Bayesian modeling of crossover studies of rare diseases including escape phase

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Abstract

Early-escape design (Amery and Dony 1975; Temple 1994) limits patient's exposure to ineffective therapy by allowing patients escape from the randomized treatment or taking rescue medications. Typically, the escape rate or time to escape or the amount of rescue mediation is used as the study outcome, and the treatment effect is evaluated using only data prior to escape. However, data after escape phase can provide useful information; ignoring data after escape costs power that are valuable for studies of rare diseases or studies constrained by small sample size. Motivated by a recently completed crossover study of rare disease with early escape design, we propose a Bayesian approach that utilizes data from both before and after escape for evaluating treatment effect.

Key Words: Bayesian, crossover, early-escape, rare disease

1. Background

Studies for rare diseases face the challenge of limited number of participants, thus require alternative design and analysis methods for evaluation of the safety and efficacy of a therapeutic intervention (Evans and Ildstad 2001; Wilcken 2001; Lagakos 2003; Gerss and Kopcke 2010). Early-escape design (Amery and Dony 1975; Temple 1994) limits patient's exposure to ineffective therapy by allowing patients escape from the randomized treatment or taking rescue medications. Because the clinical endpoint are used in defining escape criteria, the escape rate or time to escape, or the amount of rescue mediation is typically used as the study outcome and treatment effects are usually evaluated using only data prior to escape. However, ignoring data after escape can cost study power that are extremely valuable for rare disease study. Here, we propose a Bayesian statistical modeling strategy utilizing data both before and after escape.

This research is motivated by a study of Familial Mediterranean Fever (FMF), a rare genetic autoinflammatory disorder resulting in recurrent episodes of fever and other complications. The aim of the FMF study was to study an IL-1 inhibitor therapy in treating colchicine resistant or intolerant FMF patients. Currently, there is no proven treatment available for these patients. This is a two-arm study with active treatment and placebo. The design was a multi-center, randomized, double-blind, 4-period crossover clinical trial with early-escape design. Patients who developed at least 2 attacks in a given treatment course were allowed to escape to the other treatment arm until the end of that course and then resumed their assigned sequence. Double-blind was maintained during

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the entire course of the study. The hypothesis of the study was that the active treatment is more effective than placebo in reducing frequency of FMF attacks. The primary study outcome was the FMF attack, the secondary outcome was the escape rate. The primary analyses performed Bayesian modeling utilizing data before the escape phase. Data after escape were utilized in the ITT analyses, and various sensitivity analyses. Here, we examined additional analytical considerations motivated by but not limited to this trial.

This study addresses analysis of longitudinal bivariate binary (escape) and count (attack rate) outcome. Methods for the analysis of bivariate or mixed type bivariate outcomes have been studied, such as seemingly unrelated regressions (Zellner 1962; Rochon 1996; Verzilli, Stallard et al. 2005), bivariate or multivariate random effect models (Reinsel 1982; Reinsel 1984; Schafer and Yucel 2002; Riley, Abrams et al. 2007), Bayesian latent variable models for mixed discrete outcomes (Dunson and Herring 2005), estimating equations for multivariate discrete and continuous outcomes (Prentice and Zhao 1991) etc. We proposed a Bayesian model that incorporates bivariate random effects for longitudinal data and allows treatment effects on the two outcomes correlate with each other. The model utilizes all available data and estimates treatment effect from both before and after escape, and accounts for crossover and other features of the design.

2. Bayesian Analysis

Let y_{ijk} denote the number of attack for patient $i, i = 1, \dots, 11$. during period $j, j = 1, \dots, 4$, either before (k=1) or after (k=2) escape, if the patient escaped during this period. Let l_{ijk} be the duration and T_{ijk} be the treatment, which takes the value of 0 for placebo and 1 for the active treatment. esc_{ij} denotes the ith patient escaped ($esc_{ij} = 1$) or not ($esc_{ij} = 0$) during period j. CO_{ijk} indicates the carryover effect. $CO_{ijk} = 1$ when the treatment switched from the active treatment to placebo. Since escape always happens right or shortly after an attack, there is likely an inflation of attack rate for the before escape course, we introduce another variable BE_{ijk} to indicate a before escape course.

