EDITORIAL

Viewpoint: Randomised controlled trials using invasive 'placebo' controls are unethical and should be excluded from Cochrane Reviews

Allan M Cyna, David Costi, Philippa Middleton

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Placebo controls are frequently used to 'blind' participants, trial personnel and outcome assessors to intervention and control in clinical trials. Effective blinding of treatment reduces the risk of performance bias (differences between groups in the care provided apart from the intervention being evaluated) and detection bias (differences between groups in how outcomes are ascertained, diagnosed or verified). A placebo has traditionally been defined as an "inert or innocuous substance",[1] such as a 'sugar pill'. However, some randomised controlled trials (RCTs) have been shown to erroneously use the term 'placebo' to describe an invasive intervention that exposes participants, allocated to a control group, to risks of serious harm.[2][3] In this context therefore, the term 'placebo' describes an invasive intervention which is neither inert nor innocuous.

In a recent study of local anaesthesia RCTs, over half the RCTs used an invasive 'placebo' control.[2] The 'placebo' interventions mostly involved deep-needle insertion through body tissues with potential damage to nerves, vessels and other structures such as liver and bowel. These interventions exposed control group participants to risks of serious morbidity.[2][3] The invasive 'placebos' equated to grade 3 or 4 on the Serious Harm and Morbidity (SHAM) 0–4 point scale, a scale that was recently developed to assess the degree of invasiveness, and therefore risk of harm, of placebos used in local anaesthesia research (specifically, nerve block trials).[2] The SHAM risks in patients allocated to a control group are designated: grade 0 = no risk (no intervention); grade 1 = minimal risk (for example, skin allergy to dressing); grade 2 = minor risk (for example, subcutaneous haematoma, infection); grade 3 = moderate risk (with or without placebo injection) (for example, neuropraxia); and grade 4 = major risk (blindness in eye block controls, bowel perforation or liver laceration in transversus abdominis plane (TAP) block controls).[2] It should be noted that the SHAM scale was not intended for use in pharmacological trials where intravenous saline is used as a placebo control for administration of an intravenous study drug. The same researchers also found that some ethics committees rejected studies because of ethical concerns about the control group, whereas other ethics committees approved the use of the same control; these examples illustrate the considerable differences in opinion in whether it is ethical to use invasive 'placebo' controls.[2]

We suggest that invasive 'placebos' that risk serious harm are unnecessary for scientific validity. There are examples where the study can be adequately blinded using a less invasive alternative with little or no compromise to the scientific validity of the trial.[4] For example, in investigations of TAP blocks, the invasive 'placebo' control injection of saline risks liver laceration and bowel perforation. However, control group patients and outcome assessors could be blinded by using the same preparation in the control group as the intervention group, but without the skin penetration. The site of the block could be prepared with antiseptic and draped, ultrasound used to identify nerves, the skin indented with a blunt cannula, and any other manoeuvre performed to mimic the intervention non-invasively. Dressings can then be placed in an identical way in both groups. "This process would confer on control group patients a SHAM-1, rather than a SHAM-4, risk, and yet still allow for a double-blind study design without exposing control participants to an invasive procedure."[5] In many cases an identical dressing in control group participants, over the sham block site, may be all that is required for patients and outcome assessors to be blinded. When no suitable alternative is possible, outcome assessors can usually be blinded without an invasive 'placebo'.[6] While proponents of invasive 'placebos' may point out that, "Clinical trials are not designed to promote the patient's best interest; they are designed to answer valuable scientific questions",[7] most clinical trials do not need an invasive 'placebo' for them to be considered useful and scientifically valid. Trials using an invasive 'placebo' control frequently expose control group participants to serious risks to which they would never be exposed in the clinical setting.

The adequacy of the consent process, particularly in the context of vulnerable populations such as children, has also been questioned recently by two of the authors,[8] especially if an invasive intervention risking serious harm is to be administered to control-group patients that would never be used in a clinical situation, for example, injections of saline into the eye, epidural space or abdomen. Several paediatric studies have exposed children allocated to control groups to risks of suffering a permanent nerve injury, a globe perforation of the eye or an epidural haematoma. It is difficult to imagine a parent agreeing to an invasive procedure risking serious harm to their child with no possible benefit.[8] Indeed, it is likely that many patients will

not understand the full implications of participating in a study and will trust their doctor or researcher to do the right thing ethically by not placing them at unnecessary risk.[5]

Studies with SHAM grade 3 or 4 are considered to be those with an invasive 'placebo' where control participants are placed at potential serious risk.[2][3] These controls are non-compliant with the Declaration of Helsinki, whereby "patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm."[9] This Declaration is a statement of ethical principles for medical research involving human participants. It is currently endorsed by medical associations from 85 countries and accepted almost universally as the "bedrock of protection for research subjects" when conducting clinical trials.[10] The Declaration states that there exists "an ethical onus on the doctor never to sacrifice the interests of the individual in the interests of science and society".[9] Many journals explicitly state that they will only publish studies where the methodology is consistent with the Declaration.

As with other valuable resources of scientific knowledge, *The Cochrane Library* is ideally placed to promote ethical as well as scientifically valid research. In this regard, Cochrane Reviews need to be more explicit in their support of ethical research by encouraging authors to exclude studies using invasive 'placebos' that pose any risk of serious or irreversible harm. Specifically in the area of local anaesthesia, review authors should exclude studies where invasive 'placebo' interventions (SHAM Grades 3 or 4) are administered to control group participants. The SHAM scale concept could be of relevance to other clinical research settings, and members of The Cochrane Collaboration should be encouraged to look at the possible generalisability and applicability of the SHAM scale in future Cochrane Reviews. In short, the clinician's guiding principle for caring for patients – *primum non nocere* ('first, do no harm') – should also be a primary concern of researchers investigating healthcare interventions.

Author Information

Allan M Cyna[1], David Costi[1], Philippa Middleton[1]

[1]Women's and Children's Hospital, University of Adelaide, Australia

Declarations of interest

The authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available upon request) and declare: (1) no receipt of payment or support in kind for any aspect of the article; (2) no financial relationships with any entities that have an interest related to the submitted work; (3) that they are employed by Women's and Children's Hospital, University of Adelaide, Adelaide, South Australia; that AM Cyna has received an NHMRC grant 2007–2010 and Cochrane incentive award scheme 2010, and has received travel/accommodation/meeting expenses from the Association of Anaesthetists Great Britain and Ireland and Malaysian Society of Anaesthetists at meetings where he was an invited speaker; that Costi D received a SPANZA Research Grant 2010; but otherwise the authors/spouse/partner/children have no financial relationships with entities that have an interest in the content of the article; and (4) that there are no other relationships or activities that could be perceived as having influenced, or giving the appearance of potentially influencing, what was written in the submitted work.

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