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Title

Participant recruitment and attrition in placebo- versus non placebo-controlled randomised trials of surgery: a systematic review

Review Question

Is the problem of participant recruitment and attrition different in placebo-controlled surgical intervention trials, when compared to open-label, non-placebo-controlled surgical intervention trials?

Background

Despite widespread acceptance that a placebo control is essential to maintaining scientific rigour in the evaluation of clinical interventions, the use of surgical placebos introduces difficulties completing such randomised trials with a sufficient number of eligible patients (1, 2). In particular, the inherently invasive nature of surgical placebos often involving the risks of anaesthesia undermines patient willingness to participate in a procedure of potentially no benefit, thereby generating issues with recruitment and cohort retention (1-3).

Randomised control trials (RCTs) in surgery are well-known to suffer from these difficulties in recruitment, and the addition of a surgical placebo adds to especially lower rates of recruitment (1, 3). Indeed, only 15% of published RCTs involve surgical interventions and only 24% of currently used surgical therapies are supported by results of RCTs (2). While some authors suggest that these recruitment problems may be addressed by methods such as TV and newspaper advertising, recruitment usually remains slow and has been previously reported as the reason for early termination of multiple studies (2).

Retaining participants can also be problematic in randomised placebo-controlled trials of surgical intervention with participant withdrawals introducing attrition biases. Attrition refers to losses in participant information either due to drop-out or missing data over the duration of a longitudinal study (4). Such losses can create imbalances in study groups introducing methodological problems (attrition bias) and a reduction of statistical power due to a reduced sample size (4, 5). Although imputation methods exist that address this problem, none of these are replacements for lost information. Attrition compromises the strength of a study's findings in both internal validity and generalisability.

Previous studies have identified predictors of participant attrition, including longer delays between consent and first contact, lower patient education levels, minority race, prolonged duration of screening and symptom severity (6, 7). Other studies have also described study design characteristics that minimise the effects of attrition, including an intent-to-treat study design, participant reimbursement, intent-to-attend next visit discussion, study visit target windows and optimised quality care to limit participant burden (7, 8).

Despite the placebo control being the gold-standard for testing the effectiveness of an intervention, some studies have found that non-surgical placebo-controlled RCTs are characterised by higher subject drop-out rates when compared to non-placebo controlled RCTs (9, 10). Within placebo-controlled randomised trials, placebo arms face higher participant losses compared to treatment arms, possibly due to a lack of efficacy and/or patient perceived allocation of placebo prompting withdrawal (9-11). Moreover, the extent of attrition in placebo-controlled (or sham surgery) trials of surgical interventions has not been explored empirically, largely owing to the scarcity of placebo-controlled surgical trials. In comparison to placebo pills, placebo surgeries involve higher risks and are more invasive to participants, thus in theory possibly creating greater difficulties in retaining participants.

Our study will explore the problem of attrition and recruitment failure in placebo-controlled surgery trials in comparison to surgical trials that use a non-placebo comparator. The primary objective is to investigate differences in participant recruitment and attrition rates in placebo-controlled surgery trials in comparison to open-label, non-placebo-controlled surgery trials for the same intervention. Secondary analyses will explore study characteristics for their association with recruitment and attrition rates.

Methods

Search for studies

This review will include:

1.) Randomised placebo-controlled trials of surgical interventions
2.) Non-placebo-controlled (open-label) trials of similar surgical interventions and conditions

This study will utilise a previously identified set of randomised placebo-controlled trials of surgical interventions from an ongoing review (9) (PROSPERO ID CRD42019117364). We updated a previous electronic search for all published RCTs conducted on humans that compared a surgical intervention to a placebo surgical intervention (10). Surgery was defined as "any intervention that changes anatomy and requires a skin or other epithelial layer incision or suturing" (10). A surgical placebo, or sham surgery, was defined as an "imitation procedure" that cannot be differentiated by the patient, that lacks the key therapeutic step. RCTs will be grouped according to their surgical interventions and clinical conditions, and this informed the search for overlapping RCTs.

For each surgical intervention used in placebo-controlled RCTs we identified in the first search we conducted a systematic review of the literature to identify published RCTs conducted on humans assessing the *same surgical intervention and clinical condition*, but where the comparator was a non-surgical treatment group instead of placebo surgery.

The search to locate eligible non-placebo-controlled RCTs proceeded in the following order of preference: First, we used the Cochrane Database of Systematic Reviews, and DARE (from inception to current date) to identify any systematic review assessing the surgical procedure and condition of interest. We updated the search strategies of these reviews, and included eligible RCTs included in these reviews. Second, where we did not find a systematic review,

we formulated our own electronic search strategies with the help of a medical librarian, using a randomised trial/systematic review filter, combined with a filter specific to the clinical aspects of each group of placebo-controlled RCTs. For these, we searched MEDLINE, EMBASE and CENTRAL, from their inception to the present. The syntax of the search strategies is contained in Appendix 1 (NEED TO COLLATE FROM DROP BOX FOLDER)

Two investigators independently assessed the results of each search strategy, first screening titles and abstracts, and recording the reasons for exclusion. Two independent investigators conducted a full text review of papers included following the title/abstract screening. We resolved any discrepancies in included studies through discussion, and if necessary, using a third investigator for arbitration.

Data extraction

All data will be extracted independently by two investigators, and arbitrated by a third investigator if necessary. Cohen's kappa statistic and raw agreement scores will be calculated to determine inter-rater reliability.

