PRACTICAL TIPS FOR SURGICAL RESEARCH

Blinding: Who, what, when, why, how?

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Blinding refers to the concealment of group allocation from one or more individuals involved in a clinical research study, most commonly a randomized controlled trial (RCT). Although randomization minimizes differences between treatment groups at the outset of the trial, it does nothing to prevent differential treatment of the groups later in the trial or the differential assessment of outcomes, either of which may result in biased estimates of treatment effects. The optimal strategy to minimize the likelihood of differential treatment or assessments of outcomes is to blind as many individuals as possible in a trial.

Randomized controlled trials of surgical interventions are frequently more difficult to blind than RCTs of medications, which typically achieve blinding with placebos. However, imaginative techniques may make blinding more feasible in surgical trials than is commonly believed by many researchers. In this article we discuss the importance of blinding and provide practical suggestions to researchers who wish to incorporate blinding into their surgical studies.

Objectives of this article

By the end of this article, the reader will be able to appreciate the significance and rationale of blinding, recognize which individuals to blind, learn strategies for blinding in difficult situations and develop approaches for managing situations in which blinding is impossible. The following article is divided into 4 sections: Why should I blind? Who should I blind? How can I blind individuals in surgical trials? and What should I do if I can't blind?

Why should I blind?

Rigorous, well-conducted RCTs provide the best estimates of the impact of surgical interventions.[1] However, if RCTs are difficult to conduct rigorously in an area, the methodology is more likely to be faulty, and the results may be misleading. Moreover, rather than performing a critical appraisal of the available literature, clinicians' decisions may be influenced by the fact that an RCT design was used, and erroneous conclusions may guide clinical practice.

Blinding is a critical methodologic feature of RCTs. Although randomization minimizes the selection bias and confounding that plagues cohort and case–control studies[2] and therefore minimizes the likelihood of prognostic differences between intervention groups, its use does not prevent subsequent differential cointerventions or biased assessment of outcomes. Note that allocation concealment is completely different from blinding. The former seeks to eliminate selection bias during the process of recruitment and randomization, whereas the latter seeks to reduce performance and ascertainment bias after randomization.[3] Furthermore, if bias is introduced during a trial because of differential treatment of groups or biased assessment of outcomes, no analytical techniques can correct for this limitation. Thus, surgeons must interpret the results from unblinded trials with caution.

Whereas few would question the reduction in bias that blinding can achieve, empirical evidence suggests that blinding in trials does indeed make a difference. In a systematic review of 250 RCTs identified from 33 meta-analyses, researchers observed a significant difference in the size of the estimated treatment effect between trials that reported "double-blinding" compared with those that did not ($p = 0.01$), with an overall odds ratio 17% larger in studies that did not report blinding.[4] Other studies have confirmed this finding.[5,6] Therefore, trialists should make every effort to incorporate blinding into their trial designs and readers should look for descriptions in the published reports of which investigators were blinded.

WHO SHOULD I BLIND?

Differential treatment or assessment of participants potentially resulting in bias may occur at any phase of a trial. If possible, trialists should blind 5 groups of individuals involved in trials: participants, clinicians (surgeons), data collectors, outcome adjudicators and data analysts.

If participants are not blinded, knowledge of group assignment may affect their behaviour in the trial and their responses to subjective outcome measures. For example, a participant who is aware that he is not receiving active treatment may be less likely to comply with the trial protocol, more likely to seek additional treatment outside of the trial and more likely to leave the trial without providing outcome data. Those aware that they are receiving or not receiving therapy are more likely to provide biased assessments of the effectiveness of the intervention — most likely in opposite directions — than blinded participants.[7] Similarly, blinded clinicians are much less likely to transfer their attitudes to participants or to provide differential treatment to the active and placebo groups than are unblinded clinicians.[7]

Blinding of data collectors and outcome adjudicators (sometimes the same individuals) is crucial to ensure unbiased ascertainment of outcomes. For example, in a randomized controlled trial of cyclophosphamide and plasma exchange in patients with multiple sclerosis, neither active treatment regimen was superior to placebo when assessed by blinded neurologists, but there was an apparent benefit of treatment with cyclophosphamide, plasma exchange and prednisone when unblinded neurologists performed the assessments.[8] Although subjective outcomes are most at risk of ascertainment bias, seemingly objective outcomes often require some degree of subjectivity and therefore are at risk of bias as well.

