the covariance structure of the correlated observations on a given patient as:

$$V_i = \phi A_i^{1/2} R(\alpha) A_i^{1/2} \quad (4)$$

Where, A_i is a diagonal matrix of variance function and $R(\alpha)$ is the working correlation matrix that is indented to approximate the true correlation matrix. In practise, we need the specification of working correlation matrix. An important property of GEE methods show that, even if the selected working correlation matrix is wrong, the resulting regression coefficient is still consistent and asymptotically normal, provides easiness for practises (Fitzmauurice, 1995; Pepe and Anderson, 1994). In practice, working correlation matrix would be chosen to be the most reasonable for data based on either statistical criteria or biological background. For the appropriate choice of correlation structures, readable studies were presented by (Crowder, 1985; Diggle et al., 1994; Heagerty and Zeger, 2000; Horton and Lipsitz, 1999; Pan and Connect, 2002; Wang and Carey, 2003).

RESULTS

We use the GENMOD procedures, which can accommodate the analysis of correlated data, in SAS program to estimate the regression parameters for GEE method. The mean response (sedation level) is modelled as a multinomial regression model using the explanatory variables age, sex and the others described in Table 1. The multinomial responses for individual children are assumed to be correlated. The SAS statements that fit the model by the GEE methods were in Table 2.

The Class statement and the Model statement specify the model for mean of the sedation variable response as a multinomial regression with group, age, sex and other variables as independent variables including two ways interaction terms for group variable. The Repeated statements invokes the GEE method and specifies the correlation structure. The option Subject=Case specifies that individual subjects are identified in the input data set by the variables. Contrast provides a means for obtaining a test for a specified hypothesis concerning the model parameters. Ind shows independent working correlation matrix. Cumulative Logit is used as Link function for multinomial response.

Conclusion

The PROC GENMOD output is summarized in Table 3. The correlations are sufficiently small, thus the use of the independence working correlation structure appears to be satisfactory. We compare GLM with assumption no correlation and GEE results in this Table. It is easy to say there is no distinguishes for main effects between both methods and the parameter estimates are identical for each group in both methods. Thus, we see that only Group D is significant at $\alpha = 0.05$ and negative sign suggests a negative effect on the mean counts. Looking p-values and Contrast values in Table 4 we conclude that, Group D (Diazem) is significantly different from the other medication groups and there is no significantly difference between the other medication groups.

The use of generalized estimating equations can be a valuable tool in medical applications when response values are clearly correlated and independent variables include categorical data as well as continuous variables.

Table 3. Analysis of parameter estimation for GLM and GEE.

GLM				GEE			
Parameter	**Estimate**	**Standard error**	**p**	**Parameter**	**Estimate**	**Standard error**	**p**
Group_c	-4.6158	15.6919	0.7686	Group_c	-4.6158	7.7932	0.5537
Group_d	-63.0109	27.2959	0.0210	Group_d	-63.0109	13.6951	<.0001
Group_l	18.2469	29.3089	0.5336	Group_l	18.2469	18.4159	0.3218
Group_m *	0.0000	0.0000	-	Group_m *	0.0000	0.0000	-
Age	0.0460	0.1601	0.7738	Age	0.0460	0.0980	0.6388
Sex	-0.2133	0.3722	0.5665	Sex	-0.2133	0.2549	0.6388
Disease	-0.2162	0.3295	0.5117	Disease	-0.2162	0.2474	0.4026
Weight	-0.0385	0.0425	0.3646	Weight	-0.0385	0.0228	0.0914
Comp	0.0641	0.0871	0.4619	Comp	0.0641	0.0471	0.1735
Test	0.1734	0.2505	0.4888	Test	0.1734	0.1177	0.1408
Adopt	0.5265	0.1265	<.0001	Adopt	0.5265	0.0811	<.0001
SBP	-0.0052	0.0133	0.6962	SBP	-0.0052	0.0080	0.5155
PUL	-0.0076	0.0089	0.3967	PUL	-0.0076	0.0051	0.1343
OSAT	-0.0411	0.1373	0.7649	OSAT	-0.0411	0.0769	0.5933
NB	0.0204	0.0219	0.3524	NB	0.0204	0.0117	0.0821

Table 4. Contrast statement results for GEE analysis.

Contrast	Df	Chi-square	p-value
C-D	1	11.36	0.0008
C-L	1	1.21	0.2704
C-M	1	0.32	0.5724
D-L	1	7.68	0.0056
D-M	1	11.17	0.0008
L-M	1	0.76	0.3818

Furthermore, GEE handles missing data and time-dependent explanatory variables, such as systolic blood pressure and oxygen saturation, are especially useful for binary and discrete count as multinomial and poisson. Although, there were a large number of explanatory variables, two ways interaction terms and multinomial categorical response in our model, we obtained highly significant result using GEE. Finally, it is noted that linear predictor terms, distributions, link functions and working correlation matrix should be chosen carefully for robust analysis.

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