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ENDGAMES

STATISTICAL QUESTION

What is an open label trial?

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Researchers assessed the effectiveness of prazosin combined with scorpion antivenom in assisting recovery from scorpion sting. An open label randomised controlled trial study design was used. The control treatment was prazosin alone. The setting was a hospital and research centre in Mahad, a region of India. Participants were patients with grade 2 scorpion envenomation, older than 6 months, and with no cardiorespiratory or central nervous system abnormalities. In total, 70 patients were recruited and allocated to treatment (35 to prazosin and scorpion antivenom, and 35 to prazosin alone) by block randomisation.[1]

The primary endpoint was resolution of the clinical syndrome within 10 hours of treatment, as assessed by the researchers. The secondary endpoints included the time needed for complete resolution of the clinical syndrome. The proportion of patients who showed complete resolution of the clinical syndrome within 10 hours of treatment was significantly greater in the prazosin plus antivenom group than in the prazosin alone group (91.4% *v* 22.9%; difference 68.5%, 95% confidence interval 51.8% to 85.2%; P<0.001). The mean time needed for complete resolution of the clinical syndrome was significantly shorter in the antivenom plus prazosin group (8 *v* 17.7 h; difference −9.7 h, −6.9 to −12.4); P<0.001). The researchers concluded that recovery from a scorpion sting was hastened by simultaneous administration of scorpion antivenom plus prazosin compared with prazosin alone.

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

a) After randomisation, participants were aware which treatment they had been allocated to

b) The trial was liable to allocation bias

c) The trial design minimised ascertainment bias

d) Allocation concealment was not possible in the above trial

Answers

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

The aim of the trial was to assess the effectiveness of prazosin (a commonly used vasodilator) combined with scorpion antivenom in aiding the recovery of patients after a scorpion sting. An open label randomised controlled trial study design was used. The control treatment was prazosin alone. Because this was an open label trial, the participants, investigators, and all peripheral staff were not blinded to the treatment allocation—that is, they were aware which treatment the participants had been allocated to after randomisation (*a* is true). Open label trials are sometimes referred to as "non-masked" or "unblinded." If the trial is a non-pharmacological study, such as a trial of devices, or psychological and physical treatments, it may be referred to simply as "open."

After recruitment to the trial, the participants were allocated to treatment using block randomisation. Block randomisation has been described in a previous question.[2] Each participant had an equal probability of being allocated to treatment—prazosin combined with scorpion antivenom or prazosin alone. Therefore, the trial was not liable to allocation bias (*b* is false). Allocation bias is a systematic difference between participants in how they are allocated to treatment.[3] It could have occurred if the researchers had chosen which treatment the patients received. For example, the researchers may have favoured prazosin combined with scorpion antivenom and wished to show that it was more effective than prazosin alone. They may then have allocated patients who they thought would recover more quickly from the scorpion sting to prazosin combined with scorpion antivenom. The randomisation of participants meant that allocation bias did not occur. It also ensured that the two treatment groups were similar in baseline characteristics and thereby minimised confounding.

The trial participants and researchers were not blinded to the treatment allocation. Therefore, the trial was liable to ascertainment bias, sometimes referred to as detection bias (*c* is false). Ascertainment bias is the systematic distortion of the assessment of outcome measures by the investigators or trial participants because they are aware of treatment allocation. It results in an exaggerated difference between the treatments in outcome. In the above trial, the primary endpoint was resolution of the clinical syndrome within 10 hours of treatment. The researchers reported that every 30 minutes one of them assessed the patient at the bedside for symptoms of sweating, salivation, cool extremities, priapism, hypertension or hypotension, and tachycardia. Ascertainment bias would have occurred, for

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example, if the researcher favoured prazosin combined with scorpion antivenom, wishing to show that it was more effective than prazosin alone. Because the researchers were aware of the treatment allocation, this could have biased their assessment—subconsciously or otherwise—towards prazosin combined with scorpion antivenom.

In an open trial, ascertainment bias can also occur on behalf of the participants. Participants know their treatment allocation and, for example, might be disappointed if not allocated their preferred treatment, with the result that they report worse scores for the outcome measures than were experienced. Ascertainment bias on behalf of the participants is unlikely to have occurred in the above trial because the primary outcome was based on the researchers' assessment of clinical symptoms. When ascertainment bias occurs on behalf of the investigators it is called assessor bias, and when it occurs on behalf of the participants it is known as response bias. More generally, ascertainment bias is more likely to occur when outcomes are measured subjectively.

Double blind randomised controlled trials are seen as the gold standard when assessing the effectiveness of treatments. The above trial could have been made double blind by giving the prazosin alone treatment group a placebo scorpion antivenom. The researchers suggested that the lack of blinding was a clinically relevant and pragmatic way of assessing the effects of treatment in a trial undertaken with restricted resources in a rural setting in India. Despite the lack of blinding, the trial was important because evidence for the benefit of scorpion antivenom in the treatment of scorpion sting and its efficacy compared with that of commonly used vasodilators was scarce. Furthermore, the results of the above trial might be used to inform the sample size for a future randomised controlled trial that incorporated double blinding.

Allocation concealment and blinding in clinical trials are often confused.[4] Allocation concealment involves not disclosing to patients and those involved in recruiting participants the allocation sequence before participants are recruited and allocated to treatment. The allocation sequence is the order in which participants will be allocated to treatment after recruitment. Blinding involves not disclosing to participants, investigators, and all peripheral staff the treatment allocation after random allocation. Allocation concealment is always possible in trials, and it is essential if blinding is to be achieved (*d* is false). However, blinding cannot always be achieved in trials. In the trial above the researchers ensured allocation concealment but, because of the nature of the treatments, it was not possible to blind participants to their allocated treatment after they had been randomly allocated.

Allocation concealment in the trial above ensured that selection bias was minimised. Selection bias, described in a previous question,[3] would have been a systematic difference for eligible trial participants between those who were recruited and those who were not. For example, the member of the research team who recruited patients may have wished to demonstrate that one of the treatments, such as prazosin combined with scorpion antivenom, was more effective. If that researcher was aware of the allocation sequence, he or she may have been less likely to recruit a patient who was thought unlikely to respond well to treatment if the next treatment in the sequence was prazosin combined with scorpion antivenom.

Open label trials do not have to involve randomisation or include a control treatment. Phase I and phase II trials, described in a previous question,[5] are often open label.

Competing interests: None declared.

1 Bawaskar HS, Bawaskar PH. Efficacy and safety of scorpion antivenom plus prazosin compared with prazosin alone for venomous scorpion (Mesobuthus tamulus) sting: randomised open label clinical trial. *BMJ* 2010;341:c7136.
2 Sedgwick P. Treatment allocation in trials: block randomisation. *BMJ* 2014;348:g2409.
3 Sedgwick P. Selection bias versus allocation bias. *BMJ* 2013;346:f3345.
4 Sedgwick P. Allocation concealment versus blinding in randomised controlled trials. *BMJ* 2013;347:f5518.
5 Sedgwick P. Phases of clinical trials. *BMJ* 2011;343:d6068.

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