The Relationship of Study Findings to Publication Outcome in Anaesthesia Research
Post Implementation of Mandatory Trial Registration

Background:

Publication bias is defined as the selective submission and acceptance for publication of studies with positive over those with negative results (1) and is an issue that continues to be demonstrated in multiple fields of medicine. Recently, we conducted a review of 1052 abstracts presented at the American Society of Anesthesiologists (ASA) annual meetings 2001-2004 (2). From this review, the odds ratio (OR) for abstracts with positive results proceeding to journal publication was 2.01, demonstrating the presence of significant positive publication bias in the anesthesia literature over the period examined.

Publication bias has a deleterious influence on the accuracy and interpretation of the evidence base used for clinical decision making. It contributes to significant waste in research through the under-reporting of work (3). In an attempt to address the problem of publication bias, the major medical journals have introduced compulsory prospective registration of clinical trials as a pre-requisite for acceptance for publication (4). The International Committee of Medical Journal Editors (ICMJE) released a statement in 2004 encouraging this practice as a required standard for acceptance for publication (4). However, a significant number of journals still do not appear to follow this requirement of prospective registration of randomised controlled trials (5).
In addition, previous studies in many areas of medicine have revealed significant discrepancies between data included on trial registries and that presented in corresponding published papers (6-9). This includes trial registration occurring post data collection completion, and changes to primary outcomes and sample sizes. De Oliveira et al performed a review of RCTs published in 2013 in the five highest impact factor anaesthesia journals (10), and found that 64% of the trials were not prospectively registered, and 48% of the registered trials had a major discrepancy compared to their trial registry entry.

The purpose of our study is to determine whether the introduction of compulsory trial registration in 2004 has resulted in a decrease in publication bias. We will estimate publication bias in a population of clinical research published after compulsory trial registration and compare this with our previous estimate of publication bias, which included clinical research published prior to compulsory trial registration (2). We will use the same methods that we used previously to estimate publication bias (2). Namely, we will review all abstracts presented at the ASA Annual Meeting between 2010-2013 and assess whether abstracts that reported positive findings were published more frequently in MEDLINE indexed journals as full manuscripts than those that reported negative findings. We will compare the post compulsory trial registration publication bias with the pre compulsory trial registration publication bias and we will test for a statistically significant difference. The timeline of 2010-2013 is chosen as a period 5 years after implementation by the ICMJE of mandatory trial registration.
Methods:

Population – All randomized controlled studies conducted in time period

Intervention - Compulsory trial registration

Comparator – No compulsory trial registration

Outcome – Odds ratio of being published if statistically significant compared with not being statistically significant

Potential Confounders/Modifiers – Study Size, Abstract Score

All abstracts from the 2010-2013 ASA Annual Meeting will be identified from the ASA Abstracts website. We will use this timespan as it allows at least 6 years to have elapsed for subsequent publication of studies in the peer reviewed literature, and findings from our recent review demonstrated that at 6 years post abstract presentation, 97.4% of the positive abstracts and 96.3% of the negative abstracts that went on to publication, had been published (2).

All abstracts performed as RCTs in humans will be included in a database constructed with Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA). We will use the same methods to estimate publication bias in the post compulsory trial registration abstracts as we did in our previous review (2). A trial will be considered to be an RCT if the individuals in the trial were prospectively assigned to one of two or more alternative forms of healthcare using a random method of allocation (11). Studies will firstly be assessed as either “positive” or “negative”. Positive studies will be defined as studies showing a statistically significant result in the direction of the experimental treatment for the primary outcome compared to the control treatment in the conference abstract. Where the primary outcome is not clearly defined, the first reported outcome will be utilized. Studies showing no difference in outcome between treatment groups will be counted as positive if the stated objective was to show
treatment equivalence or non-inferiority. We will define negative studies as those that failed to show a statistically significant difference in the direction of the experimental treatment over the control treatment, or failed to show equivalence or non-inferiority if that was the stated aim. Some abstracts comparing interventions may have no clear “experimental” and “control” group but will be considered positive if a difference was shown between the groups. If there is initial uncertainty over whether the result of the abstract was positive or negative, two authors will discuss and make a consensus decision guided by the above definitions.

A systematic literature search will then be performed via PubMed and Medline to identify any subsequent publication of the study. The search strategy will include seven separate searches in the order of the first author’s name, the second author’s name, the last author’s name, the first author’s name AND keywords, the second author’s name AND keywords, the last author’s name AND keywords, and keywords alone.

The following baseline characteristics will be recorded: the month and year of presentation of the conference abstract (Note: the ASA Meeting is held in October each year) and of the journal publication if published, the author details, and reported study size. Whether a study that proceeded to journal publication had completed full recruitment at the time of conference abstract will be noted by comparison of sample sizes in meeting abstract and subsequent publication. Studies which do not state that full recruitment has occurred explicitly will be classified by us as uncompleted at the time of conference presentation if the number of participants in the final journal publication is different to that of the conference abstract.
The quality of the conference abstract will be assessed by a scoring system consisting of 13 variables (see Appendix) adapted from a checklist previously devised by Hopewell et al. (12) that was based on existing reporting standards (13). We also aim to record the time to publication from conference abstract presentation date (October of that year) of those studies that proceed to journal publication.

Statistical Analysis

Statistical analyses will be performed using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) and Stata (Copyright 1996–2014 StataCorp LP, 4905 Lakeway Drive, College Station, TX 77845 USA).

1) The primary endpoint will be a comparison between the OR from our previous study and from this current study. We define a 33% decrease in OR as clinically significant. This corresponds to a new OR of 1.33.

2) Sample size calculation: Using the database from our previous study (2), a simulation was run (see attached R code) which determined that a similar sample size of 1052 abstracts would be required to detect an estimated 33% decrease in OR, with 80% power.

3) The OR (for this current study sample of ASA abstracts from 2010-2013) between positive and negative studies for journal publication will be calculated as a raw OR.

4) The OR adjusted for study size and abstract score in a multivariable logistic regression model will then be calculated.
5) Abstract scores, being ordinal data, will be compared between published and unpublished studies as well as between positive and negative studies, using ordered logistic regression. This will also be done as a multivariable analysis, incorporating both publication status and positivity/negativity as well their interaction term. Similar comparison will be made for study size.

6) Time to publication will be compared between positive and negative studies as a secondary analysis, using Cox regression modeling, with adjustment for the same covariates included, and generation of Kaplan-Meier survival curves.

References:
5 Wager E, Williams P. "Hardly worth the effort"? Medical journals' policies and their editors' and publishers' views on trial registration and publication bias: quantitative and qualitative study. BMJ 2013; 347: f5248.


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Title:
The relationship of study findings to publication outcome in anaesthesia research post implementation of mandatory trial registration

Date:
2018

Persistent Link:
http://hdl.handle.net/11343/198339

File Description:
Protocol pt.2