Bias may also be introduced during the statistical analysis of the trial through the selective use and reporting of statistical tests. This may be a subconscious process spurred by investigators eager to see a positive result, but the consequences are profound. The best method to avoid this potential bias is blinding of the data analyst until the entire analysis has been completed.

This rationale strongly suggests that the blinding of as many individuals as is practically possible limits bias in clinical trials. In the past, many researchers have referred to trials that blinded several groups of individuals as "double-blind." This term is ambiguous, inconsistently applied, and has different meanings to different individuals.[9] Blinding is not an all-or-nothing phenomenon; researchers may blind any of the involved groups. Furthermore, even within one of the groups (such as outcome adjudicators), some individuals may be blinded while others are aware of group allocation. Thus, it is far preferable for researchers to explicitly state which individuals in the trial were blinded, how they achieved blinding and whether they tested the successfulness of blinding.

HOW CAN I BLIND INDIVIDUALS IN SURGICAL TRIALS?

Blinding is unequivocally more difficult to incorporate in trials of surgical interventions than in trials of medical therapies.[10–12] Whereas medical trials usually incorporate placebo medications to achieve blinding, surgical treatments often result in incisions and scars that may differ between groups. Furthermore, if a trial purports to compare surgical therapy to nonoperative management, it will often be impossible to conceal group allocation from at least some of the individuals involved in a trial (such as the patients and surgeons).

Researchers should consider methods to blind each individual involved in a trial separately and search for the simplest, least invasive technique of achieving blinding. Determining the feasibility of blinding patients is usually simple. If the trial involves 2 similar procedures (such as a comparison of division versus nondivision of the short gastric vessels during laparoscopic Nissen fundoplication[13]), trialists may incorporate blinding by simply not informing patients of their treatment allocation. If, however, researchers are comparing surgical therapy to nonoperative management (such as a comparison of surgery versus surveillance for small aneurysms[14]), patients can only be blinded with ethically questionable methods like sham surgery.[15]

Although surgeons can rarely be blinded, it may be possible for researchers to blind other members of the treatment team and thus limit the potential for differential treatment. For example, whereas surgeons would clearly need to know whether patients were assigned to the division or nondivision group of the fundoplication study,[13] the nurses, dieticians and other practitioners administering postoperative care could feasibly have been blinded by simply not informing them of the group allocation. In some cases, this might require more creative but feasible blinding techniques such as covering different incisions with large dressings.

Similarly, the individuals collecting data or adjudicating outcomes may often be blinded by use of relatively simple techniques. In a systematic review of all trials in orthopedic trauma over 10 years, researchers determined that over 85% of trials could have blinded at least some of the individuals assessing outcomes.[16] In contrast, less than 10% of

trials actually incorporated blinding of outcome assessors. The reviewers considered 3 techniques of blinding that could have been incorporated into these trials: using an independent individual unaware of the treatment allocation; concealing incisions or scars; and digitally altering radiographs to mask the type of implant (Fig. 1)

Whereas researchers should search for creative methods such as these to blind individuals in their trials, if they choose to incorporate a novel technique (such as manipulation of radiographs), they must ensure that the blinding process itself does not introduce bias by impairing the ability to accurately assess the outcome. Ideally, trialists will also test the successfulness of the blinding, although this should be undertaken before initiating a trial because there are dangers to testing the success of blinding once a trial has been completed.[17] Researchers should look for 3 qualities in a novel blinding technique: it must successfully conceal the group allocation; it must not impair the ability to accurately assess outcomes; and it must be acceptable to the individuals that will be assessing outcomes.[18]

Finally, researchers can always blind the individuals performing the statistical analysis by simply labelling the groups with nonidentifying terms (such as A and B). Although this seems intuitive, surprisingly few researchers actually report blinding the data analysts in trials.[16]

What should I do if I can't blind?

