Bias in cervical total disc replacement trials

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Abstract

Purpose of review Cervical disc replacement (CDR) has emerged as a motion-preserving alternative to anterior cervical discectomy and fusion in selected cases. Despite favorable literature, CDR is not universally accepted because of concerns regarding bias in the existing literature. The purpose of this review is to identify the possible biases in the disc replacement literature.

Recent findings Recent studies that compare CDR and ACDF have demonstrated equivalent or superior outcomes, lower rates of secondary surgery, and equivalent safety at medium-

and long-term follow-up. In our review, we identified four types of bias that may affect the CDR literature: publication bias, external validity, confounding bias, and financial conflicts of interest.

Summary Bias, whether intentional or unintentional, can impact the interpretation and outcome of CDR studies. Recognition of this issue is critical when utilizing the existing literature to determine the efficacy of CDR and designing future studies.

Keywords Cervical radiculopathy · Cervical disc replacement · Anterior cervical discectomy fusion · Bias

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Introduction

Bias has been defined as any process at any stage of inference that tends to produce results or conclusions that differ systematically from the truth [1]. In medical research, bias can lead to the misinterpretation of results, which in turn can lead to unnecessary procedures, unforeseen complications, or other unanticipated outcomes. Bias can be deliberate or unintentional. There are established research practices that are intended to reduce the effect of bias in clinical research studies including randomization method, allocation sequence concealment, participant blinding, outcome assessor blinding, outcome measurement, interventionist training, withdrawals, intent to treat analyses, clustering, and baseline characteristics.

In the CDR literature, concerns about bias are frequently raised, in part, due to the heterogeneity of the published literature. There are some studies in the recent literature that are favorable for CDR [2, 3–8, 9, 10, 11]. Conversely, there are other studies that do not report similar improvements in outcome or reductions in secondary surgery with cervical disc replacement [12, 13]. Despite the frequently raised concern

about bias in CDR literature, there are few studies that have specifically assessed potential biases in the outcome of CDR trials.

The purpose of this paper is to identify and define sources of bias that may confound the CDR literature including publication bias, external validity, confirmation bias, and financial conflict of interest. We feel that this review will help to guide future investigators, surgeons, and patients in the interpretation of the disc replacement literature.

Publication bias

Publication bias is a process by which the research that appears in the published literature is systematically unrepresentative of the population of completed studies [14]. Therefore, secondary surveys of the literature (such as systematic reviews or meta-analyses) that analyze only published papers will be biased because they will not include unpublished studies. Publication bias is most commonly discussed in the context of disproportionate reporting of positive, favorable research results.

Publication bias is a complex, multifactorial process that is likely related to both author and journal factors. Studies with positive results (showing that the experimental group is more successful than the control group) are more likely to be published in the peer-reviewed, scientific literature, particularly in high-impact journals. A recent survey of high-impact journals found that 67% of articles favored a new technology whereas only 6% of articles favored the conventional treatment [15]. Therefore, at the editorial level, journals may favor publication of studies with positive results. The subjectivity of the peer review process is also partially responsible for the difficulty publishing negative results. Previous studies have demonstrated that the agreement between reviewers is poor and little better than random chance [16, 17]. In the authors' experience, reviewers are much less likely to agree upon publication of a study with negative results. Studies with a negative or equivocal outcomes, even if of superior quality, may have more difficulty with publication than studies with a positive outcome, due to reviewer heterogeneity [18]. However, despite poor reviewer reliability, editors place considerable weight upon reviewers' recommendations in the decision for acceptance or rejection of a manuscript [19]. Further study is necessary to determine if there are specific topics within the spine literature, such as disc replacement, in which it is more difficult to publish negative results.

Despite a plethora of systematic reviews on cervical disc replacement, only a few studies assess publication bias directly [20–31]. There are several studies that have demonstrated a publication bias in the cervical disc replacement literature [32, 33]. Therefore, systematic reviews of cervical disc replacement literature are challenging to interpret because there are likely studies with equivalent or negative results that have not

been reported and not included in these reviews. For example, although the Discover artificial disc replacement investigational device exemption study (NCT00700739 and NCT00432159) has been concluded, the full study results have not been published. Only smaller subanalyses of the Discover IDE have been reported [13]. According to the best available information on clinicaltrials.gov, the overall success rate of the Discover artificial disc replacement trial was 33% in the study patients and 90% in the control ACDF population at 12 months (<https://clinicaltrials.gov/ct2/show/results/NCT00700739?sect=X70156&term=discover+disc&rank=2#outcome1>, accessed October 25, 2016). Failure to report negative results such as the results above may result in publication bias because future meta-analyses will not include all available subjects.