2.1 Methods

We assume the number of attacks during each course (or sub-course if the patient escaped during a period) y_{ijk} follows a Poisson distribution with parameter μ_{ijk}, logarithm transformation of which is a function of the treatment effect T_{ijk}, the carryover effect CO_{ijk}, and the before escape course effect BE_{ijk}, with corresponding coefficient β_t, β_{co}, and β_{be}. The intercept β_0 represents the mean logarithm event rate under placebo without carryover and before escape course effects. We also include a subject-specific random effect β_i to account for the repeated measure feature of the study. The model for event rate is as follows:

$$y_{ijk}|\mu_{ijk},\ l_{ijk} \sim Poisson(\mu_{ijk} l_{ijk}),$$

$$\log(\mu_{ijk}) = \beta_0 + \beta_t T_{ijk} + \beta_{co} CO_{ijk} + \beta_{be} BE_{ijk} + \beta_i.$$

We assume esc_{ij} follows a Bernoulli distribution with parameter π_{ij}. Since a patient is allowed to escape only when he/she experiences more than one attack during each course, π_{ij}, the escape probability has two components. When the number of attacks $y_{ij1} \leq 1$,

$\pi_{ij} = 0$. When $y_{ij1} \geq 2$, we assume that logit(π_{ij}) is a function of the treatment T_{ij1} with regression coefficient α_t. The intercept $\alpha_0$represents logit of the escape probability under placebo. Subject-specific random effect α_i models the dependency between repeated measures of escape of the same subject. Explicitly, the model for escape rate is as follows:

$$esc_{ij} \sim Bernoulli(\pi_{ij}),$$

$$\pi_{ij} = \delta_0 \mathrm{I}_{[0,1]}(y_{ij1}) + \mathrm{I}_{[2,)}(y_{ij1}) \mathrm{logit}^{-1}(\alpha_0 + \alpha_t T_{ij1} + \alpha_i).$$

Here, δ_0 is a point mass at 0; $\mathrm{I}_{[0,1]}(y_{ij1}) = 1$ if $y_{ij1} \leq 1$, 0 otherwise; and $\mathrm{I}_{[2,)}(y_{ij1}) = 1$ if $y_{ij1} \geq 2$, 0 otherwise.

Since it is reasonable to assume the primary outcome and escape rate are correlated, joint modeling of the two enables better characterization of the relationship between outcomes and design variables. To model the dependency between escape and number of attacks, we introduce two types of 'links'.

Link 1: $\begin{pmatrix} \beta_i \\ \alpha_i \end{pmatrix} \sim \mathrm{N}_2(0, \Sigma)$, $\Sigma = \begin{bmatrix} \sigma_\beta^2 & \rho\sigma_\beta\sigma_\alpha \\ \rho\sigma_\beta\sigma_\alpha & \sigma_\alpha^2 \end{bmatrix}$.

Link 2: $\begin{pmatrix} \beta_t \\ \alpha_t \end{pmatrix} \sim \mathrm{N}_2(0, \Sigma_\mathrm{t})$, $\Sigma_\mathrm{t} = \begin{bmatrix} s_{\beta_t}^2 & r s_{\beta_t} s_{\alpha_t} \\ r s_{\beta_t} s_{\alpha_t} & s_{\alpha_t}^2 \end{bmatrix}$.

The first link is equivalent to a bivariate random effect, where the random subject effect for the event rate and the random subject effect for the escape probability are assumed to follow a bivariate normal distribution with mean 0 and variance covariance matrix Σ. The correlation coefficient ρ denotes the dependency between the two random effects given that a patient is eligible to escape. It is expected that patients experiencing more attacks are more likely to escape, i.e., $\rho > 0$. If ρ is not statistically significantly different from 0, it means that the tendency of experiencing more attacks is not related to the tendency of escape, given that the patient is eligible for escape (i.e., has had no less than 2 attack during a treatment course).

The second link assumes that the treatment effect on the event rate and the treatment effect on the escape rate are correlated. The correlation again is modeled by a bivariate normal distribution with a correlation coefficient r, where r represents that treatment effect on the attack rate is correlated with the treatment effect on escape rate. If r is not statistically significantly different from 0, it means that how the treatment affects the primary outcome does not depend on how it affects escape rate, given that the patient is eligible for escape. Figure 2 shows the directed acyclic graph (DAG) of the whole model. Data in dashed squares are observed only when a patient escaped during a course of treatment.

We considered several different models. We named the base model as model one, where carryover and before escape effects were not considered for the event rate, i.e.: $\log(\mu_{ijk}) = \beta_0 + \beta_t T_{ijk} + \beta_i$. The two type of 'links' were also not considered in the base model. Instead we assumed that β_t and α_t are independent and β_i and α_i are

independent. Other models were built upon the base model by considering either carryover effect, before escape effect or both, and by considering either of the two types of 'links' or both.

