EDITORIAL

Publication Bias in Clinical Trials: a Veterinary Perspective

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Publication bias can be defined as studies with positive results are more likely to be published, published earlier, or published in journals with high impact factors than studies with negative results [1,2]. In clinical trials that use human subjects, if the bias is present, it possibly distorts clinical decisions; as a result, this issue has been debated in medical literature for many years [3]. Whatever reasons, publication bias receives less attention in veterinary clinical literature, a major source providing essential knowledge for veterinarians who want to improve their clinical practices and decisions. Therefore, in this manuscript, I raised the issue for debating in our veterinary community, and the outline includes: how publication bias in clinical trials impacts a human and an animal, how about the bias from a pilot study in veterinary clinical literature, who participated in, and how to reduce the bias.

It is clear that publication bias in clinical trials is a serious problem for medicine [4]. For example, If only one-half of completed studies are positive and only those results are reported, this may cause clinicians a distorted view of the efficacy of the intervention; as a result, they may misleadingly give a treatment to their patients. Unreported adverse effects of the trials can, more seriously, be dangerous to a patient's life. Moreover, systematic reviews and meta-analysis which rely primarily on published data further magnify this bias to obtain greater statistical power. Unreported clinical studies, as a consequence, cause wasted resources and may result in other investigators redoing the same futile studies. In the aspect of human health, therefore, failure to publish results is unfair to the patients who have voluntarily participated at some possible inconvenience, discomfort, and risk [5]. In my view, how a human suffers from the publication bias in medical clinical research is, of course, similar to how an animal suffers from that in veterinary clinical research. An animal may unnecessarily be injured, pained, or even dead because investigators, although they do well on literature search before starting an experiment, still do not know anything about unpublished data; thus, they may unintentionally repeat unreported studies. Additionally, to make new drugs and biological products for human beings, certainly, an animal, often a laboratory animal, is used in a beginning phase of clinical trials. Even without the publication bias, the more the new drugs and biological products are made, the more the animals are used.

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Most animals, if not all, suffer during an experiment and then are killed after the study. With the publication bias, there is no doubt that number of animals used must further increase. In my opinion, anyone who has to use an animal for a study should keep in mind the 3 R's principles: reduction, refinement, and replacement of an animal used in the study.

Although publication bias can be assessed through systematic reviews and by examining funnel plots [2,6]; however, in my pilot study, I did just a preliminary analysis on articles published in the section *"Small Animals"* of the *Journal of American Veterinary Medical Association (JAVMA)*, a premier veterinary clinical journal, in all 24 issues of 2008. Of 126 articles, numbers of articles categorically based on types of study designs were: 49 prospective studies, 43 retrospective studies, 28 clinical (case) reports, and only 6 randomized clinical trials. Of 6 randomized clinical trials, 5 are positive results and only 1 is negative results. Therefore, in this situation, publication of positive results is 5 times greater than that of negative results. Is this due to publication bias? The answer, simply, is we don't know because we can't access data how many clinical trials have been conducted, how many studies yield positive or negative results, and how many studies whether with positive or with negative results have been submitted; indeed, we do know only how many articles published. Therefore, we still cannot rule out a tedency for the bias in *JAVMA*. However, it is a good sign for reducing the bias that *JAVMA* allows a study with negative results to be published.

Authors, sponsors, editors, and peer reviewers are all participated in publication bias [5]. Although it is unclear whether publication bias results from authors or sponsors dismissing negative trials or from editors and peer reviewers rejecting them after submission, authors instead bear a major responsibility because a process of publication must begin with them. In deed, some reports indicate that publication bias is typically caused by investigators who do not submit their research for publication, rather than rejection by journals [7]. Investigators with negative or inconclusive results may be pessimistic about their chances for publication of their findings; hence, they do not submit their results for publication. For business reasons, clinical research sponsors, usually drug companies, may contribute to publication bias when they refuse to publish a full or a part of a clinical trial with results that are inferior to their products. In addition, public research from drug companies is more likely to be favorable to their product because they often used inappropriate comparators chosen or multiple, selective trials [8]. Journals may also contribute to publication bias when they refuse to publish null studies, but not in the case of *JAVMA*.

Because publication bias in clinical trials arises from multiple sources, therefore, to reduce it has to use multiple procedures. In medical community, mandatory clinical trial

registration initially proposed in 2005 [9] and reviewed in 2007 [10] by *International Committee of Medical Journal Editors (ICMJE)* may be the most effective method. If investigators want to publish their clinical trials in *ICMJE* member journals such as *Journal of American Medical Association, New England Journal of Medicine*, and the *Lancet* or other journals requiring such registration, they must submit the trials in recommended registries before starting the studies. International Clinical Trial Registry Platform operated by World Health Organization is a primary registry. In addition, investigators can also submit the trials in other registries that meet several criteria: be accessible to the public at no charge, be open to all prospective registrants, be managed by a not-for-profit organization, be a mechanism to ensure the validity of the registration data, and be electronically searchable [9,10]. Registration ensures that all registered studies must present to the public whether published in a peer-review journal or posted in open-access database; therefore, this method can reduce the bias more effectively [11,12]. Unfortunately, such registration is required only in the trials with human subjects but not with animals. Can we govern registration of clinical trials that use an animal? The answer, at present, may be not because of tremendous pressure from the stake holders. For instance, research sponsors may argue that such registration will destroy their competitiveness by allowing competitors full access to their research plan [9].

For journals, both transparency of editorial policies and strength of peer review process are essential not only to minimize publication bias but also to prevent scientific misconduct and other potential bias. Some authors suggested that 2 steps of peer-review process in which reviewer can see only the material and method section of the manuscript in the first step then decide whether the manuscript is high quality to be published. The next step the reviewer see the result and decide again to publish the manuscript [13]. Research with high quality or rigor on the materials and methods, regardless of the results, should be valuable enough to be published.

In conclusion, clinical studies especially clinical trials guide life-or-death clinical decisions whether for physicians or for veterinarians, where their professionals operate under oaths of ethical conduct. To reduce publication bias in the final step of research and all sources of potential bias that may occur during conducting research is necessary to get accurate evidence available for clinical decision making.

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