General characteristics of included RCTs

i) Year of study
ii) The study population (age, sex, location, education level, ethnicity)
iii) The total study sample size
iv) The condition for which surgery was performed
v) Type of intervention, dichotomised as open, or minimally invasive/percutaneous surgery.
vi) Presence of a pilot or lead-in phase
vii) Planned length of follow up
viii) Number of follow up timepoints
ix) Any reported methods or incentives to improve recruitment or follow up, including financial, gifts or lotteries, and reminders

Risk of bias

We will use the Cochrane Risk of Bias tool (11) to extract items not related to attrition.

Outcome data

i) *Recruitment rate*, defined as the number enrolled expressed as a proportion of those eligible for the study
ii) *Subject dropout*, defined as a refusal to progress further with the study. This will be reported as a proportion of total number recruited, and where available, will be characterised at different timepoints:
    a. Prior to randomisation
    b. Prior to the intervention
    c. Prior to first follow up
    d. Prior to final follow up
    e. Overall

iii) *Subject loss to follow up*, defined as the inability of investigators to obtain information at planned timepoints for reasons other than *subject dropout*. Where available, this will be characterised at different timepoints:
   a. Prior to first follow up
   b. Prior to final follow up
   c. Overall

iv) *Subject cross-over rates*, defined as an unplanned protocol violation resulting in subjects in the control group receiving the intervention, and vice versa. This will be reported as a proportion of the subject group, and characterised as:
   a. Subjects crossing over into the surgical intervention
   b. Subjects crossing over into the non-surgical intervention
   c. Overall

v) *Overall attrition of participants*, defined as a composite (or addition) of dropout, loss to follow up and cross-overs, expressed as a proportion of total sample size

vi) Stoppage prior to recruitment of planned sample size. Where available, the reason for stoppage will be recorded, including due to poor recruitment rates.

The primary outcomes of interest will be rates of attrition (due to dropout, loss to follow up and cross-over), participant recruitment rates and number of studies with unplanned stoppage.

Statistical Analyses

The extracted data will be tested for heterogeneity and either fixed or random effect meta-analysis will be used to summarise attrition rates (overall, dropout, loss to follow up, and cross over) in placebo vs. non-placebo-controlled trials overall and stratified by trial groups (subject to data availability).

Due to the data nature (varying follow-up duration) mixed effect Poisson regression will be used to examine Incidents Rate Ratio (IRR) and Incident Rate Difference while controlling for potential confounders (e.g. age, type of intervention, etc.)

References

1. Campbell MK, Entwistle VA, Cuthbertson BH, Skea ZC, Sutherland AG, McDonald AM, et al. Developing a placebo-controlled trial in surgery: issues of design, acceptability and feasibility. Trials. 2011;12:50.
2. Wartolowska K, Collins GS, Hopewell S, Judge A, Dean BJ, Rombach I, et al. Feasibility of surgical randomised controlled trials with a placebo arm: a systematic review. BMJ Open. 2016;6(3):e010194.
3. Hare KB, Lohmander LS, Roos EM. The challenge of recruiting patients into a placebo-controlled surgical trial. Trials. 2014;15:167.
4. Dumville JC, Torgerson DJ, Hewitt CE. Reporting attrition in randomised controlled trials. Bmj. 2006;332(7547):969-71.
5. Peterson JC, Pirraglia PA, Wells MT, Charlson ME. Attrition in longitudinal randomized controlled trials: home visits make a difference. BMC Med Res Methodol. 2012;12:178.
6. Siddiqi AE, Sikorskii A, Given CW, Given B. Early participant attrition from clinical trials: role of trial design and logistics. Clin. 2008;5(4):328-35.

7. Karlson CW, Rapoff MA. Attrition in randomized controlled trials for pediatric chronic conditions. J Pediatr Psychol. 2009;34(7):782-93.
8. Sylvia LG, Reilly-Harrington NA, Leon AC, Kansky CI, Ketter TA, Calabrese JR, et al. Methods to limit attrition in longitudinal comparative effectiveness trials: lessons from the Lithium Treatment - Moderate dose Use Study (LiTMUS) for bipolar disorder. Clin. 2012;9(1):94-101.
9. Kemmler G, Hummer M, Widschwendter C, Fleischhacker WW. Dropout rates in placebo-controlled and active-control clinical trials of antipsychotic drugs: a meta-analysis. Arch Gen Psychiatry. 2005;62(12):1305-12.
10. Fava M, Evins AE, Dorer DJ, Schoenfeld DA. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. Psychother Psychosom. 2003;72(3):115-27.
11. Fabricatore AN, Wadden TA, Moore RH, Butryn ML, Gravallese EA, Erondu NE, et al. Attrition from randomized controlled trials of pharmacological weight loss agents: a systematic review and analysis. Obesity Reviews. 2009;10(3):333-41.
9. Teemu Karjalainen, Sam Adie, Lucy Busija, Ian Harris, Rachelle Buchbinder, Justine Naylor, Adriane Lewin, Juuso Heikkinen. Placebo effects in randomised trials of surgical interventions: a meta-epidemiological study. PROSPERO 2019 CRD42019117364 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019117364
10. Wartolowska K, Judge A, Hopewell S, et al. Use of placebo controls in the evaluation of surgery: systematic review. BMJ. 2014;348(may21 2):g3253-g3253.
11. Higgins J, Altman DG, Gotzsche, P. C. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.