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Notes on Crossover Design

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Introduction

When studying treatments for non-curable chronic diseases, including asthma, angina pectoris, hypertension, epilepsy, migraine etc., the crossover design, in which each eligible patient is randomly assigned to receive more than one treatment according to a pre-determined treatment sequence, has been often proposed to improve power or save the number of patients needed for a parallel groups design [1,2]. This is because each patient serves as his/her own control in a crossover trial and thereby, we can eliminate the variation of responses between patients when comparing treatments. The simplest crossover design is the AB/BA design, in which patients are randomly assigned to either the AB group in which patients receive treatment A first and then crossover to receive treatment B, or the BA group in which patients receive treatment B first and then crossover to receive treatment A. Because of its simplicity, the AB/BA design, also called the simple crossover or 2 x 2 design [3], has accounted for a large proportion of crossover trials used in practice [1,4-6]. Although the crossover design is of use, there are limitations due to its design features.

Treatments with Rapid and Short Effects

The duration of a crossover design is expected to be longer than that of a parallel groups design, because patients receive more than one treatment. The longer the duration of a trial, the higher is the probability that participated patients can discontinue treatments prematurely or be lost to follow up. Thus, the crossover design should generally reserve for treatments with a rapid, short and reversible effect, which can be quickly measured.

Carry-Over Effects

One major concern in crossover data analysis is the carry-over effect, which is the residual effect due to earlier treatments on the latter patient responses. The carry-over effects can occur due to (1) a treatment effect may carry over from one period to the next period physically or psychologically; or (2) a treatment effect may vary according to the level of patient response [3,4]. If there are carry-over effects, our assessment of the relative treatment effect can be biased if we cannot adequately adjust the carry-over effects. However, it can be challenging to disentangle the treatment effect from the residual effects of earlier treatments. Although there are numerous publications addressing models to account for the carry-over effect [7-13], as noted elsewhere [1,2,14-17], most of these models are assumed for mathematical interests and convenience. Furthermore, accounting for the carry-over effects can often cause a substantial loss of efficiency in estimation of the relative treatment effect [1]. Under the most commonly-used the AB/BA design, [18] noted that adjusting the carry-over effect is equivalent to exclude all data obtained at the second period. The advantage of use the crossover design instead of the parallel groups design to gain efficiency would be completely gone in this case. Thus, we may not wish to employ the crossover design if one cannot ensure based on his/her best clinical knowledge to nullify the carry-over effects with an adequate washout period [14,16].

Random Effects Models and Estimation

When modeling the data under a crossover design, we need to consider two important factors -- the responses taken from the same patients are likely correlated and period effects on patient responses probably exist. We commonly include in models terms representing random effects due to patients to create a positive intra class correlation between responses within patients. We further assume that these random effects follow a normal distribution and derive the maximum likelihood estimator (MLE) on the basis of the marginal likelihood (which is involved with non-closed form integrals). Although we may employ now *Proc Glimmix* in SAS [19] to avoid writing our own sophisticated iterative numerical procedures for obtaining the MLE, the normal assumption for these random effects is somewhat arbitrary and is difficult to justify. The conditional distribution approach, which does not require patient random effects to follow any specified parametric distribution recently proposed by [20], can alleviate this concern.

Small Trial Size and Exact Methods

Since the main motivation of using a crossover design is to save the number of patients needed for a parallel groups design, a crossover trial is frequently of a small size [6]. Thus, it is essentially important that we can develop exact test procedures and exact interval estimators of the relative treatment effect for a crossover design. Statistical methods (including the MLE) derived from large sample theory may not be theoretically appropriate when the number of patients is in a trial is small. The recent development of exact tests and exact interval estimators in both categorical and frequency data can be especially of use [20-27].

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