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Test and estimation in binary data analysis under an incomplete block crossover design

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ABSTRACT

Under a random effects logistic regression model, we compare two experimental treatments with a placebo in dichotomous data under an incomplete block crossover trial. We develop procedures for testing non-equality of treatments, as well as interval estimators for the relative treatment effects. We employ Monte Carlo simulations to evaluate the performance of these test procedures and interval estimators in a variety of situations. Finally, we use the data taken as a part of the crossover trial that compared the low and high doses of an analgesic with a placebo for the relief of pain in primary dysmenorrhea to illustrate the use of these test procedures and estimators developed here.

1. Introduction

Because each patient serves as his/her own control, the crossover trial has been often used to improve power or reduce the number of patients needed for the parallel groups design when one studies non-curative treatments to chronic diseases, including angina pectoris, epilepsy, hypertension or asthma (Smith et al., 1985; Rhind et al., 1985; Fleiss, 1986; Hills and Armitage, 1979; Grizzle, 1965). To reduce the logistic supports, the length of duration and the risk of being lost to follow up in a crossover trial, however, we may consider assigning each patient to receive only a subset of treatments under comparison by use of an incomplete block design (Senn, 2002). For example, consider the double-blind placebo controlled crossover trial studying the effect of taking 12 and 24 μg of formoterol solution aerosol versus the placebo (Senn, 2002). For practical reasons, it was decided that each patient would receive only two of the three treatments: the placebo, 12 or 24 μg of formoterol solution. Senn (2002) focused attentions on continuous data and discussed methods to analyze this type of data. Although the research on crossover trials has been intensive (Fleiss, 1986; Hills and Armitage, 1979; Grizzle, 1965; Senn, 2002, 2006; Jones and Kenward, 1989), none of these publications discusses procedures for testing non-equality of treatments, as well as estimation of the relative treatment effects in dichotomous data under the incomplete block crossover trial.

Assuming a random effects logistic regression model, we focus discussion on testing non-equality between two experimental treatments and a placebo in dichotomous data when patients receive two of three treatments under an incomplete block two-period crossover trial. We develop test procedures in closed form based on the weighted-least-squares (WLS) method (Senn, 2002; Fleiss, 1981). We further develop interval estimators for the relative treatment effects.

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We employ Monte Carlo simulation to evaluate the performance of these test procedures and interval estimators in a variety of situations. Finally, we use the data taken as a part of the crossover trial comparing the low and high doses of an analgesic with a placebo for the relief of pain in primary dysmenorrhea (Jones and Kenward, 1987) to illustrate the use of test procedures and estimators developed here.

2. Notation, model assumptions and methods

Consider comparing two experimental treatments A and B with a placebo (P) under a cross-over design with two periods. Let X–Y denote the group with the treatment-receipt sequence in which a patient receives treatment X at the first period and then crossover to receive treatment Y at the second period. Suppose that we randomly assign n_g patients to group $g = 1$ with P–A treatment-receipt sequence; $= 2$ with A–P treatment-receipt sequence; $= 3$ with P–B treatment-receipt sequence; $= 4$ with B–P treatment-receipt sequence; $= 5$ with A–B treatment-receipt sequence; and $= 6$ with B–A treatment-receipt sequence. As commonly assumed for a crossover design, we assume that there is no carry-over effect due to the treatment administered at an earlier period with an adequate wash-out period. If the assumption of no carry-over effect cannot be ensured on the basis of our subjective knowledge, as noted by Fleiss (1986, 1989), Senn (1992, 2002) and Schouten and Kester (2010), we should not employ the crossover design. For patient i $(=1, 2, \ldots, n_g)$ assigned to group g $(=1, 2, 3, 4, 5, 6)$, we let $Y_{iz}^{(g)}$ denote the patient response at period z $(=1, 2)$, and $Y_{iz}^{(g)} = 1$ for positive; and $= 0$, otherwise. We assume further the probability of positive response $Y_{iz}^{(g)} = 1$ for patient i $(=1, 2, \ldots, n_g)$ assigned to group g $(=1, 2, 3, 4, 5, 6)$ at period z $(=1, 2)$ is given by the following random effects logistic regression model:

$$P(Y_{iz}^{(g)} = 1 | x_{iz1}^{(g)}, x_{iz2}^{(g)}, 1_{i1}^{(g)}) = \frac{\exp(s_i^{(g)} + \eta_{\mathrm{AP}} x_{iz1}^{(g)} + \eta_{\mathrm{BP}} x_{iz2}^{(g)} + \gamma 1_i^{(g)}(z = 2))}{1 + \exp(s_i^{(g)} + \eta_{\mathrm{AP}} x_{iz1}^{(g)} + \eta_{\mathrm{BP}} x_{iz2}^{(g)} + \gamma 1_i^{(g)}(z = 2))} \tag{1}$$

