Computational Statistics and Data Analysis 80 (2014) 89–98

Contents lists available at ScienceDirect

Computational Statistics and Data Analysis

journal homepage: www.elsevier.com/locate/csda

# Notes on testing equality in binary data under a three period crossover design

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ARTICLE INFO

*Article history:*
Received 6 July 2013
Received in revised form 31 March 2014
Accepted 18 June 2014
Available online 25 June 2014

*Keywords:*
Binary data
Three-period
Crossover trial
Exact test
Random effects
Type I error

ABSTRACT

Under a random effects logistic regression model, asymptotic and exact test procedures in closed form for testing equality of binary responses are developed for comparing three treatments in a three-period crossover trial. Monte Carlo simulation is employed to evaluate the performance of these test procedures in a variety of situations. Interval estimators for the relative treatment effects are provided. The commonly-used procedures for testing the homogeneity of odds ratio (OR) is shown to be applicable for testing whether there is an interaction between treatments and periods. Finally, the data taken from a three-period crossover trial comparing two different doses of an analgesic with placebo for the relief of primary dysmenorrhea are used to illustrate the use the proposed test procedures and estimators.



## 1. Introduction

When studying treatments for non-curable chronic diseases, such as angina pectoris, epilepsy, hypertension or asthma, we may often consider use of the crossover design to improve power without recruiting additional patients into a trial (Smith et al., 1985; Rhind et al., 1985). This is because each patient serves as his/her own control and we can increase the efficiency of test procedures through reducing the variation of patient responses between treatments (Fleiss, 1986; Hills and Armitage, 1979; Senn, 2002). However, if the treatment being evaluated has a long-lasting effect, the crossover design will not be appropriate, because the effect of a treatment administered at the latter period can be confounded with the residual effects of the treatment administered at the earlier period. To alleviate this concern of carry-over effect, one commonly applies an adequate washout period between administering treatments to assure that patients are weaned off the effects of earlier treatments. Research on crossover trial has been actually extensive. Senn (2002, 2006) provided an excellent review of the literature on crossover designs. Based on a fixed effects logistic regression model (Cox and Snell, 1989), Gart (1969) discussed testing equality of two treatment effects and developed an exact test procedure. Using the linear additive risk model (LARM) proposed by Grizzle (1965) and Zimmermann and Rahlfs (1978) discussed testing equality in patient response rates under a two-period crossover design. For the simple crossover design, Ezzet and Whitehead (1992) proposed a random effects logistic regression model with assuming random effects to follow a normal distribution and discussed estimation of treatment and period effects. Schouten and Kester (2010) also used the LARM to develop tests and sample size calculation for dichotomous data in a simple crossover design. Recently, Lui and Chang (2011) have discussed

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http://dx.doi.org/10.1016/j.csda.2014.06.015
0167-9473/

**Table 1**
Frequency of patients with response pattern ($Y_{i1}^{(g)} = r, Y_{i2}^{(g)} = s, Y_{i3}^{(g)} = t$), where $r, s$ and $t = 1$ for relief, $= 0$ otherwise, at the three periods in group $g(=1, 2, 3, 4, 5, 6)$ distinguished by different treatment-receipt sequences.

| | Response pattern ($Y_{i1}^{(g)} = r, Y_{i2}^{(g)} = s, Y_{i3}^{(g)} = t$) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (1, 1, 1) | (1, 1, 0) | (1, 0, 1) | (0, 1, 1) | (1, 0, 0) | (0, 1, 0) | (0, 0, 1) | (0, 0, 0) |
| P–A–B ($g = 1$) | 1 | 1 | 0 | 9 | 0 | 2 | 2 | 0 |
| P–B–A ($g = 2$) | 4 | 0 | 0 | 9 | 1 | 0 | 0 | 2 |
| A–P–B ($g = 3$) | 1 | 0 | 8 | 3 | 1 | 1 | 1 | 0 |
| A–B–P ($g = 4$) | 1 | 8 | 0 | 0 | 1 | 1 | 1 | 0 |
| B–P–A ($g = 5$) | 1 | 1 | 7 | 2 | 0 | 0 | 0 | 3 |
| B–A–P ($g = 6$) | 0 | 4 | 3 | 1 | 5 | 0 | 0 | 1 |

A: lower dose of the analgesic.
B: higher dose of the analgesic.
P: Placebo.

testing both non-inferiority and equivalence with respect to the odds ratio (OR) under a simple crossover trial. All of these papers concentrated attention on comparison of two treatments under a two-period crossover trial. As noted by Jones and Kenward (1987), it is not uncommon to encounter trials with more than two treatments and more than two periods. For example, consider the three-period crossover trial comparing two different doses of an analgesic with a placebo for the relief of primary dysmenorrhea in dichotomous responses (Jones and Kenward, 1987). We summarize in Table 1 the data published elsewhere (Jones and Kenward, 1987). Note that the responses taken from the same patient over three periods are likely correlated and there can be period effects on the patient response. Thus, it would not be appropriate if we did not account for the intraclass correlation between responses within subjects and the period effect on patient responses in data analysis. Except for assuming a specific structural dependence between responses at the three periods (Jones and Kenward, 1987), the research on comparing three treatments over a three-period crossover trial in binary responses is limited.