Despite careful consideration of methods to blind individuals in trials, situations will invariably arise when some or all groups of individuals simply cannot ethically be blinded. Surgical researchers must accept this reality and incorporate other strategies to minimize bias when blinding is not possible. When patients or clinicians cannot be blinded, trialists should ensure that the 2 (or more) allocation groups are, apart from the intervention, treated as equally as possible. This may involve standardizing the care of participants such as cointerventions, frequency of follow-up and management of complications. Alternatively, researchers may choose to use an expertise-based trial design, in which patients are randomly assigned to different surgeons that each perform one intervention.[19] This type of RCT obviates the need for practitioner blinding because each clinician is likely to be biased in favour of the intervention they are performing. Unfortunately, expertise-based trials do not address the potential biases that may be introduced by the lack of participant blinding and may not be appropriate for all research questions.

When data collectors or outcome adjudicators cannot be blinded, researchers should ensure that the outcomes being measured are as objective as possible. Furthermore, the outcomes should be reliable (although reliable outcomes are preferable whether or not the assessors are blinded). Finally, researchers should consider using duplicate assessment of outcomes and reporting the level of agreement achieved by the assessors.

Even if researchers incorporate these methodologic precautions, they should acknowledge the limitations and potential biases introduced by the lack of blinding in the discussion section of the publication.

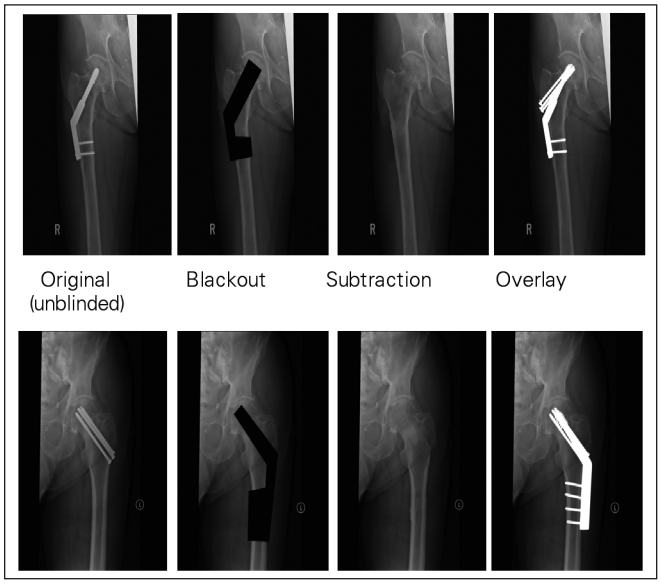

Fig. 1. Example of creative techniques to blind radiographs of femoral neck fracture reduction, fixated with either a dynamic hip screw or 3 cannulated screws.

Conclusion

Blinding is an important methodologic feature of RCTs to minimize bias and maximize the validity of the results. Researchers should strive to blind participants, surgeons, other practitioners, data collectors, outcome adjudicators, data analysts and any other individuals involved in the trial. Useful tips for surgical researchers are provided in Box 1. Although few surgical trials currently incorporate

Box 1. Tips for blinding in surgical trials

Blind as many individuals as possible in the trial

- Participants (patients)
- Practitioners (surgeons, nurses, dieticians, etc.)
- Data collectors
- Outcome adjudicators
- Data analysts

Blinding may often be possible using simple techniques

- If possible, do not inform patients of what group they are in
- Conceal incisions and scars
- Use independent outcome assessors
- Alter digital radiographs or images

If blinding is not possible

- Standardize the treatment of the groups (apart from the intervention)
- Consider an expertise-based trial design
- Use objective, reliable outcomes if possible
- Consider duplicate assessment
- Acknowledge the limitations

blinding, it may be possible to achieve blinding using novel, creative techniques. If blinding is not possible, researchers should incorporate other methodologic safeguards but should understand and acknowledge the limitations of these strategies.

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