

ENDGAMES

STATISTICAL QUESTION

Sham treatments

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Researchers assessed the effects of continuous positive airway pressure on blood pressure in patients with moderate to severe obstructive sleep apnoea and recently diagnosed but untreated systemic hypertension. Blood pressure was measured using 24 hour ambulatory monitoring. A randomised double blind placebo controlled trial study design was used. The intervention was optimal therapeutic continuous positive airway pressure. Control treatment was sham continuous positive airway pressure delivered at a very low pressure. In total, 169 patients were assigned to continuous positive airway pressure and 171 to control treatment.¹

The primary outcome was mean 24 hour ambulatory blood pressure. For each patient the change at three months from baseline in the primary outcome was recorded. Statistical analysis was undertaken by the principle of intention to treat. When compared with sham continuous positive airway pressure, the within group change at three months in mean 24 hour ambulatory blood pressure of the continuous positive airway pressure group decreased by 1.5 mm Hg (95% confidence interval 0.4 to 2.7; $P=0.01$). It was concluded that continuous positive airway pressure was associated with a significant reduction in blood pressure in patients with obstructive sleep apnoea and systemic hypertension.

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

- The control treatment of sham continuous positive airway pressure is described as an active control
- The response by the control group quantified the placebo effect
- The use of sham continuous positive airway pressure allowed the assessment of the therapeutic effect of optimal therapeutic continuous positive airway pressure
- The current version of the Declaration of Helsinki precludes the use of sham treatments in randomised controlled trials

Answers

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

The aim of the above trial was to assess the effectiveness of continuous positive airway pressure on blood pressure in patients with moderate to severe obstructive sleep apnoea and recently diagnosed but untreated systemic hypertension. The trial was designed as a randomised double blind placebo controlled trial. The intervention was optimal therapeutic continuous positive airway pressure. The control treatment was a placebo, which consisted of continuous positive airway pressure delivered at a very low pressure, an intervention that is not known to have any therapeutic effects. The placebo is described as a sham treatment. The term “placebo” is typically used in pharmacological studies, whereas “sham treatment” is used for non-pharmacological studies, including those of devices and of psychological and physical treatments.

If the control treatment in a trial is an intervention—such as a drug, therapy, or medical device—with established effectiveness, it is referred to as an active control. The control in the above trial was a sham treatment with no known therapeutic effects, so it is referred to as a negative control (*a* is false).

The within group change at three months from baseline in mean 24 hour ambulatory blood pressure for the intervention group is made up of two components—the direct response to the provision of treatment plus non-specific treatment effects not directly ascribed to the active treatment. These non-specific effects include the placebo effect and the natural course of blood pressure in the trial participants. The placebo effect represents the patient's response to investigation, including the response to a therapeutic ritual, subsequent response to observation and assessment, and response to the patient-doctor interaction. There is probably a complex association between these components. The natural course of blood pressure is represented by the change that would have occurred in the absence of any intervention in patients with moderate to severe obstructive sleep apnoea and recently diagnosed but untreated systemic hypertension.

The response by the control group provided an estimate of the non-specific treatment effects described above—that is, the placebo effect plus the natural course of blood pressure over the three month study period (*b* is false). Therefore, the

therapeutic benefit of the intervention is estimated by the difference between the intervention and control groups in the within group change at three months from baseline in mean 24 hour ambulatory blood pressure (*c* is true).

The Declaration of Helsinki is a statement of ethical principles intended to guide medical research involving human subjects. It was first published by the World Medical Association in 1964. The current version, published in 2008, does not preclude the use of placebos in randomised controlled trials. No reference is made to “sham treatments” or “sham procedures,” but these terms are synonymous with the more widely used “placebo.” Therefore, *d* is false. However, the declaration states that new interventions must be tested against the intervention that has been proved to be most effective unless (a) “no current proven intervention exists” or (b) there are “compelling and scientifically sound methodological reasons [why] the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no

treatment will not be subject to any risk of serious or irreversible harm.” Nonetheless, the ethics of placebo controlled trials continue to be widely debated. In particular, it is argued that there are sound reasons, including ethical and statistical ones, for using placebos even if safe and effective treatments are already available. For this reason, the next version of the declaration (due to be published in 2014) will probably provide more ethically nuanced guidance in relation to the use of placebos in research.

Competing interests: None declared.

- 1 Duran-Cantolla J, Aizpuru F, Montserrat JM, Ballester E, Teran-Santos J, Aguirregomoscorta JI, et al; on behalf of the Spanish Sleep and Breathing Group. Continuous positive airway pressure as treatment for systemic hypertension in people with obstructive sleep apnoea: randomised controlled trial. *BMJ* 2010;341:c5991.

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