Blinding in surgical randomized clinical trials in 2015

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Abstract

Lack of blinding in randomized clinical trials can bias the effect estimates of the observed intervention. In trials assessing nonpharmacological interventions (e.g. surgical randomized clinical trials) blinding is usually more difficult. In this mini-review the blinding and reporting of blinding was assessed from surgical randomized clinical trials that were published in leading medical and surgical journals in 2015. Conducting a systematic search on PubMed, a total of 99 studies were deemed as relevant and blinding status assessed. Blinding was explicitly stated for practitioners, patients and outcome observers in 3%, 37% and 52%, respectively. The blinding status was not clearly stated in a large proportion of studies or had sometimes a misleading classification. Hence, authors and journals publishing RCTs should pay attention that status of blinding is unambiguously reported.

Introduction

There is great agreement that randomised clinical trials (RCTs) produce the most reliable evidence about the benefits and risks of newly developed or already existing clinical interventions, ultimately leading to better care for patients.[1] The quality of a RCT depends on several methodological issues that need to be considered. Blinding of practitioners, participants and outcome assessors are crucial to avoid performance and detection bias.[2] Compared to drug trials, surgical RCTs face several challenges. For example, surgeons can normally not be blinded. Nevertheless, patients and outcomes assessors can usually be blinded and investigators of RCTs should undertake every possible effort to incorporate blinding, especially when "soft" endpoints are evaluated.[2-4] A systematic review from 2008 found that only 10% of outcome assessors in orthopaedic trauma RCTs were blinded.[5] This number is worrying especially when having in mind that most guidelines and clinicians decisions are based on RCTs.[6] Therefore, this mini-review assessed the blinding and reporting of blinding in the most prestigious medical and surgical journals in 2015.

Methods

A search in PubMed was conducted from the 1.1.2015 until the 31.12.2015 for any surgical RCTs in the ten general medical journals with the highest impact factor as well as in the ten surgical journals with the highest impact factor (according to the Thomson Reuters InCites Journal Citation Reports; search strategy within the Appendix). Included were surgical RCTs which compared different surgical interventions or one surgical intervention versus a conservative treatment. Excluded were studies which assessed different teaching methods, treatments before surgery (e.g. chemotherapy versus chemo-radiotherapy), different drugs during surgery (e.g. anesthesia trials), and different interventions after surgery (e.g. physical training, different pain management programs). The following information was extracted from all relevant publication: Population, intervention and control, description of the blinding status of the surgeon, patient and the outcome assessor, and the primary outcome. All methods of blinding were accepted without any classification. Primary outcomes were further stratified into (i) patient reported outcomes, (ii) "hard" outcomes that are easy to measure and not readily subject to observer bias (no room for interpretation; e.g. mortality, BMI);[7] (iii) "soft" outcomes that are more subjective (influenced at least to some degree by the judgement or effort of the outcome

assessor; e.g. complications, lymph node detection rate);[7] and (iv) no specification of primary outcome.

Results

The computer aided search yielded 301 publications from PubMed. Based on titles, abstracts and full text 99 publications were classified as relevant. The most common reasons for exclusion were that the intervention tested in the RCT was not specifically surgery related (e.g. different drugs given; n=72), that the intervention took place before or after surgery (n=44) or that the study was not an RCT (n=30; Figure 1a). In 57 RCTs it was explicitly stated that the surgeon was not blinded (Figure 1b). In 39 studies no specific statement regarding the surgeon was given; however, 5 out of these 39 studies mentioned that the trial was “open-labeled” or “single-blind” together with the information who was blinded (e.g. outcome assessor). Within three of the 99 RCTs blinding of the surgeon was possible and also reported. Patients were blinded in 37 out of the 99 RCTs. In 40 studies it was clearly stated that patients were not blinded, while it remained unclear in 31 RCTs. However, in 8 out of these 31 studies it was either highly unlikely that patients were blinded (i.e. surgical intervention *versus* alternative treatment) or they were stated as “open-labeled” or “single-blind” together with the information who was blinded (e.g. outcome assessor). The outcome assessor clearly stated as blinded in 51 RCTs while the assessment was not blinded in 24 RCTs. Furthermore, 24 studies remained unspecific about the blinding of the outcome assessor (including 3 “open-labeled” studies and one “single-blind” study with blinded patients). The primary outcomes of the 48 studies that had unblinded (n=24) outcome assessors or were unspecific about the status of the outcome assessor were the following (Figure 1c): (i) Patient reported outcomes (e.g. pain, disease specific score; n=12); (ii) easy to measure “hard” clinical outcome (e.g. mortality, change in BMI; n=19); (iii) had a “soft” clinical endpoint that could potentially be influenced (consciously or subconsciously) by the outcome assessor (e.g. complications, lymph node detection rate; n=15); (iv) did not specify the primary outcome (n=3).

Discussion

This mini-review indicates that 52% (51 out of 99 RCTs) of outcome assessors of surgical RCTs that were published in high impact journals, were blinded to treatment allocation. This number is

considerably higher than the 10% blinded outcome assessors of all orthopedic RCTs in peer reviewed journals from 1995 until 2004.[5] However, the systematic research in this study was only conducted in high impact journal, as they were deemed to have the highest impact on decision making. Hence, these results cannot be transferred to all peer-reviewed surgical RCTs. The majority of the remaining 48 RCTs where outcome assessors were not blinded or the status was not specified, had a patient reported primary outcome or a "hard" clinical outcome (n=12, n=19, respectively; Total n=31), hence, there was no urgent need in this studies to blind the outcome assessors. However, a total of 15 studies had a "soft" outcome where blinding of outcome assessors would have been possible (e.g. complications, lymph node counts).

Additionally, the analysis presented here shows that the blinding status of surgeon, patient and outcome assessors remains often unclear even in prestigious journals. It is clear that surgeons can usually not be blinded and that it is often complicated to blind patients in surgical studies (e.g. open *versus* laparoscopic operation). Nevertheless, the status of blinding should be reported for each of those involved subjects. The commonly used terms like "double-blind" or "single-blind" were often used without further specification, or even worse, were misleading. For example, a study which was labeled as "single blind" but stated that "the patients, investigators who completed follow-up, vascular-laboratory personnel, core laboratory evaluators, and members of the clinical-events committee were unaware of the treatment received"[8] or as an "open label" and specified later that outcome assessors were blinded.[9, 10] Hence, authors and journals publishing RCTs should pay attention that ambiguous wording such as "double-blind" without a clear specification is avoided.[4]

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Figure Legend:

Figure 1: Study selection (a), blinding status of involved persons (b), and primary outcomes for the study with outcome assessors who were not blinded or where the blinding status was unclear (c).