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ENDGAMES

STATISTICAL QUESTION

What is a crossover trial?

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Researchers evaluated the effectiveness of the cannabinoid dronabinol on central neuropathic pain in patients with multiple sclerosis.[1] The effectiveness of cannabinoids in relieving pain caused by central lesions in multiple sclerosis had not been investigated previously. A randomised double blind placebo controlled crossover trial study design was used. The intervention was orally administered dronabinol at a maximum dose of 10 mg daily or corresponding placebo. Each treatment period was for three weeks, separated by a three week washout period. All analgesic drugs, except for paracetamol, were discontinued at least one week before the start of the trial.

The primary outcome was spontaneous pain intensity in the last week of each treatment period measured using a numerical rating scale. The researchers reported that, when compared with placebo, dronabinol had a significant analgesic effect on central pain in patients with multiple sclerosis. Although the effects were modest they were clinically relevant. The number of patients with adverse events was higher during active treatment, especially in the first week of treatment. The functional ability of the patients with regard to their multiple sclerosis did not change.

Which of the following statements, if any, are true?

a) All participants received both treatments in the same sequence order

b) Each participant acted as his or her own control

c) The purpose of the washout period was to allow the effects of the first treatment to dissipate before starting the second treatment

d) The crossover study design required more participants than if a "between subjects" study design had been used to compare dronabinol and placebo

Answers

Statements *b* and *c* are true, whereas *a* and *d* are false.

The aim of the trial was to investigate the effectiveness of the cannabinoid dronabinol for central neuropathic pain in patients with multiple sclerosis. A randomised double blind placebo controlled crossover trial study design was used. The trial consisted of two treatment periods, and the participants received both treatments in successive order. For each patient, the order in which treatments were received—dronabinol followed by placebo, or vice versa—was determined at random (*a* is false). Each treatment period lasted for three weeks, separated by a three week washout period. The primary outcome of spontaneous pain intensity was recorded in the last week of each treatment period.

The crossover trial is a "within subject" study design. In the above trial each patient received both treatments. Therefore, the effectiveness of dronabinol was compared with placebo within each patient. Hence, the differences between treatments were paired and each participant acted as his or her own control (*b* is true). The advantage of such a design was that the characteristics of the treatment groups were the same at baseline. Therefore, confounding was minimised in the comparison of treatments. The comparisons between treatments were also made more precise because comparison within subjects removed any natural biological variation that may have occurred in the measurement of the outcome measure.

The use of placebos in clinical trials has generated much ethical debate. In the trial above, it would have been unethical to expect patients to receive placebo and therefore tolerate a period when no effective treatment for central neuropathic pain was offered. Furthermore, before the trial started the effectiveness of cannabinoid dronabinol was not known. Therefore, it would also have been unethical to expect patients to receive a treatment with unknown effectiveness. Therefore, the patients were able to take paracetamol when needed during both treatment periods. The researchers reported no difference between the treatment periods in the amount of paracetamol used by the participants. Although the use of paracetamol would have made it difficult to estimate the effectiveness of dronabinol, it was unlikely to have confounded the comparison of dronabinol with placebo in relieving spontaneous pain.

The above trial incorporated a three week washout period between treatments. During this time the participants were not allowed any of the treatments received in the trial. The purpose of the washout period was to minimise any carryover of effects, including pharmacological and psychological ones, of the treatment received in the first period to the second treatment

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period (*c* is true). However, it would have been unethical to expect patients to tolerate a period during which it was not possible to have treatment for their pain. Therefore, patients were able to take paracetamol when needed. The researchers reported that there was no significant carryover of effects between treatment periods. Details of how to test for a significant carryover of treatment effects are beyond the scope of this article.

The length of a washout period in a crossover trial will depend on the condition and the treatments received. An alternative approach to minimising the carryover of treatment effects in a crossover trial is to have a near immediate switch of treatments, or a washout period with a decreased dosage of the treatment received in the first period. To minimise any potential carryover effects from the first treatment period, the outcome measures are typically recorded towards the end of the treatment periods.

In the trial above, it was important that a patient's underlying condition and potential to respond to treatment remained unchanged from the first to the second treatment period. Otherwise a period effect may have existed—that is, a systematic difference between the first and second treatment periods in the outcome scores for a treatment. If a period effect existed then the average pain intensity score for patients who received—for example, dronabinol in the first treatment period—would have differed (either better or worse) from that seen in those who received dronabinol in the second period. The researchers did not report whether a significant period effect existed. The presence of a period effect might have suggested there was a learning effect with respect to the recording of spontaneous pain intensity. It is hoped that if a period effect had occurred, it would have applied equally to both treatments. By randomising patients to the treatment sequence—dronabinol followed by placebo, or vice versa—any period effect would potentially have averaged out and been minimised in the comparison of treatments.

The above trial provided a more precise comparison of dronabinol with placebo than would have been gained from a "between subject" study design. If dronabinol had been compared with placebo using a between subject trial study design, participants would have been randomly allocated to dronabinol or placebo and would have received the same treatment for the entire study period. At the end of the study, the effectiveness of the treatments would have been established by comparing the outcomes between the two independent groups of patients. By using a within subject study trial design to compare treatments, fewer patients were needed than if the comparison had been made using a between subject design (*d* is false).

A crossover trial study design is typically used when the condition being investigated is chronic and treatment is for the short term relief of symptoms rather than a cure. The example above is probably the simplest crossover study design; it is described as a two period crossover trial because participants received two treatments in successive treatment periods in an order decided at random. Other crossover designs have been described in previous questions, including the "n of 1" trial study design.[2] Unlike the crossover trial study design above, where treatments were compared in effectiveness by averaging the within patient differences across a sample, an "n of 1" trial involves finding the most effective treatment for the individual patient. The "n of 1" trial study design is still prone to the carryover of treatment effects as well as the period effect as described above.

Competing interests: None declared.

1 Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ* 2004;329:253.
2 Sedgwick P. What is an "n-of-1" trial? *BMJ* 2014;348:g2674.

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