In this paper, we propose a random effects logistic regression model for testing equality between treatments in dichotomous responses under a three-period crossover trial. We derive both the asymptotic and exact test procedures in closed forms for testing equality between treatments. We employ Monte Carlo simulation to evaluate the performance of these test procedures. We provide interval estimators for the relative treatment effects. We further show that test procedures for testing the homogeneity of OR can also be used to examine whether there is an interaction between treatments and periods. Finally, we use the data (Table 1) taken from a trial comparing two different doses of an analgesic with a placebo for the relief of primary dysmenorrhea (Jones and Kenward, 1987) to illustrate the use the proposed test procedures and interval estimators.

## 2. Notation, model assumptions and methods

Consider comparing two experimental treatments A and B with a placebo (P) in a three-period crossover design. For clarity, we use the treatment-receipt sequence $X$–$Y$–$Z$ to denote that a patient receives treatments $X$, $Y$ and $Z$ at periods 1, 2 and 3, respectively. Suppose that we randomly assign $n_g$ patients to group $g = 1$ with P–A–B treatment-receipt sequence; $= 2$ with P–B–A treatment-receipt sequence; $= 3$ with A–P–B treatment receipt sequence; $= 4$ with A–B–P treatment-receipt sequence; $= 5$ with B–P–A treatment-receipt sequence; and $= 6$ with B–A–P treatment-receipt sequence. As commonly assumed for a crossover design, 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 this assumption of no carry-over effect cannot be ensured on the basis of our subjective knowledge, as noted by Fleiss (1986, 1989), Senn (2002) and Schouten and Kester (2010), we may not want to consider using the crossover design. For patient $i(=1, 2, \ldots, n_g)$ assigned to group $g(=1, 2, 3, 4, 5, 6)$, let $Y_{iz}^{(g)}$ denote the binary outcome at period $z(=1, 2, 3)$, setting $Y_{iz}^{(g)} = 1$ for a positive response, and $= 0$, otherwise. Let $X_{iz1}^{(g)} = 1$ if patient $i$ in group $g$ at period $z$ receives treatment A, and $= 0$, otherwise. Similarly, let $X_{iz2}^{(g)} = 1$ if patient $i$ in group $g$ at period $z$ receives treatment B, and $= 0$, otherwise. We further let $1_{i1}^{(g)}$ and $1_{i2}^{(g)}$ represent the indicator functions of period covariates, defining $1_{i1}^{(g)} = 1$ for period $z = 2$, and $= 0$, otherwise; as well as $1_{i2}^{(g)} = 1$ for period $z = 3$, and $= 0$, otherwise. We assume that the probability of a positive response for patient $i$ in group $g$ at period $z$ is given by the following random effects logistic regression model:

$$P(Y_{iz}^{(g)} = 1 | x_{iz1}^{(g)}, x_{iz2}^{(g)}, 1_{i1}^{(g)}, 1_{i2}^{(g)}) = \frac{\exp(\mu_i^{(g)} + u + \eta_1 x_{iz1}^{(g)} + \eta_2 x_{iz2}^{(g)} + \gamma_1 1_{i1}^{(g)} + \gamma_2 1_{i2}^{(g)})}{1 + \exp(\mu_i^{(g)} + u + \eta_1 x_{iz1}^{(g)} + \eta_2 x_{iz2}^{(g)} + \gamma_1 1_{i1}^{(g)} + \gamma_2 1_{i2}^{(g)})}, \quad (1)$$

where $\mu_i^{(g)}$ denotes the random effect due to the $i$th patient in group $g$ and follows an unspecified probability density function $f_g(\mu)$, $u$ denotes the intercept, $\eta_1$ and $\eta_2$ denote the respective effect of treatments A and B relative to the placebo, as well as $\gamma_1$ and $\gamma_2$ represent the respective effect of periods 2 and 3 versus period 1. Since we do not assume that the random effect $\mu_i^{(g)}$ follows any specified probability density function, our methods can be regarded as a semi-parametric approach.