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Notes on estimation in Poisson frequency data under an incomplete block crossover design

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ABSTRACT

For comparison of two experimental treatments with a placebo under an incomplete block crossover design, we develop the weighted-least-squares estimator (WLSE) and the conditional maximum likelihood estimator (CMLE) of the relative treatment effects in Poisson frequency data. We further develop the interval estimator based on the WLSE, the interval estimator based on the CMLE, the interval estimator based on the conditional-likelihood-ratio test and the interval estimator based on the exact conditional distribution. Using Monte Carlo simulations, we find that all interval estimators developed here can perform well in a variety of situations. The exact interval estimator derived here can be especially of use when both the number of patients and the mean number of event occurrences are small in a trial. We use the data taken as part of a double-blind randomized crossover trial comparing salbutamol and salmeterol with a placebo with respect to the number of exacerbations in asthma patients to illustrate the use of these estimators.

1. Introduction

The crossover design has been often employed to reduce the number of patients needed for a parallel groups design when one studies a treatment for non-curable chronic diseases, including epilepsy, angina pectoris, asthma, etc [5,9,12,20,26,27,30,29]. The research on the crossover design has been intensive [3,5–11,14,15,17,18,13,16,19,21,22,24–28,31]. However, most of these

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publications have focused on discussions on the continuous data based on the normal assumptions or the binary data based on a random effects logistic risk model under the AB/BA crossover design. To reduce the number of patients assigned to receive the inert placebo, it can be sometimes desirable to compare more than one experimental treatment with a placebo in a single trial instead of separate trials, each having its own an experimental and a placebo arm. Note that the more treatments under comparison, the longer is the duration of a complete block crossover trial, and hence the more difficult is to recruit patients into a trial. Thus, we may consider use of an incomplete block design, in which each patient receives only a subset of treatments under investigation. For example, consider the double-blind placebo controlled crossover trial comparing two different doses of formoterol solution aerosol with a placebo (Senn [26, p. 213]) with respect to the forced expiratory volume in 1 s (FEV_1) (that is on a continuous scale). For practical reasons, it was decided that each patient could receive only two of these three treatments: the placebo, 12 μg or 24 μg of formoterol solution. In practice, we may encounter the frequency data, such as the number of seizures in epilepsy or the number of exacerbations in asthma [11,17,18,26,30,29]. Because these count data are discrete and are often skewed to the right, the normal assumptions can be seriously violated. Thus, statistical methods derived under the normality are probably inappropriate for use in frequency data. The discussion on estimation of the relative treatment effect in frequency data under an incomplete block design focused here is limited [10,26,28].

Assuming a random effects exponential multiplicative risk model, we derive the weighted-least-squares estimator (WLSE) [4] and the conditional maximum likelihood estimator (CMLE) for the relative treatment effect under an incomplete block crossover design in Poisson frequency data. We further derive the interval estimator based on the WLSE, the interval estimator based on the CMLE, the interval estimator based on the conditional likelihood ratio test and the interval estimators based on the exact conditional distribution. We employ Monte Carlo simulations to evaluate performance of these estimators in a variety of situations. Finally, we use the data taken as part of a crossover trial comparing salbutamol and salmeterol with a placebo with respect to the number of exacerbations in asthma patients [30,29] to illustrate the use of point and interval estimators developed here.

2. Notation, model assumptions and methods

Suppose that we compare two experimental treatments A and B with a placebo (P) under an incomplete block crossover design with two periods. Let the treatment-receipt sequence X–Y denote that a patient receives treatments X at period 1 and then cross over to receive treatment Y at period 2. Say, we randomly assign n_g patients to group g, where $g = 1$ denotes the treatment-receipt sequence P–A; $g = 2$ denotes the treatment-receipt sequence A–P; $g = 3$ denotes the treatment receipt sequence P–B; $g = 4$ the treatment-receipt sequence B–P; $g = 5$ denotes the treatment-receipt sequence A–B; and $g = 6$ denotes the treatment-receipt sequence B–A. For patient i $(= 1, 2, \ldots, n_g)$ assigned to group g $(= 1, 2, \ldots, 6)$, let $Y_{iz}^{(g)}$ denote the frequency of event occurrences at period z $(= 1, 2)$. Furthermore, let $X_{iz1}^{(g)}$ denote the indicator function of treatment-receipt for treatment A, and $X_{iz1}^{(g)} = 1$ if the corresponding patient at period z receives treatment A, and $= 0$, otherwise. Similarly, we let $X_{iz2}^{(g)}$ denote the indicator function of treatment-receipt for treatment B, and $X_{iz2}^{(g)} = 1$ if the corresponding patient at period z receives treatment B, and $= 0$, otherwise. We let $1_i^{(g)}(z = 2)$ represent the indicator functions of period by setting $1_i^{(g)}(z = 2) = 1$ for period $z = 2$, and $= 0$, otherwise. We assume with an adequate washout period that there is no carry-over effect due to the treatment administered at an earlier period on the patient response. If the assumption of no carry-over effect cannot be ensured on the basis of our subjective knowledge, as noted by Fleiss [5,6], Senn [25–27] as well as Schouten and Kester [24], we may not wish to consider use of the crossover design. We assume further that the random frequency $Y_{iz}^{(g)}$ of event occurrences on patient i $(= 1, 2, \ldots, n_g)$ assigned to group g $(= 1, 2, \ldots, 6)$ at period z $(= 1, 2)$ follows the Poisson distribution with mean that can be modeled as [11,18]

$$E(Y_{iz}^{(g)}) = \exp(\mu_i^{(g)} + \eta_{AP} X_{ix1}^{(g)} + \eta_{BP} X_{zt2}^{(g)} + \gamma 1_i^{(g)}(z = 2)), \tag{1}$$