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General Practice

Understanding controlled trials Crossover trials

This is the fifth of an occasional series on the methods of randomised controlled trials

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In a crossover trial subjects are randomly allocated to study arms where each arm consists of a sequence of two or more treatments given consecutively. The simplest model is the AB/BA study. Subjects allocated to the AB study arm receive treatment A first, followed by treatment B, and vice versa in the BA arm. Crossover trials allow the response of a subject to treatment A to be contrasted with the same subject's response to treatment B. Removing patient variation in this way makes crossover trials potentially more efficient than similar sized, parallel group trials in which each subject is exposed to only one treatment. In theory treatment effects can be estimated with greater precision given the same number of subjects.

Crossover trials are generally restricted to the study of short term outcomes in chronic diseases or processes because the disease or process needs to persist long enough for the investigator to expose the subject to each of the experimental treatments and measure the response. Also the treatment must be one that does not permanently alter the disease or process under study.

The principal drawback of the crossover trial is that the effects of one treatment may "carry over" and alter the response to subsequent treatments. The usual approach to preventing this is to introduce a washout (no treatment) period between consecutive treatments which is long enough to allow the effects of a treatment to wear off. A variation is to restrict outcome measurement to the latter part of each treatment period. Investigators then need to understand the likely duration of action of a given treatment and its potential for interaction with other treatments.

For example, Chisholm et al used a crossover design to examine the effects of replacing butter with margarine on the lipoprotein profile of subjects with hypercholesterolaemia.[1] Patients were randomised to a six week butter diet followed by a six week margarine diet, or the reverse sequence. Treatment periods were separated by five weeks' washout in which patients returned to their usual diet. The impact on lipoprotein profiles was measured from blood specimens taken in the last week of each experimental period. The assumptions are that six weeks is long enough for an experimental diet to affect lipoprotein profile and that five weeks is long enough for the effects to dissipate.

In the analysis of crossover trials it is conventional to pretest the data for evidence of carry over. If carry over is present the outcome on a given treatment will vary according to its position in the sequence of treatments. This approach is based on the questionable assumption that no carry over is present when a statistical test fails to find one. For example, Chisholm et al's hypercholesterolaemia study concluded that there was no carry over when an analysis of variance found no statistically significant interaction between treatment sequence and outcome.[1] However such tests have limited power and cannot rule out a type II error (wrongly concluding there is no carry over effect).[2]

If carry over is detected convention suggests this may be dealt with in the analysis in one of two ways. The usual approach is to treat the study as though it were a parallel group trial and confine analysis to the first period alone. The advantages of the crossover are lost, with the wasted expense of discarding the data from the second period. More importantly, the significance test comparing the first periods may be invalid.[3] A second approach, applicable only to studies with at least three treatment periods (ABB/BAA), is

to model the carry over effect and use it to adjust the treatment estimate. Such approaches, while statistically elegant, are based on assumptions which can rarely be justified in practice.[2]

The best advice is therefore to avoid using a crossover design if there is any good reason to suppose that carry over effects are likely to occur. A readable approach to the problems of designing and analysing crossover trials is provided by Senn.[2]

References

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