Heteroscedasticity of Random Effects in Crossover Design

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Abstract

A phase III clinical trial of a new drug for neutropenia induced by chemotherapy is presented and consider adding random effects in crossover design which was used in the clinical study. The diagnostics for its heteroscedasticity based on score statistic is derived for detecting homoscedasticity of errors in crossover design. A small simulation study is performed to investigate the finite sample behaviour of the test statistic which is known to have an asymptotic chi-square distribution under the null hypothesis.

Keywords: crossover, clinical study, score test, constant variance

1. Introduction

A pharmaceutical company developed a new drug using recombinant DNA technology to reduce chemotherapy-related neutropenia. The phase III clinical trial was conducted to investigate the effectiveness and safety of this drug. It was compared with the active control drug. The eligible patients were those with progressive solid tumor who were supposed to receive chemotherapy, those with a performance status of 0 to 2 as defined by ECOG, and those with a standard criteria for renal, hepatic, and hematologic status and no other serious medical illness. The following is the chracterisitcs of patients.

Gender	AB	BA	n	(%)
male	18	18	36	(56)
female	17	11	28	(44)
	35	29	64	

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Age	AB	BA
mean±sd	50.83 ± 12.17	52.38 ±14.18
min-max	29 - 73	22 - 73

2. Crossover Design

The patients were crossed over from treatment with Leucogreen(A) to Gracin(B) or B to A. 88 patients were randomly assigned to one of two sequences - AB or BA: There were two cycles.

	cycle 1		cycle 2
AB:	chemo/A/out1	wash-out	chemo/B/out2
BA:	chemo/B/out1	wash-out	chemo/A/out2

The individual reactions to treatment would be affected by the amount of chemotherapy each patients have received. The large variability between patients can be eliminated by crossover design - each patient forms his or her own control. The problems is how to avoid carryover.

The null hypothesis of no carry-over effects was accepted (P-value > 0.05), and it was concluded that the carry-over effects are the same. If different, the observations in cycle 2 are useless. The null hypothesis of no treatment effects was also accepted (P-value > 0.05).

The non-inferiority was demonstrated: The observed success rate in TRT A was 71.87% and the observed success rate in TRT B was 70.31% with the difference, 1.56%. The 95% CI was (-9.45%, 12.57%) with D=20%.

The logistic regression was used to see if there is any treatment effect for neutropenia incidence. There was no signicant differences (p-value>0.05).

3. Random Effects in Crossover Design

Now we consider adding the random effects in crossover design as follows:

$$Y_{ijk} = \alpha_{ik} + s_{ij} + \varepsilon_{ijk}$$

α_{ik} is an effect due to sequence i and period k (i=1,..,I, k=1,..,n), and s_{ij} is an effect due to subject j which may be treated as random (j=1,·,J). The large variability between patients leads to the expanded model for the variance of s_{ij}.

$$var(s_{ij}) = \sigma_s^2 w(z_{ij}, \lambda)$$

z_{ij} is a known vector for sequence i and subject j, and λ is a vector of unknown parameters. $w(z_{ij}, \lambda)$ is twice differentiable w.r.t λ, and there is a unique value λ_o of λ which recovers constant variance. The score statistic, S was derived to test whether $\lambda = \lambda_o$.

4. Simulation Study

The simulation study was conducted to investigate the chi-square approximation to the null distribution of both score statistic, S and the log-likelihood ratio statistic, W. A 80 x 3 matrix with all entries generated from N(0,1) was prepared for the matrix, **X**. The another setting was J={5, 10, 20}, i=2, n=2, and 499 replications. Since the closed form solution for the m.l.e.'s are not available, we compute them numerically.

Table 1. Simulated percentage points from the small-sample null distribution of S (W): dim(λ)=1

Level	J=5	J=10	J=20	
0.90	1.74 (2.57)	2.39 (3.04)	2.58 (3.03)	2.71
0.95	2.10 (3.31)	3.35 (4.45)	3.74 (4.04)	3.84
0.975	2.38 (3.90)	4.36 (5.80)	5.03 (5.23)	5.02
0.99	2.81 (4.76)	5.56 (7.97)	7.06 (6.32)	6.63

Table 2. Simulated percentage points from the small-sample null distribution of S (W):dim(λ)=2

Level	J=5	J=10	J=20	
0.90	2.70 (3.78)	3.70 (4.56)	4.48 (4.69)	4.60
0.95	3.30 (4.39)	4.90 (5.62)	5.64 (5.88)	5.99
0.975	3.74 (5.37)	6.13 (6.96)	7.11 (6.74)	7.38
0.99	4.01 (6.77)	7.56 (8.27)	10.1 (9.19)	9.22

Table 3. Simulated percentage points from the small-sample null distribution of S (W): dim(λ)=3

Level	J=5	J=10	J=20	
0.90	3.56 (4.61)	5.26 (5.68)	5.77 (6.13)	6.25
0.95	3.85 (5.33)	6.97 (7.16)	6.93 (7.18)	7.82
0.975	4.16 (6.14)	8.72 (8.19)	8.04 (8.80)	9.35
0.99	4.51 (6.91)	9.73 (10.3)	10.4 (10.2)	11.3

5. Conclusion

The crossover design was useful in determining whether a new drug can reduce the incidence of neutropenia, and perform as effective as the standard drug. The random effects model may be useful if there is large variability between subjects in crossover design. Simulation supports the asymptotic behavior of two test statistics, S and W. The use of the chi-square approximation for small sample leads to a conservative test. S is more conservative than W, but easier to compute. S not only checks the assumption of constant variance, but also suggests a possible cause of heteroscedasticity.

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