Chapter 9
Cross-over Trials

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Description

In a cross-over trial, each study participant serves as their own control. Although non-randomized cross-over trials can be conducted, it is preferable to randomly assign treatments. Let us assume that it is desired to compare two treatments *A* (control) and *B* (experimental) in a cross-over trial. In a non-randomized cross-over, all participants may receive treatment *A* first and then treatment *B*. In a randomized cross-over trial, all participants would receive both treatments in sequence, but the sequence order is randomized. Thus, half would receive treatment *A* followed by treatment *B* and half would receive treatment *B* followed by treatment *A*. Figure 9.1 shows the design layout for such a trial.

A full cross-over design would assign each participant to receive all treatments in a randomly selected order. Here the number of trial periods would equal the number of treatments being evaluated in the trial. An incomplete cross-over design would randomly assign participants to a sequence of treatments, but they would not receive all treatments. Thus, a 3-group 2-period cross-over design, as illustrated in Fig. 9.2, would be considered an incomplete design.

Advantages of Cross-over Designs

Cross-over trials have two advantages over parallel-group trials. The first is that precision is increased, which generally results in a reduction in the required sample size. The gain in precision is due to two factors. Since each patient serves as their

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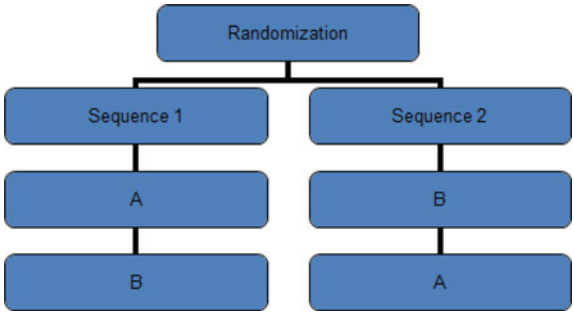

Fig. 9.1 Standard 2-group 2-period cross-over design

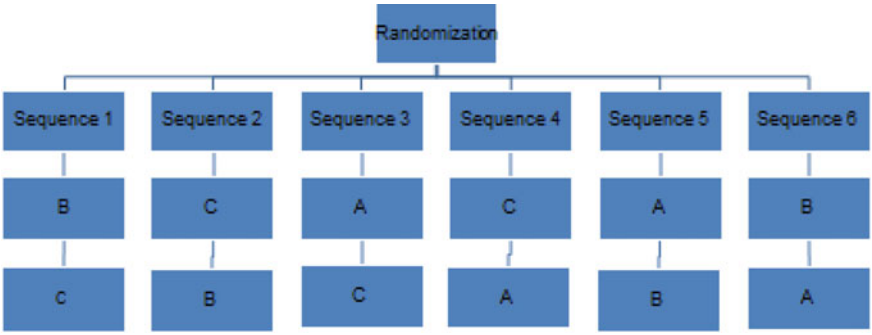

Fig. 9.2 Incomplete cross-over design 3 treatments, 2 periods

own control, then the sample size is reduced by 50%, albeit at the expense of a longer trial since participants must complete all rounds of treatment before they exit the trial.

In addition, since pre- and post-treatment responses tend to be correlated, the magnitude of the correlation will reduce the sample size requirement further.

As an example, Dunbar et al. [1] conducted a single-site randomized double-blind cross-over trial to determine if confocal laser endomicroscopy with optical biopsy and targeted mucosal biopsy (CLE-TB) improves the diagnostic yield of endoscopically inapparent Barrett's Esophagus (BE)-associated neoplasia compared to standard endoscopy with a 4-quadrant random biopsy (SE-RB) protocol.

Patients with biopsy-proven BE or biopsy-proven BE with suspected non-localized, endoscopically inapparent high-grade dysplasia (HGD) were randomly assigned to receive standard endoscopy first and CLE with TB 2–6 weeks later or to receive the two procedures in the reverse sequence. At the end of the second endoscopic procedure, the study co-investigator was allowed to unblind the endoscopist and disclose the prior pathologic diagnoses and the location of any

areas of biopsy-proven HGD. An endoscopic mucosal resection could be performed at that time if a mucosal lesion was highly suspicious for HGD or early cancer.

To obtain the target sample size, the expected yield for neoplasia of standard endoscopy with a four-quadrant random biopsy (SE-RB) protocol was estimated to be 10% and the neoplasia yield for CLE-TB was estimated to be 40%. Using an alpha of 0.05 and power of 90%, 37 patients were needed using a paired design. If this had been designed as a parallel-group trial, the target sample size would have been 47 per treatment group, or 94 in total.

The diagnostic yield for neoplasia with CLE-TB was 33.7% (95% CI 15.2–52.2%), while the diagnostic yield for neoplasia during SE-RB was 17.2% (95% CI 6.2–28.2%).