Authors suggestions for reduction of publication bias

To address publication bias, we recommend that all CDR studies' results be published including negative results, even if they are published in lower-impact journals. In addition, public reporting of primary outcome data on clinicaltrials.gov is also helpful to identify studies that are in the midst of the publication process. We also recommend that future systematic reviews evaluate public resources such as clinicaltrials.gov for additional study information. We recommend that journals consider a non-blinded peer review process to improve transparency and quality of the peer review process [34–38].

External validity

External validity refers to the extent to which the study results can be applied to situations outside of study conditions. The primary indication for CDR in the Investigational Device Exemption trials was patients with persistent cervical radiculopathy or myelopathy who have failed non-surgical treatment for at least 6 weeks or who have progressive symptoms [6, 39, 40]. Patients had imaging studies demonstrating disc pathology that was concordant with their clinical complaints. Patients with instability, osteoporosis, facet arthrosis, or other medical conditions were excluded from the disc replacement studies. Although these study conditions were designed to reduce possible confounding variables, the study conditions may have also created a study population that is not completely representative of the general population of patients with cervical pathology. If the study population differs substantially from the general population, the external validity of the study results would suffer.

Indeed, there are studies that demonstrate that most patients (60%) with cervical spine pathology would not be eligible for inclusion in a CDR study [41]. Another retrospective analysis of IDE study data concluded that cervical disc replacement in

patients with radiographic abnormalities that are relative contraindications (such as disc space collapse) may lead to poor clinical results [13]. Although poor external validity is not specifically a bias of cervical total disc replacement literature, an overly restrictive study population may be reflective of biased study design. The generalizability of the disc replacement IDE results about overall success and failure may be limited because the IDE study populations do not resemble the real-world populations of patients who have cervical complaints [42]. Due to the novelty of TDR and limited utilization compared to ACDF, there are few large, high-quality studies on the outcome of CDR or secondary surgery rates outside of IDE study data [7]. However, the available studies outside of IDE study conditions do demonstrate a benefit for CDR in reduction of costs and secondary surgery rates.

Another aspect of external validity that may affect TDR trials is expertise bias. In technically demanding procedures such as spine surgery, a surgeon's skill and expertise is expected to play an important role in the outcome of the procedure [43]. In the most commonly cited CDR studies which are IDE studies, the surgeons performing TDR and ACDF are highly selected surgeons. With any new surgical procedure, there is an inevitable learning curve. Further studies are necessary to determine if the results of TDR seen in IDE studies with highly selected surgeons are reproducible in the general population.

Authors suggestions for enhancement of external validity

To improve external validity, we recommend that database studies and large-scale research studies be performed on patients who had CDR performed outside of IDE study conditions. To address expertise bias, we recommend that cervical disc replacements require a training session before product utilization and that “learning curve” cases are also reported.

Confirmation bias

Confirmation bias occurs when one interprets information in a manner that endorses one's own preconceptions towards a hypothesis under study. Confirmation bias can lead to statistical error and may occur when researchers choose to incorporate evidence that adds confirmatory support to their intended hypothesis and choose (whether consciously or subconsciously) to ignore evidence that discredits the results that they believe in.

Confirmation bias is generally addressed by blinding study participants and investigators. However, it is not possible in most studies of CDR to blind participants or investigators due to different postoperative treatments (collar in fusions versus early mobilization in disc replacements). However, the lack of blinding in CDR studies leaves patients susceptible to confirmation bias.

Although there is little written about confirmation bias in the disc replacement literature, the differential clinical outcomes of TDR versus ACDF in some early reports are suggestive of confirmation bias. Several early reports of CDR versus fusion studies described markedly improved arm pain scores in the disc replacement group. However, this finding may be suggestive of confirmation bias since both groups of patients should have undergone adequate discectomy and nerve root decompression. Mechanical factors, such as adjacent segment degeneration, should not manifest in the early immediate postoperative period. Another observation suggestive of confirmation bias is the higher satisfaction scores in some CDR studies despite equivalent disease-specific measures such as pain scores.

