REVIEW

Blinding in trials of interventional procedures is possible and worthwhile [version 1; referees: 1 approved]

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Abstract
In this paper, we have used evidence from our earlier review of surgical randomised controlled trials with a placebo arm to show that blinding in trials of interventional procedures is feasible, and that many creative methods can be used to make the active and the placebo procedure as similar as possible. We give examples of ingenious strategies used to simulate the active procedure and make the placebo control indistinguishable from the active treatment. We discuss why it is important to blind of patients, assessors, and caregivers and the types of bias that may occur in interventional trials. Finally, we describe the benefits of blinding, from the obvious ones such as avoiding bias, as well as less evident benefits such as avoiding patient drop out in the control arm.

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Introduction

The aim of a trial is to produce unbiased evidence. As randomised controlled trials (RCTs) with a placebo arm control for many types of bias, they are regarded as the most reliable method of demonstrating treatment efficacy and provide the highest level of evidence. RCTs of interventional procedures are rare, partly because they are challenging; however, they are not impossible to perform, even if they involve a placebo arm. In this paper we will discuss why trials should be blinded and summarise the methods which have been used in the published placebo-controlled trials of interventional procedures to achieve blinding.

Blinding in interventional trials is often necessary because nowadays many procedures are performed to reduce pain and improve function and quality of life. Pain, function and quality of life are sometimes regarded as preferable outcome measures because they reflect patients’ needs and point of view. However, as these outcomes depend on patients’ subjective perception, they are prone to bias and may lead to an exaggerated treatment effect in open-label trials. Using subjective outcomes in an open-label study undermines its internal validity because it is not possible to determine how much of the reported effect is related to the investigated treatment and how much is related to bias.

Blinding of patients, surgeons, outcome assessors and caregivers

Blinding of patients

Blinding means concealing the treatment allocation from patients and any other people involved in the trial who may bias the results of the trial by knowing which groups the patients were randomised to.

Blinding of patients prevents reporting bias in patient-reported measures. For example, it has been demonstrated that non-blinded patients exaggerate the effects size by 0.56 standard deviations and that the effect is even larger in trials on interventional procedures, such as acupuncture. This bias may be caused by patients’ expectations of treatment effect and information given to them before the treatment. Patients may also report symptoms depending on their “hunches” about treatment being effective or they may give answers they believe are “correct” or expected from them, for example, because it would have been impolite not to report improvement. Therefore, it has been suggested that patients should be blinded whenever possible.

Blinding of patients also reduces adherence bias, i.e. patients in the control group not following the protocol/treatment. It may also prevent so called “contamination of the control group”, i.e. seeking additional treatment/help outside the trial and receiving concomitant treatment. Blinding improves patient retention in the trial. Risk of attrition in blinded trials is about 4% whereas in non-blinded trials it is 7%. Specifically in placebo-controlled surgical trials, subject retention is often reported as “excellent” and in our analysis the withdrawal rate was low (4%) and comparable between the treatment and the placebo arm.

Blinding of caregivers

Apart from blinding patients and assessors, it is important that caregivers and clinical/research staff do not know patient treatment allocation, because their behaviour and attitudes may influence patient responses. Patient-clinician interaction plays an important role in treatment response, and patients in trials do better as they get more attention and time from clinical staff than patients receiving standard care. Therefore, the interactions between patients and the trial team should be standardised so that the “treatment context” (similar attention from doctors, expectations, and settings) are comparable between the groups.

Strategies used to maintain blinding in interventional placebo-controlled trials

A placebo control is necessary if we want to know whether improvement is really caused by the investigated procedure. It compares the intervention of interest with a procedure that seems identical but does not involve the crucial element of believed to be “the cure”. The aim of a placebo arm is to control for effects of receiving treatment not specifically related to the investigated intervention.

It is often difficult to determine what is a specific and what is a non-specific effect in a trial, and to disentangle placebo
response from response bias or the effect of patient-doctor interactions. It is beyond the scope of this review to discuss definitions of placebo. Whether something is or is not a placebo depends on the intervention and chosen outcome variables, but in order for blinding to be successful, the control procedure has to be as similar as possible to the investigated procedure. Interventional trials differ from drug trials as they require access to the anatomical structure of interest; therefore, they involve a skin incision or an insertion of a scope.

Many published surgical trials used general anaesthesia or heavy sedation, which made blinding easier because patients were unaware of the details of surgical procedures. In such trials, only the surgical wound had to be similar in both groups. Some studies did not add any placebo procedure but simply omitted part of interventional procedure, for example, in the trial by Stone and colleagues, all patients underwent a percutaneous coronary intervention and maximal medical therapy but only patients in the active arm also had percutaneous transmyocardial revascularisation.