The other advantage of cross-over designs is that it may enhance recruitment to the trial, especially when one of the treatment groups is placebo. A cross-over design guarantees that all participants will receive an active treatment some time during their participation in the trial.

Period Effects

Because each person serves as their own control, one potential problem with interpretation of results in a cross-over trial is the potential for responses to change over time, independent of the treatment given. For example, if a medical condition has a seasonal component, the difference in effect from the first treatment to the second could be due to a period effect rather than a true difference in effectiveness of the two treatments. When the order of receiving the treatments is randomly assigned, for example when half the patients receive treatment *A* in the first period and half receive treatment *A* in the second period, then the period effects are balanced by the random assignment of treatment sequence.

Carry-over Effects

Another potential problem is the carry-over effect. If treatment *A* has some residual effect after the participant stops receiving treatment *A* and then the participant immediately receives treatment *B*, the residual effect of treatment *A* cannot be separated from the effect of treatment *B*. In this instance, random assignment of the order of receiving the treatments may not resolve the issue. It is possible that the length and magnitude of residual effects differs among different treatments. If treatment *B* has no residual effect, but treatment *A* does, then the group that receives *A* second will not have their response to *A* affected by the earlier treatment *B*, while those who receive treatment *B* second will have their response to *B* affected by the carry-over effect of *A*.

Wash-out

One strategy to address the problem of carry-over effects is to incorporate a wash-out period in between treatments. Of course, the wash-out period needs to be long enough to allow wash-out of any of the potential treatments.

Drop-Outs

As suggested earlier, if a participant leaves a trial early, then the effect of the missing data has a greater impact than when a participant leaves a parallel-group trial early. In a cross-over trial, data collected for the participant for any of the treatments they received before leaving the study have limited utility since the design is dependent on each participant serving as their own control.

Analysis

The problems with carry-over effects and drop-outs can be seen in the following statistical model for a 2-group 2-period cross-over trial. Assume the following parameters for the model:

$\pi =$ the period effect: the expected secular difference between period 2 and period 1

$\tau =$ the treatment effect: the expected difference due to treatment between treatments A and B

$\lambda_a =$ carry-over due to treatment A

$\lambda_B =$ carry-over due to treatment B

$\mu_i =$ effect due to patient i: the response we should expect of patient i were we to treat the patient in period 1 with B

In the presence of cross-over, the model can be expressed in the following 2 by 2 box:

	Expected Response	
Group	Period 1	Period 2
AB	$\mu_j + \tau$	$\mu_j + \pi + \lambda_A$
BA	μ_K	$\mu_K + \pi + \tau + \lambda_B$

It can be shown that in the presence of carry-over effects the model cannot be solved for the treatment effects. When carry-over effect can be ignored, the responses can be modeled as follows:

	Expected Response	
Group	Period 1	Period 2
AB	$\mu_j + \tau$	$\mu_j + \pi$
BA	μ_K	$\mu_K + \pi + \tau$

Now the treatment effects of A and B can be estimated. As an alternative, the mixed-effects model, a flexible statistical model often used for the analysis of longitudinal data, can be used to estimate carry-over effects [2].

When the outcome measure is continuous, then repeated measures analysis of variance can be used. For a binary outcome measure, such as complication within 30 days of the procedure (yes, no), then a more sophisticated form of repeated measures analysis using generalized estimating equations (GEE) can be used. For studies where the outcome measure is survival or some other time to event outcome, survival analysis methods are not useful because once a participant has an event (such as mortality) before all treatments have been received, there is no opportunity to observe the event again on the remaining treatments.

When a Cross-over Design Is Not Useful

Thus, cross-over designs have important limitations that limit their utility in trials of procedures, especially invasive procedures. Cross-over trials are not useful when one or more of the treatments will result in a permanent change to the participant, such as curing the condition. Similarly, cross-over designs are generally not useful for acute conditions because of the potential that the condition may resolve before the participant completes the full sequence of treatments, such as influenza. Finally, any medical condition or treatment that carries a significant likelihood that the patient will be unable to continue in the trial is not suitable for a cross-over trial.

Example: The NIDCD/VA Hearing Aid Trial

One example of a trial for which the medical condition and the treatments being evaluated was suitable for a cross-over design was the VA/NIDCD Hearing Aid Trial [3]. The objective of the trial was to compare the benefits provided to patients with sensorineural hearing loss of 3 commonly used hearing aid circuits. It was designed as a 3-period, 3-treatment cross-over trial. The study was conducted at eight audiology laboratories in Department of Veterans Affairs medical centers across the USA in a sample of 360 patients with bilateral sensorineural hearing loss.

