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Placebo effects in randomised trials of surgical interventions: a meta-epidemiological study

Citation

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

Review question [1 change]

This review will address three specific questions:

1) What proportion of the surgical intervention effect size is represented by the placebo effect?

2) What is the size of the surgical placebo effect?

3) What is the difference between the surgical intervention effect size in placebo-controlled surgical trials compared to non-placebo-controlled surgical trials?

Secondary review questions are

1) Is there evidence of heterogenous treatment effect in musculoskeletal surgery, i.e. does the variance differ between active surgery groups versus non-surgery groups (due to subgroup of responders to surgery) ?

2) Is there difference in participant attrition rates between placebo-surgery and comparable open label studies

Searches [1 change]

We will perform an update of a previous electronic search (Wartolowska K, et al. Use of placebo controls in the evaluation of surgery: systematic review. BMJ. 2014 May 21;348:g3253; supplementary appendix 1), searching MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) for all published RCTs conducted on humans that have compared a surgical intervention to a placebo surgical intervention.

The updated search will be performed from 1st January 2013 until 21st November 2018.

We will not apply any language restrictions.

We will also screen the placebo-controlled surgical trials from the previous search (results up to 2013) for those which fulfil our inclusion criteria, and will also search the reference lists of the included articles to identify studies not captured in the original search

For each surgical intervention type for the placebo-controlled RCTs identified in the first search, we will search MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify published RCTs conducted on humans assessing the same surgical intervention, but in which the comparator is a non-surgical treatment group (referred to hereafter as ‘overlapping’ RCTs).

We will also search for systematic reviews on same conditions from DARE from its inception until date of search.

The search strategy will include terms relating to or describing the intervention and the conditions. Full strategies for each condition will be developed after the first search is completed, and they will be published with the final manuscript.

Additional search strategy information can be found in the attached PDF document (link provided below).

Types of study to be included

Randomised controlled trials.

No language restrictions will be imposed.

Condition or domain being studied [1 change]

The placebo effect in surgical trials: any condition that is treated surgically and has been assessed in a placebo-surgery controlled trial. Primary analysis examines study effect size in placebo surgery; its components (non-specific versus therapeutic effect), and whether study design affects the effect size.

Secondary analyses will assess 1) magnitude of variance within groups (receiving surgery versus non-surgical) in musculoskeletal conditions. 2) attrition rates in placebo-surgery versus open label studies.

Participants/population

We will include populations as defined in the original placebo-surgery controlled trials.

Intervention(s), exposure(s)

Placebo-surgery.

Comparator(s)/control

1) Any surgical procedure against what the the placebo-surgery was compared in the trial.

2) Any non-active or non-operative control against which the surgical procedures identified in the placebo-controlled surgical trials were compared.

Main outcome(s) [2 changes]

The effect size from each included RCT.

We will use the same outcome for the analysis across the overlapping non-placebo-controlled RCTs (comparing surgery with non-surgical treatment in same conditions). The effect size selected will be, in order of priority: a measure of pain, function, disease specific quality of life, and generic quality of life. In conditions that are not painful, we will extract the outcome most often used as primary outcome in the included trials. We will use validated outcomes wherever possible. For pain, we will use measures of overall pain related to the anatomic region in preference to more specific measures (e.g. pain at rest, night pain, maximum pain). Similarly, for function, we will use measures of overall region-specific function in preference to more specific measures (e.g. walking distance, stiffness).

Measures of effect

We will give priority to any pre-specified timepoint described in the surgical placebo trial(s). Where this is not present, or is irregular across studies, a timepoint will be selected that reflects the maximum benefit (or harm) of the surgical intervention being assessed based on content expert opinion. If the exact timepoint is not uniform across studies, we will

extract the closest timepoint following the timepoint we selected as most important. Where the timepoints are also unclear, priority will be given to overall summary measures across all timepoints.

SMD is used as the summary measure in the primary analysis (comparing effect sizes in placebo-surgery trials versus open label trials)

Additional outcome(s) [2 changes]

In separate secondary analyses, we will use variability (SD) of the primary outcome and overall participant attrition rate (further divided to recruitment rate, subject drop out rate, loss to follow-up rate, cross over rates) as well as the rate of study early stoppage

Measures of effect

In separate secondary variability analysis assessing variances between active and non-active groups in musculoskeletal surgery, we will use variance ratio as summary measure (variance of active group versus variance in the placebo/inactive group).

In the secondary analysis assessing attrition rates in placebo-surgery trials versus open label surgery trials, we will use both incidence rate ratio and incidence ratio difference

Data extraction (selection and coding)

Two investigators (at minimum) will independently assess the results of each search strategy, first screening titles and abstracts, and recording the reasons for exclusion. Two independent investigators will conduct a full text review of papers included following the title/abstract screening. We will resolve any discrepancies in included studies through discussion, and if necessary, an independent investigator will act as an arbitrator.