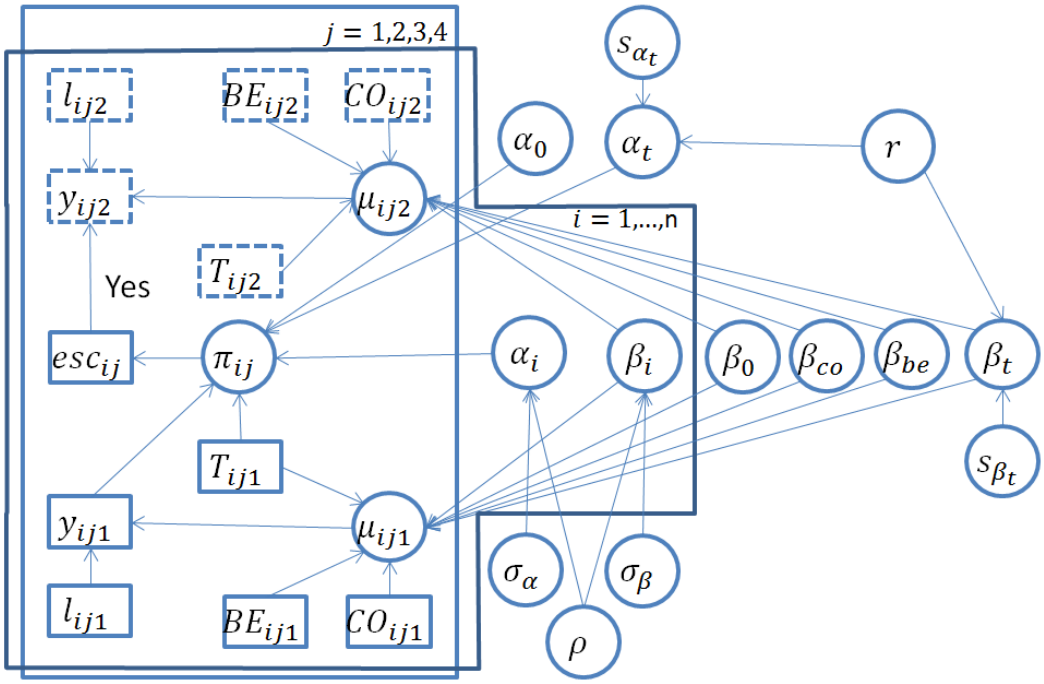

Figure 2: Directed acyclic graph (DAG) of the Bayesian model. Data in dashed squares are observed only when a patient escaped during a course of treatment.

Priors for the intercepts and regression coefficients of the carryover effect and the before escape course effect were specified as follows:

$$\beta_0 \sim N(0, \sigma^2),$$
$$\alpha_0 \sim N(0, \sigma^2),$$
$$\beta_{co} \sim N(0, \sigma^2),$$
$$\alpha_{co} \sim N(0, \sigma^2),$$
$$\beta_{be} \sim N(0, \sigma^2),$$
$$\alpha_{be} \sim N(0, \sigma^2).$$

When neither of the two types of 'links' were considered, priors for the regression coefficients of the treatment effect and the random subject effects were specified as follows:

$$\beta_t \sim N(0, \sigma^2),$$
$$\alpha_t \sim N(0, \sigma^2),$$

$$\beta_i \sim N\left(0, \sigma_\beta^2\right), \quad \sigma_\beta \sim U(0, B),$$
$$\alpha_i \sim N\left(0, \sigma_\alpha^2\right), \quad \sigma_\alpha \sim U(0, A).$$

When the 'links' were considered, an inverse-Wishart distribution was used as priors for the variance covariance matrices. The correlation coefficients ρ and r were not explicitly modeled, but calculated from the estimated variance covariance matrices.

$$\begin{pmatrix}\beta_i \\ \alpha_i\end{pmatrix} \sim \mathrm{N}_2(0,\ \Sigma) \text{ and } \Sigma \sim \mathrm{IW}(\mathrm{R},\ \mathrm{k}),$$

$$\begin{pmatrix}\beta_t \\ \alpha_t\end{pmatrix} \sim \mathrm{N}_2(0,\ \Sigma_\mathrm{t}) \ and \ \Sigma_\mathrm{t} \sim \mathrm{IW}(\mathrm{R},\ \mathrm{k}).$$

Hyperparameters were set such that all priors are relatively noninformative. Specifically, $\sigma^2 = 100$ for the variance of the intercepts and regression coefficients; $A = B = 10$ for the standard deviation for the random effects when the random effects were assumed independent; $k = 2$ and $\mathrm{R} = \begin{pmatrix}0.01 & 0 \\ 0 & 0.01\end{pmatrix}$ in the inverse-Wishart priors for the variance covariance matrix of the random effects or the treatment effect when the 'links' were considered. WinBUGS (Lunn, Thomas et al. 2000) and Markov chain Monte Carlo (MCMC) were used to fit the models. AIC was calculated to choose the model that fits the data the best among the models we considered.