To the authors' knowledge, there is no instrument to assess the effect of confirmation bias or preoperative expectations on outcome. However, recent studies in the lumbar literature have demonstrated that preoperative expectation is a significant factor in postoperative outcome even 1 year out from surgery [44]. Other recent studies that have incorporated blinding to control confirmation bias have demonstrated surprising results in the placebo treatment groups [45, 46]. A recent meta-analysis of 16 trials with subjective outcomes determined that non-blinded subjective outcomes were associated with exaggerated treatment effectiveness compared to blinded outcomes [47–49]. Additionally, the duration of confirmation bias is unclear in the literature. Although it is plausible that confirmation bias would affect early outcome, the authors would hypothesize that, at some point, the initial study euphoria would abate and the effect of confirmation bias would be reduced.

Confirmation bias may particularly influence the rate of secondary surgery in disc replacement studies, since the decision for secondary surgery is subjective. There has been at least one report describing a higher secondary surgery rate in ACDF patients inside of IDE study conditions compared to concurrent patients (at the same institution) who had ACDF at the same institution outside of an IDE study [50]. The implication of the above study is that providers or patients in the disc replacement studies were more willing to revise a failed ACDF and offer a secondary surgery in IDE study conditions than in non-IDE study conditions due to confirmation bias. However, the effect of patient or provider expectations on the decision for secondary surgery is difficult to quantify. The IDE studies generally utilize radiographic outcomes that are also generally consistent with the expected secondary surgery rates.

Secondary surgery is an inherently subjective decision. Patients who have a poor outcome from an index procedure may or may not choose not to undergo a secondary procedure. If patients with significant pain believe that stress is transferred to adjacent discs from a fusion, they may be more likely to undergo a secondary procedure. To account for this subjectivity, the FDA-defined success criterion in many FDA trials

includes a composite measure that includes clinical outcome and secondary surgery to account for patients with a poor outcome who chose not to undergo additional surgery [51].

Author suggestions for confirmation bias

The authors suggest that future studies are performed to specifically evaluate the effect and duration of confirmation bias in the surgical literature. Particularly since cervical collars have themselves been shown to have little effectiveness, it may be possible to design future CDR studies with identical postoperative conditions (without a cervical collar). Finally, IDE study results should report objective, radiographic measures in addition to subjective clinical outcome measures. Future studies should also utilize checklists to reduce bias in clinical research [52].

Financial conflict of interest

Funding can create a significant bias in clinical research at the journal, editorial, and author level. Journal-level conflict of interest usually takes the form of publication bias. At the journal level, the disc replacement studies are very likely to be published if they report positive results even if they are industry funded [53]. Previous studies have reported that a substantial proportion of orthopedic medical device studies are industry funded [54]. Funding may also be related to publication bias since a majority of industry-funded studies report positive results [55–58]. Additionally, in many specialties, it has been demonstrated that articles with positive results are more likely to be published in high-impact factor journals [59, 60]. Almost all of the large, prospective, randomized disc replacement studies are industry funded since disc replacements are a relatively new innovation that have only recently received FDA approval. There are no public domain disc replacements. Thus, there is little financial incentive for industry to dedicate time or resources into the publication process for ineffective products that are not likely to be financially successful. Therefore, the majority of disc replacement studies with positive results are industry funded.

However, another interesting aspect of journal-level conflict of interest is editorial bias [61]. Recent articles have suggested that the editors of prominent journals have failed to maintain a firewall between the business and editorial departments, resulting in a form of financial conflict of interest related to sales and advertising of journal articles or subscriptions. There is at least one prominent example of a non-spine journal (*New England Journal of Medicine*) that may have taken actions that belie a conflict of interest. Possible editorial-/journal-level actions that are related to conflict of interest include creating several editorial or commentary articles on a single side of a controversial issue to influence readers. For instance, reprints of the *New England Journal of Medicine*

VIGOR study describing Vioxx generated \$697,000 or more [62–64]. Although editorial-level conflict of interest has not been reported specifically in the context of TDR, editorial-level COI is an underreported issue in the major spine journals. Over 30% of the editorial board members of the five major spine journals have financial conflicts of interest with industry [65]. Editorial-level conflicts are often reported online or on the journal website, but not on the specific article text. Further study is needed as to whether there are editorial-level conflicts in disc replacement studies. Recent actions taken by spine journal editors on other topics in spine surgery, including creating special embargoed issues with multiple redundant commentaries, demonstrate the ability of journal editors to advocate about specific issues [66, 67].