When light sedation or local anaesthesia are used, surgical staff have to simulate the actual intervention to preserve the blinding. The complexity of a surgical procedure can make blinding challenging, and ingenious ideas are required to make the real and placebo interventions indistinguishable.

**Imitation of incision/ surgical access point**

If a procedure requires open surgery, then it will leave an obvious mark where the incision has been made, which will have to be imitated in the placebo group. There have been very few trials involving full skin incision, in both the surgical and placebo arms. In the seminal trials on internal mammary artery ligation, a skin incision was made to expose the arteries in all patients but no ligation was made in the placebo group. Similarly, Guyuron and colleagues used a skin incision to expose superficial nerves and muscles, which were cut during the active surgery but, in the placebo group, the integrity of these structures was maintained.

Trials investigating transplantation of dopaminergic neurones as a treatment for Parkinson’s disease not only required skin incision but also burr holes in the skull.

However, most of the published placebo-controlled surgical trials used minimally-invasive methods to access the structure of interest. For example, the placebo procedure involved laparoscopy but without ablation, endoscopy without radiofrequency energy delivery, bronchoscopy without radiofrequency energy delivery, or bronchoscopy without valve placement. Therefore, most of the studies required a small incision to mimic the portals created during the laparoscopy or arthroscopy, or to mimic the incision through which an intravascular catheter was inserted. Interestingly, Sutton and colleagues used three incisions in both groups so that patients could not tell apart a diagnostic laparoscopy from a laparoscopic surgery; even though the third instrument port was not necessary in the placebo group. Trials using endoscopy and bronchoscopy were even easier to blind as natural orifices were used to insert the scope, and the incision or actual procedure site was not visible to patients, caregivers, and assessors.

**Simulation of an interventional procedure**

Typically, the preparation for the placebo procedure and the active procedure was as similar as possible and imitated the visual, auditory, and physical cues. In order to mimic the sounds, surgeons were required to talk through the procedure steps, ask for instruments, use suction or ask for a laser or other device to be activated, even though it was not used in the placebo group.

Clinical staff performing the intervention were screened from the patients’ view either by a surgical drape or by arranging the operating room in a way that the patient could not see the procedure. In the trial by Stone and colleagues, patients were heavily sedated and wore opaque goggles. In a trial by Maurer and colleagues, the manufacturer delivered tools that looked identical but did not contain an implant, which allowed for blinding of patients and clinical staff.

Surgeons also attempted to imitate sensory cues, for example, by manipulating the knee as if the actual arthroscopy were performed, injecting saline to imitate tidal irrigation, or by splashing saline on the knee to simulate lavage. In a trial on meniscectomy, surgeons used a mechanical shaver (without the blade) pushing it firmly against the patella to simulate the sensations the patient would experience during the surgery. In a trial on intragastric balloon for obesity, operators manipulated the endoscope as during the balloon insertion to create the sensation of resistance in the stomach.

Even smell during the surgery was imitated to make the placebo procedure indistinguishable from surgery. For example, in the trial by Deviere and colleagues there were concerns that patients could have known the allocation because the copolymer used in the active arm had a distinct smell. In trials on vertebroplasty, a container with cement was opened during placebo procedure to help with blinding.

**Inactive nature of the placebo**

It is important that the procedure used for blinding does not have any therapeutic effect. For example, the results of the vertebroplasty trials were criticised because the elements of placebo procedure could have had an effect on the reported pain, namely, a potential pharmacological anaesthesia due to injection of an anaesthetic into the facet capsule and peristeum.

On the other hand, the procedure used for blinding may have diagnostic use, as with diagnostic laparoscopy or diagnostic laparoscopy with biopsy. In the trial by Sihvonen and colleagues, all participants underwent diagnostic arthroscopy, but only after they had been confirmed to be eligible for inclusion in the trial was the envelope with the assignment opened and the assignment revealed to the surgeon.
Duration of the procedure
Many trials specifically stated that the duration of procedure in the surgical and control arms were matched, either by imitating the elements of the surgical procedure or by keeping all patients in the operation room for the same duration of time\(^\text{34,38,45,47,48,60,61}\). However, in some trials, the placebo procedure was shortened in comparison to the actual surgery because it was believed it would have been ethically unacceptable to prolong the placebo intervention\(^\text{49,53}\).