Patients were randomly assigned to 1 of 6 sequences of linear peak clipper (PC), compression limiter (CL), and wide dynamic range compressor (WDRC) hearing aid circuits. All patients wore each of the 3 hearing aids, which were installed in identical casements, for 3 months. Thus, the trial was double-blind.

Outcome measures included results of tests of speech recognition, sound quality, and subjective hearing aid benefit, administered at baseline and after each 3-month intervention with and without a hearing aid. At the end of the experiment, patients ranked the 3 hearing aid circuits.

The investigators concluded that each circuit provided significant benefit in quiet and noisy listening situations. The CL and WDRC circuits appeared to provide superior benefits compared with the PC, although the differences between them were much less than the differences between the aided and unaided conditions.

Note that this trial was a nearly ideal setting in which to conduct a cross-over trial. Sensorineural hearing loss is a chronic condition that changes very slowly over time, especially during the nine-month treatment period (3 months per device) for each patient. Thus, period effects were not expected. In addition, the effect of wearing a hearing aid was not expected to change the participant's unaided hearing acuity. Thus, no carry-over effects were expected. Finally, the withdrawal rate was expected to be low given the nature of the condition and the treatments.

Example: Epinephrine and Thoracic Epidural Anesthesia

Niemi and Breivik conducted a double-blind randomized cross-over trial in 12 participants that assessed the effectiveness of epinephrine combined with a small-dose infusion of ropivacaine and fentanyl after major thoracic or abdominal surgery [4].

Patients scheduled for major thoracic or upper abdominal surgery were selected for the study. After titration to optimal epidural analgesia with a triple component mixture on the day of surgery, patients were randomly allocated to receive one of the two trial epidural analgesic mixtures on the first postoperative day and the alternative epidural mixture on the second postoperative day.

Patients were excluded if they had any contraindications to insertion of an epidural catheter, such as infection, anatomical abnormalities of the spine, or full anticoagulation. Also excluded were patients with incomplete or unstable analgesia caused by technical epidural catheter problems, including epidural catheter insertions that were too high or too low.

Before the induction of general anesthesia, an epidural catheter was inserted at an appropriate level between the 6th and 12th thoracic interspace, depending on the site of surgery. All patients received a standard anesthesia protocol during surgery and a standard epidural infusion post surgery. The patients were allowed to self-administer one 4-mL bolus of the epidural analgesic mixture, up to twice per hour. All patients received rectal acetaminophen 1 g, every sixth hour.

For each patient, two coded 100-mL plastic bags containing ropivacaine 1 mg/mL and fentanyl 2 μg/mL, with and without epinephrine 2 μg/mL, were prepared by the hospital pharmacy. At 8:00 am on the first postoperative day, the epidural infusion was changed, as determined by the randomization procedure, from the triple mixture to one of the two coded epidural mixtures. This was infused at the same rate as the triple epidural mixture for up to 3 h, or for as long as the patient could tolerate any increased pain after receiving the predetermined rescue medication. At this time, the epidural infusion was changed back to the ropivacaine–fentanyl–epinephrine mixture, a bolus of 5 mL was given, and the infusion continued at the same rate as before the blinded study period started. The patients were observed for another 5 h for pain intensity and side effects. On the second postoperative day at 8:00 am, if the patient still had optimal analgesia with the same infusion rate of the ropivacaine–fentanyl–epinephrine epidural mixture, the study was repeated with the alternative, coded epidural mixture.

Whenever the patients were dissatisfied with pain relief, they were allowed to self-administer one 4-mL bolus of the epidural analgesic mixture infused at the time, up to twice per hour. When pain intensity increased to severe pain when coughing, despite the epidural bolus doses, morphine 1–5 mg was added and titrated intravenously by one of the investigators. If pain when coughing remained severe, the epidural infusion was changed back to the unblinded epidural infusion with epinephrine. The amounts of epidural mixture actually administered and any IV morphine were recorded hourly.

For pain at rest and when coughing, pain intensity remained low and unchanged during the blinded test period with epinephrine. Without epinephrine and as soon as after 2 h, there was a highly significant difference in pain intensity from baseline ($P < 0.001$) and between the periods with and without epinephrine ($P < 0.001$). This difference increased as long as the mixture without epinephrine was infused. When the epidural infusion was changed back to the mixture with epinephrine, the pain intensity decreased within the next 15 min so that after 1 h there was no difference in pain intensity compared with baseline.

Conclusion

Cross-over trials are generally not an acceptable design for trials of procedures, especially invasive procedures and those that will result in a permanent change in the participant's medical condition. However, because of their efficiency, they can be useful when the assumptions that allow a cross-over design are met. They may be useful for trials in surgical patients where an aspect of care is being evaluated, such as choice of anesthesia regimen.

References

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