By far the most scrutiny on financial conflict of interest has occurred at the investigator-author level. There is potential for industry funding to influence surgeon perceptions of new technology, reporting of outcomes, and reporting of adverse events. Other areas of spine surgery, such as the studies describing the utilization of recombinant human BMP-2, have been heavily scrutinized due to author-investigator conflict of interest [66, 67]. Obviously, authors who have financial incentives that are tied to the outcome of a particular product have a significant interest in the outcome of the research. There is at least a perception that authors who have financial conflicts may be tempted to emphasize positive findings and to gloss over negative findings, perhaps unconsciously. Although there has not been a specific study in the TDR literature that proves individual conflict of interest influencing the outcome of a study, further study with non-conflicted investigators is necessary.

Authors' suggestions for financial conflict of interest

Full disclosure of pertinent relationships and outside relationships at the journal, editor, reviewer, and author level is necessary for transparency around financial conflict of interest. Such disclosures are required by physicians and also by medical device manufacturers according to The Physician Payment Sunshine Act (PPSA). Additionally, further studies are necessary to determine the extent to which industry sponsorship influences specific CDR research.

Conclusions—moving forward

In conclusion, the purpose of this review was to identify and define sources of bias that may confound the cervical total disc replacement literature. Bias can be generated at any stage in the research process and can impact the results generated in a study and how these results are interpreted by readers and investigators. Bias can be deliberate, but it can also be unintentional. In our review, we identified four types of bias that

may affect the CDR literature: publication bias, external validity, confounding bias, and financial conflicts of interest. Publication bias exists as a source of bias because studies with positive results are more likely to be published in peer-reviewed scientific journals. In order to combat publication bias, we recommend that journals publish all TDR trial results, including studies with equivalent or negative results, and that journals move to a non-blinded peer review process. Threats to external validity exist because many patients with cervical spine pathology do not fit into IDE study conditions. To address threats to external validity, we recommend that future TDR studies be performed outside of IDE study conditions. Confirmation bias occurs when an investigator or subject interprets information in a manner that endorses their preconceptions towards a hypothesis and ignores evidence that discredits the results. Confirmation bias can be negated by blinding treatment groups. Although this may be difficult to do in TDR trials, we recommend an attempt be made to blind investigators in future TDR trials. Finally, financial conflict of interest is another source of bias that can influence research.

In summary, bias, whether intentional or unintentional, can impact the interpretation and outcome of cervical disc replacement studies. If investigators and journals are diligent, bias can be minimized by employing a few key strategies and tools throughout the research and publication process. In the future, it is essential that all parties make an effort to eliminate bias and publish sound studies that contribute to the body of literature on cervical disc replacement.

Compliance with ethical standards

Conflict of interest Kris Radcliff reports personal fees from Globus Medical, personal fees from DePuy, personal fees from Stryker, personal fees from Medtronic, personal fees from Orthopedic Sciences, Inc., personal fees from NuVasive, personal fees from 4 Web Medical, other from LDR Medical (now Zimmer), outside the submitted work, and shareholder status at Rothman Institute.

Sheeraz Qureshi is a board or committee member for the following organizations: AAOS, Cervical Spine Research Society, Musculoskeletal Transplant Foundation, and NASS. He is on the editorial or governing boards of the following organizations: Clinical Orthopaedics and Related Research, Contemporary Spine Surgery, Global Spine Journal, Spine, and Spine Journal. Dr. Qureshi has also received speaking/consultancy fees from the following organizations: Globus Medical, Medtronic, Medtronic Sofamor Danek, Orthofix, Inc., Stryker, and Zimmer.

All other authors declare no conflict of interest.

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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