Additional procedures that may reveal allocation
Interventional treatment often requires additional procedures, such as diagnostic scans or medication to prevent infection\(^\text{43,56,62}\), blood clots\(^\text{60}\), transplant rejection\(^\text{65}\), or epileptic fits\(^\text{43}\). For example, in the trial by Freed and colleagues, both groups received identical preoperative evaluation, intraoperative sedation and pain control, underwent two PET scans and a MRI scan, and received phenytoin\(^\text{53}\). In some trials, the same medication was given in both groups, whereas in others unnecessary treatment was omitted or imitated, for example by injecting saline instead of antibiotics\(^\text{66}\).

Standardisation of interventions and care
The active and placebo procedure have to be indistinguishable but they also have to be stable and standardised. Standardisation of the procedure itself may be difficult but is important because surgeons vary in their experience, and gain experience throughout the trial.

Some of the changes observed in a trial may not be related to the treatment or the placebo intervention, but may be caused by the natural course of the disease, spontaneous remissions or fluctuations in the severity of symptoms or regression to the mean\(^\text{27,65}\). Some changes may be a result of just being in a trial either because of lifestyle changes that are part of the protocol such as self-monitoring using diaries or avoiding alcohol or due to so called “Hawthorne effect”, which refers to change in the behaviour when people, both patients and doctors, know that they are being observed\(^\text{27}\). Finally, it has been demonstrated that adhering to a protocol improves the performance of doctors, and that patients who adhere to treatment regimes have better outcomes\(^\text{49}\). Therefore, it is important to standardise pre- and post-operative care, and the explanations given to the patients. For example, in a trial by Sihvonen and colleagues all procedures were standardised and recorded on video; the post-operative care was also standardised, and all patients received the same exercise programme and walking aids\(^\text{48}\).

Blinding after the surgery
Most trials blinded the assessors while the surgeon and other staff in the operating room were aware of the group assignment, and did not participate in further treatment, post-operative care or follow-up of the patient\(^\text{49,48,67}\). In a trial by Thomsen and colleagues, the post-operative care and assessment was done at a different hospital than the surgery\(^\text{31}\). In a trial by Cotton and colleagues a post-operative care was provided by the referring physician, who was blinded when deciding on treatment, and when this was not sufficient, by the evaluating physician at the study site (who was also blinded)\(^\text{37}\).

Bias specific to surgical trials
There are other types of bias that are specific to surgical trials. For example, in trials on upper gastrointestinal tract bleeding, the endoscopic procedure was not performed if the rate of blood loss was too fast, or the endoscopy was judged to be life-threatening and posed an unacceptable risk\(^\text{48-70}\). In other trials, some patients were excluded because they could not tolerate endoscopy, or due to anatomical conditions that made the surgery impossible to carry out (laser could not be aimed at the bleeding arteries)\(^\text{71}\). Alternatively, some patients were not included in a trial because they were no longer eligible, for example because the bleeding had stopped\(^\text{30}\) or they no longer reported the symptoms on the day of the study\(^\text{31}\).

Conclusions
Blinding in trials of interventional procedures is possible and many creative methods have been used to maintain the blinding. Interventional procedures are challenging to blind, but the effort is worthwhile because of the obvious benefits, such as avoiding bias, as well as the less evident benefits, such as avoiding patient drop-out in the control arm.

Competing interests
No competing interests were disclosed.

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This manuscript is a narrative overview of methods of blinding in trials of procedures, using the previous review by these authors as the source of data. It explains the rationale for blinding and gives examples (subgrouped) of how blinding was achieved in previous trials. The authors wisely avoid a detailed discussion of the placebo effect and concentrate on the need for blinding based on empirical evidence of bias resulting from not blinding.

The paper reinforces the need for blinding in procedural trials which is a reasonable demand that is increasingly being heeded. In other words, the message is important.

The paper is very well written. I only have minor comments, below:

1. Page 2, second last paragraph, “crucial element of believed to be the cure” should read “crucial element believed to be the cure”
2. The evidence of bias resulting from not blinding may be one sided. Opposing evidence should be discussed, such as Berkmann ND, The Empirical Evidence of Bias in Trials Measuring Treatment Differences which shows that the effect of blinding may even be in the opposite direction and the classic Schultz article from 1995 which gives a lower estimate of effect exaggeration from unblinding. There are several other summaries and meta-epidemiological studies in this area.

References

Is the topic of the review discussed comprehensively in the context of the current literature? Yes

Are all factual statements correct and adequately supported by citations? Yes

Is the review written in accessible language? Yes
Are the conclusions drawn appropriate in the context of the current research literature?
Yes

**Competing Interests:** No competing interests were disclosed.

**Referee Expertise:** Orthopaedics, Epidemiology

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.