Two independent investigators will extract one effect size from each included RCT. We will resolve any discrepancies in included studies through discussion, and if necessary, an independent investigator will act as an arbitrator.

For continuous outcomes, we will extract the mean change from baseline and standard deviation (SD) of the change in each group. Where change from baseline is not reported, we will extract the mean and SD of the outcome in the placebo and intervention groups at the specified follow-up time point. We will use information on baseline and final means to calculate the mean change in each group. We will use data available in the article, such as t and p-values from repeated measures tests to estimate standard deviation of change. If this information is not available, we will impute standard deviation of change using validated methods.

Two authors will also extract the following study characteristics independently:

1) The study population (age, sex, location);

2) The total study sample size;

3) The condition for which surgery was performed;

4) Type of intervention, dichotomised as open, or minimally invasive/percutaneous surgery;

5) Whether a primary outcome was specified, either explicitly by the study authors, or via a sample size calculation;

6) Type of outcome, dichotomised as either a prespecified primary (or an outcome that was used for a sample size calculation) or a prespecified secondary outcome.

Risk of bias (quality) assessment

We will assess reporting of allocation concealment, blinding of patients, care-givers, or outcome assessors, and attrition

(defined as a dropout rate or crossover rate of 20% or more). We will use the Cochrane risk of bias tool.

Strategy for data synthesis

We will standardise effect sizes using Hedges' g. We will convert the direction of effect of these standardised mean differences such that a positive value indicates improvement.

For dichotomous outcomes, we will calculate odds ratios for each study. If data for the same outcome are reported in continuous format in some studies and in dichotomous format in other studies, we will convert dichotomous effect sizes (odds ratios) into standardised mean differences.

We will use I^2 statistics to assess statistical heterogeneity when more than two studies are available. We will use random effects meta-analysis to combine results of individual studies.

If sufficient numbers of studies are available, we will also undertake meta-regression analysis to identify characteristics of study design that influence magnitude of placebo effect.

The review questions posed will be addressed as follows:

Question 1: we will calculate proportion attributable to contextual effect as a ratio of the change in the placebo group relative to change in the intervention group.

Question 2: we will perform this analysis in a subset of placebo-controlled surgical trials that also contain a non-operative control. We will calculate the placebo effect as difference between the change in the placebo group and change in the non-operative control group. We will also calculate the proportion of the total observed placebo effect (PPE) that is not accounted for by non-specific effects using the formula: [1 - change in the non-operative control group /change in the placebo group].

Question 3: for each surgical intervention, we will compare summary effect sizes of the primary outcome from placebo-controlled RCTs to non-placebo RCTs. We will conduct a meta-regression analysis to estimate the difference between the magnitude of surgical effect from placebo-controlled and non-placebo-controlled trials, through the assessment of a multiplicative interaction between group allocation and the presence of placebo control.

Analysis of subgroups or subsets [1 change]

In all analyses, we will explore significant clinical or statistical heterogeneity through subgroup analyses using study level covariates including sample size (dichotomised as <100 or >100), type of intervention (dichotomised as open vs. endoscopic/minimally invasive/percutaneous surgery), allocation concealment (yes versus no/unclear), blinding of outcome assessors (yes versus no/unclear), and whether a primary outcome was specified (yes/no, either explicitly by the study authors, or a by inclusion of a sample size calculation). Sensitivity analysis will use the primary outcomes defined by the primary authors.

We will also perform a subgroup analysis comparing the magnitude of effect size in pain, function and global improvement in trials addressing musculoskeletal conditions.

Contact details for further information

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Organisational affiliation of the review [1 change]

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Type and method of review

Epidemiologic, Meta-analysis, Methodology, Systematic review, Other

Anticipated or actual start date

22 November 2018

Anticipated completion date [3 changes]

23 August 2022

Funding sources/sponsors

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The funding sources will not participate in the conduct of this review

Conflicts of interest

Language

English

Country

Australia, Finland

Published protocol

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https://www.crd.york.ac.uk/PROSPEROFILES/117364_PROTOCOL_20200521.pdf

Stage of review [1 change]

Review Completed published

Details of final report/publication(s) or preprints if available [1 change]

Karjalainen T, Heikkinen J, Busija L, et al. Use of Placebo and Nonoperative Control Groups in Surgical Trials: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022;5(7):e2223903. doi:10.1001/jamanetworkopen.2022.23903

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2794704

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Epidemiologic Research Design; Epidemiologic Studies; Humans; Placebo Effect; Placebos; Randomized Controlled Trials as Topic; Reproducibility of Results; Research Design; Surgical Procedures, Operative; Treatment Outcome

Date of registration in PROSPERO

07 January 2019

Date of first submission

20 November 2018

Stage of review at time of this submission [3 changes]

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note

Review completed. Added publication and link to the paper

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The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

07 January 2019

15 May 2020

09 November 2020

23 August 2022