where $s_i^{(g)}$ denotes the random effect due to the ith patient assigned to group g and follows an unspecified probability density function $f_g(s)$; $X_{iz1}^{(g)}$ denotes the indicator function of treatment-receipt for treatment A, and $= 1$ if the patient at period z receives treatment A, and $= 0$, otherwise; $X_{iz2}^{(g)}$ denotes the indicator function of treatment-receipt for treatment B, and $= 1$ if the patient at period z receives treatment B, and $= 0$, otherwise; $1_i^{(g)}(z = 2)$ denotes the indicator function of period 2, and $= 1$ for period 2, and $= 0$, otherwise; η_{AP} and η_{BP} denote the respective effect of treatments A and B relative to the placebo, as well as γ represents the effect of period 2 versus period 1. Because we randomly assign patients to a group with various treatment-receipt sequences, we may assume that the probability density functions $f_g(s)$ are equal for all g and we let $f_0(s)$ denote these common probability density functions. On the basis of model (1), the OR of a positive response for a given fixed period on the same patient between treatment A and placebo is equal to $\varphi_{\mathrm{AP}} = \exp(\eta_{\mathrm{AP}})$. When there is no effect due to treatment A, $\varphi_{\mathrm{AP}} = 1$ (i.e., $\eta_{\mathrm{AP}} = 0$). When treatment A increases the probability of positive response, $\varphi_{\mathrm{AP}} > 1$. When treatment A decreases the probability of positive response, $\varphi_{\mathrm{AP}} < 1$. The OR of a positive response for a given fixed period on the same patient between treatment B and placebo is given by $\varphi_{\mathrm{BP}} = \exp(\eta_{\mathrm{BP}})$. Let $n_{rc}^{(g)}$ denote the number of patients in group g $(=1, 2, 3, 4, 5, 6)$ with the vector of response $(Y_{i1}^{(g)} = r, Y_{i2}^{(g)} = c)$, where $r = 1, 0$, $c = 1, 0$, among n_g patients. The random frequencies $\{n_{rc}^{(g)} | r = 1, 0, c = 1, 0\}$ then follow the quadrinomial distribution with parameters n_g and $\{\pi_{rc}^{(g)} | r = 1, 0, c = 1\}$, where $\pi_{rc}^{(g)}$ denotes the cell probability that a randomly selected patient i from group g has the vector of response $(Y_{i1}^{(g)} = r, Y_{i2}^{(g)} = c)$. We can estimate $\pi_{rc}^{(g)}$ by the unbiased consistent sample proportion estimator $\hat{\pi}_{rc}^{(g)} = n_{rc}^{(g)}/n_g$. As shown in the Appendix, we can express the OR of a positive response between treatment A and placebo for a fixed period on a given patient under model (1) in terms of $\pi_{rc}^{(g)}$'s as

$$\varphi_{\mathrm{AP}} = [(\pi_{01}^{(1)} \pi_{10}^{(2)})/(\pi_{10}^{(1)} \pi_{01}^{(2)})]^{1/2} \tag{2}$$

regardless of $f_0(s)$. Similarly, we can express the OR of a positive response between treatment B and a placebo for a fixed period on a given patient under model (1) in terms of $\pi_{rs}^{(g)}$'s as

$$\varphi_{\mathrm{BP}} = [(\pi_{01}^{(3)} \pi_{10}^{(4)})/(\pi_{10}^{(3)} \pi_{01}^{(4)})]^{1/2}. \tag{3}$$

Furthermore, we can show that the OR of a positive response between treatments B and A for a fixed period on a given patient under model (1) is equal to

$$\varphi_{\mathrm{BA}} (= \exp(\eta_{\mathrm{BP}} - \eta_{\mathrm{AP}})) = [(\pi_{01}^{(5)} \pi_{10}^{(6)})/(\pi_{10}^{(5)} \pi_{01}^{(6)})]^{1/2}. \tag{4}$$

When substituting $\hat{\pi}_{rc}^{(g)}$ for $\pi_{rc}^{(g)}$ in (2), we obtain the consistent estimator for $\eta_{\mathrm{AP}} (= \log(\varphi_{\mathrm{AP}}))$ as

$$\hat{\eta}_{\mathrm{AP}} = \left(\frac{1}{2}\right) \log((n_{01}^{(1)} n_{10}^{(2)})/(n_{10}^{(1)} n_{01}^{(2)})). \tag{5}$$