Three-factor designs unable to examine the interactions (Part 1)

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ABSTRACT: Three-factor designs that are unable to examine the interactions include crossover design and Latin square design, which can examine three factors, namely, an experimental factor and two block factors. Although the two design types are not quite frequently used in practical research, an unexpected research effect will be achieved if they are correctly adopted on appropriate occasions. Due to the limit of space, this article introduces two forms of crossover design.

KEYWORDS: statistics, medical; research design; factor analysis, statistical

Crossover design and Latin square design are two special design types, which are able to examine three factors, including one experimental factor and two block factors. The crossover design has three forms, namely, two-period crossover design, three-period crossover design and $3 \times 3$ crossover design. The first two design types are usually adopted to solve research problems which aim to examine a two-level experimental factor and two block factors. The third design type is used to solve research problems which have a three-level experimental factor and two block factors. The Latin square design can be seen as the extension of the random block design due to the fact that it examines one more block factors than the random block design. It also requires that the three factors involved in the research have no interactions, and the levels of the three factors are required to be equal. Due to the limit of space, this article will introduce the first two forms of crossover design.

1 Two-period crossover design

1.1 Example 1 A study aimed to investigate the efficacy of a traditional Chinese medicine compound A in enhancing working capacity at plateau by using placebo as the control. Ten healthy people in similar conditions were recruited as the research subjects. Each subject received the two drugs once at two different time points (winter and spring). Two subjects in the most similar conditions were paired, and the researcher randomly decided the order in which one of the pair received the drugs and let the other of the pair receive the drugs in the opposite order. Research subjects and time points were regarded as two important non-experimental factors that can not be ignored. Table 1 listed the design form and the result. The observational index was PWC170\cite{11}. Question: which design should the research adopt?
In example 1, the experimental factor is "drugs", which has two levels: A (traditional Chinese medicine compound) and B (the placebo); the two block factors are "experimental time" (winter and spring) and "research subjects" (individual difference). The observational index is "PWC170". Since the subjects were paired and each subject received the two drugs once at two time points, example 1 belongs to the paired two-period crossover design.

If the ten subjects are equally divided into two groups, and the researcher randomly decides the order in which one group receives the two drugs (for example, AB), and let the other group receive the two drugs in the opposite order (for example, BA), it belongs to the two-period crossover design of two groups.

1.2 Definition When the research design involves a two-level experimental factor and the specialty requires both levels to be conducted on each research subject, the crossover design can be adopted. If the research subjects are paired by similar conditions and the two subjects in each pair receive two levels of the experimental factor in an opposite order, it is called the paired two-period crossover design; if the research subjects are divided into two groups, it is called the two-period crossover design of two groups. The two-period crossover design can also be called $2 \times 2$ crossover design.

1.3 Characteristics of the design The crossover design is able to examine the influence of a two-level experimental factor and two block factors (individual difference and order) on the result. The influence of the order in which the two levels of the experimental factor are conducted on each research subject is dynamically balanced. Both the experimental factor and the order have two levels, and the number of the research subjects is required to be even so that they can be paired or equally divided into two groups.

The crossover design requires a washout period between the two periods in which the two levels of the experimental factor are conducted on each research subject. The washout period means an interval of time to eliminate the remaining influence of the former treatment. Because the individual difference is viewed as a block factor, the influence of the two levels of the experimental factor on the observational index must be transient, meaning that before the research subject receives the second treatment, the observational index has become normal. One advantage of the crossover design compared to the design of one factor with two levels is that it reduces sample size effectively.

1.4 Design form First, decide whether to use the paired two-period crossover design or the two-period crossover design of two groups. The paired two-period crossover design needs to pair the total 2n research subjects into n pairs, then randomly decide the order in which one participant of the pair receives the two treatments, and let the other receive the two treatments in the opposite order. The two-period crossover design of two groups requires the researcher to equally divide the total 2n research subjects into two groups, randomly decide the order in which one group receives the two treatments and let the other group receive the two treatments in the opposite order.
1.5 Application scope When a study involves a two-level experimental factor, and the specialty requires each research subject to receive the two treatments once, the crossover design can be adopted.