2.2 Results

Table 1 shows the AIC of ten models we considered. The models include the base model (model 1) where treatment is the one and only covariate for the attack rate and no 'links' were considered, i.e., the treatment effect on attack rate and escape were assumed to be independent and the two random subject effects were also modeled as independent

Table 1: 10 models and AIC

Model	***AIC***
1. M1	300.7
2. M1+CO	303.8
3. M1+Link1	306.2
4. M1+Link1+Link2	308.4
5. M1+CO+Link1	309.1
6. M1+CO+Link1+Link2	311.8
7. M1+BE	271.8
8. M1+BE+CO	273.7
9. M1+BE+Link1	275.2
10. M1+BE+Link1+Link2	276.5

of each other. Other models built upon the base model by considering additional covariates for attack rate, such as the carryover effect and/or the before escape course effect, or additional correlations defined by the two 'links'. We also considered models

M1+LINK2, and M1+CO+ BE+Link1+Link2, etc., but carry-over effect and the correlation coefficient from link2 were never statistically significantly different from zero, so the results were not shown in the above table. AIC always increased when an additional carry-over effect was included in the model, for example, AIC increased when we added carry-over effect in model 1 (model 2 vs. model 1), in model 3 (model 5 vs. model 3), etc. Similarly, an additional 'link' (either link1 link2) in the model also increased AIC. However, adding a before escape course effect (BE) in an existing model decreased AIC. The best model is model 7, i.e., the base model with additional before escape course effect. Model 9 with base model plus an additional 'link1' and the before escape effect is also among the top models, whose AIC only slightly increased compared to the best model (model 7).

Table 2 shows the posterior parameter estimates and their 95% credit intervals of models 7 and 9. The two models gave very close parameter estimates. The mean attack rate under placebo is about 1.6 per month, and about 0.7 per month under the active treatment. This gives a different in event rate about 0.9 per month, a reduction of more than 50%. The escape rate is much higher under placebo (45%) than under the active treatment (18%). But, given that a participant was eligible to escape, i.e., had more than 1 attack during a treatment course, the treatment had no effect on the probability of escape. The correlation between the two random effects was also not significantly different from zero.

Table 2: Posterior parameter estimates (mean and 95% credit interval) of models 7 and 9

Parameter	***7. M1+BE***	***9. M1+BE+Link1***
μ_P	1.601 (1.227, 2.029)	1.596 (1.222, 2.033)
μ_R	0.681 (0.485, 0.926)	0.684 (0.488, 0.922)
$\mu_R - \mu_P$	-0.920 (-1.396, -0.489)	-0.912 (-1.380, -0.474)
β_t	-0.444 (-0.841, -0.033)	-0.435 (-0.839, -0.016)
e^{β_t}	0.656 (0.431, 0.967)	0.662 (0.432, 0.984)
β_{be}	1.381 (0.947, 1.809)	1.402 (0.975, 1.856)
π_P	0.452 (0.281, 0.615)	0.453 (0.258, 0.628)
π_R	0.181 (0.072, 0.297)	0.181 (0.067, 0.301)
$\pi_R - \pi_P$	-0.271 (-0.474, -0.062)	-0.272 (-0.482,-0.046)
OR_{esc}	0.297 (0.077, 0.744)	0.302 (0.073, 0.781)
α_t	-0.063 (-2.174, 2.164)	-0.230 (-1.908, 1.603)
ρ	N/A	-0.250 (-0.931, 0.826)

3. Conclusions and Discussions

When data from both before and after escape is available, utilizing all available data should improves the power of the study, which is particular important for small sample studies of rare diseases. In this study, we modeled data from both before and after escape phase. When examining treatment effect on both the primary and secondary outcomes, the analysis involves joint modeling of repeated measures of mixed bivariate outcomes:

binary (escape) and counts (number of attack) where two types of 'links' were used, one correlates the two subject-specific random effects of escape and event rate and the other correlates the treatment effects on the two outcomes. The model is able to incorporate other features of the design such as crossover and repeated measures. Here, we only considered non-informative priors for all model parameters, i.e., no information on whether the active treatment is better than the placebo *a priori*. Three different type of priors: non-informative, enthusiastic and skeptical, are recommended for Bayesian analyses of small sample size study (Spiegelhalter, Abrams et al. 2004).

Typically, analyses of early escape trial do not consider modeling data after escape, even when the data is available after escape. The ability to utilize all available information is particularly valuable for rare disease studies. We argue data after escape could provide useful information to assist better evaluation of treatment efficacy, and thus should be collected, and should be carefully considered in statistical analyses approach.

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