2 Three-period crossover design

2.1 Example 2 In order to describe the protocol of a clinical trial designed to directly test the effects of *Garcinia cambogia*-derived hydroxycitric acid (HCA) on food intake, satiety, weight loss and oxidative stress levels, and to serve as a model for similar trials, a total of 48 healthy, overweight or obese individuals (with body mass index range of 25.0 to 39.39 kg/m²) between the ages of 50 to 70 participated in a double-blind crossover study designed to examine the effects of two doses of *Garcinia cambogia*-derived HCA on food intake, satiety, weight loss and oxidative stress levels. Food intake represented the primary outcome measure and was calculated based on the total calories consumed at breakfast, lunch and dinner meals during each test meal day.

A three-period within-subject’s crossover design with two doses of *Garcinia cambogia*-derived HCA (2 800 mg/d and 5 600 mg/d) was used. The order the participants receiving each dose of *Garcinia cambogia*-derived HCA was counterbalanced and determined through randomization. Participants were blinded to their assigned condition throughout the study. Thus, participants completed a total of three 6-week conditions and two 6-week washout periods following a baseline food test day.

Participants initially completed a baseline food test meal day at the Clinical Research Center of the University of Florida, during which they consumed breakfast, lunch and dinner, as well as completed satiety assessments before and after meals. Following the baseline food test meal day, participants were randomly assigned to receive one of two doses of *Garcinia cambogia*-derived HCA in capsule form for a six-week duration. After six weeks, participants were asked to complete a second food test meal day. Following this food test day, participants completed a six-week washout period and then returned to the study site to complete a third food test meal day, which served as a baseline for their next assigned condition. Participants were asked to complete the next condition, in which they received one of the two doses of *Garcinia cambogia*-derived HCA in capsule form for a six-week duration. After completing the next assigned condition, participants again completed a fourth food test meal day. Participants completed a second six-week washout period and then completed a fifth test meal day, which served as the baseline for their next condition. Participants were be asked to complete the third and final condition in which they received one of the two doses of *Garcinia cambogia*-derived HCA in capsule form, for six weeks to complete their final food intake test day.

Example 2 involves a two-level experimental factor: “drug doses”, of which the two levels are “2 800 mg/d” and “5 600 mg/d”. Not like the two-period crossover design, it has three periods. The two block factors are “participants” and “periods”, respectively. Table 2 listed the form of the design. Since the subjects were not paired, example 2 belongs to the three-period crossover design of two groups.

<table>
<thead>
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<th>Participants</th>
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<th>1</th>
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<th>3</th>
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<td>68</td>
<td>B (xx)</td>
<td>A (xx)</td>
<td>B (xx)</td>
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</tbody>
</table>

A and B represent the two doses of *Garcinia cambogia*-derived HCA; xx represents the value of food intake. HCA: hydroxycitric acid.

2.2 Definition When a two-level experimental factor (A and B) is involved in a research design, and the specialty requires that each participant receives the two treatments once at three different periods in the order of ABA or BAB, the three-period crossover design is adopted. If the participants are paired, it is called the paired three-period crossover design; if the participants are equally divided into two groups, it is called the three-period crossover design of two groups.

2.3 Characteristics The three-period crossover design can be used to examine a two-level experimental factor and two block factors (individual difference and order). The order in which the participants receive each treatment will be counterbalanced and determined through randomization. There are two washout periods during the research. Compared to the two-period crossover design, the three-period crossover design carries a more serious confounding effect.

2.4 Design form First, decide whether to use the paired three-period crossover design or the three-period crossover design of two groups. The paired three-period crossover design requires to pair the 2n participants into n pairs, and randomly decide the order in which one participant in the pair receives each treatment (for example, ABA) and let the other receives each treatment in the opposite order (for example, BAB). The three-period crossover design of two groups requires to randomly and equally divide the 2n participants into two groups, randomly decide the order in which one group receives each treatment (for example, BAB) and let the other group receive each treatment in the opposite order (for example, ABA).

2.5 Application scope When a two-level experi-
mental factor is involved in research, and the specialty requires each subject to receive the two treatments once at three periods, the three-period crossover design can be adopted.

REFERENCES


无法考察交互作用的三因素设计(一)

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摘要：无法考察交互作用的三因素设计包括交叉设计和拉丁方设计两种。这两种设计类型较为特殊，所考察的3个因素包括1个实验因素和2个区组因素。尽管这两种设计在实际科研中运用的频率不是很高，但若在合适的场合正确运用这两种设计类型，将有效控制样本量，取得很好的实验效果。由于篇幅限制，本文重点介绍交叉设计的前两种类型。

关键词：统计学，医学；研究设计，因素分析，统计学