Double-Organ Bias in Published Randomized Controlled Trials of Glaucoma

Fehim Esen, MD,* Mehmet Köstek, MD,†
Ahmed S. Emekli, MD,† and Muhsin Eraslan, MD*

Purpose: Most of the statistical tests used in significance testing are based on the assumption that each data entry is independent from other entries, however, we observe that in many articles researchers include data from 2 eyes as independent variables while performing these statistical tests. The aim of this study was to formally survey the prevalence of the above-mentioned "double-organ bias" in randomized controlled trials (RCT) of glaucoma.

Materials and Methods: We did a PubMed search with the terms "glaucoma" and limitations "Humans" and "Randomized Controlled Trials" in 15 highest-impact-factor ophthalmology journals between November 2002 and November 2012. We only included RCTs published as an original article, where the aim was treating glaucoma. Two independent observers (M.K. and A.S.E.) read through each article and classified the articles according to treatment modality (medical, laser, or surgical) and presence of double-organ bias.

Results: The PubMed search yielded 270 articles. A total of 130 articles qualified for the survey. Eighty-five of the RCTs were medical studies, 11 were laser studies, and 34 studies evaluated the outcome of a surgical procedure. In 17 of the 130 articles (13.1%), double-organ bias was found. Prevalence of the double-organ bias was not significantly different between medical (12.9%), laser (14.7%), and surgical (9.1%) studies.

Conclusion: Double-organ bias was observed around 13.1% of the published RCTs, leading to inaccurate statistical testing.

Key Words: randomized controlled trial, glaucoma, statistics, double-organ bias, 2 eyes bias

(*J Glaucoma* 2016;25:520–522)

Improper use of statistics tests is an important problem, affecting scientific output.[1,2] An important issue in ophthalmology research is that a substantial number of articles in ophthalmology journals give the study outcomes in either eye of a study patient as an independent data point. Although this important limitation was highlighted in a number of publications,[3–7] we had the observation that such improper statistical testing still continued to appear even in high-impact-factor journals.

Most of the statistical tests used in significance testing are based on the assumption that each data entry is independent from other entries. We also know that a change observed in 1 eye of a patient cannot be considered independent of what is observed in the other eye of the same individual. Therefore, it is improper to do statistical testing on 50 eyes of 25 patients in significance testing. In this study, we aimed to formally tabulate the frequency of this above-mentioned "double-organ bias" in randomized controlled trials (RCT) of glaucoma.

MATERIALS AND METHODS

A PubMed search was done with the terms "glaucoma" and limitations "Humans" and "Randomized Controlled Trials" in 15 highest-impact-factor ophthalmology journals, between November 2002 and November 2012. Among these articles, we only included RCTs published as an original article, where a treatment modality (medication, laser intervention, or surgery) was used to treat glaucoma. Meta-analyses, reviews, letters, brief reports, extension studies, and secondary analyses of previously published data and studies not intended to treat glaucoma were excluded. The included journals and number of included articles are listed in Table 1.

Two independent observers (M.K. and A.S.E.), read through each article and classified the articles according to the studied treatment modality and presence of double-organ bias. The 2 authors had disagreement for the presence of the double-organ bias in 6.1% (n = 8) of the cases and for the study type in 4.5% (n = 6) of the cases. Three authors (F.E., M.K., and A.S.E.) came together and solved these disagreements by discussion. The presence of a biostatistician or epidemiologist among the authors was further tabulated, to study whether it had an influence on the prevalence of the bias.

RESULTS

The PubMed search yielded 270 articles and 130 of them qualified for the survey (listed in Supplement 1, Supplemental Digital Content 1, http://links.lww.com/IJG/A81). Eighty-five of the RCTs included only medical intervention to treat glaucoma. Eleven studies included laser treatments and 34 studies were designed to assess the outcome of a surgical procedure. In 17 of the 130 published articles (13.1%), double-organ bias was observed (Fig. 1A). Prevalence of the double-organ bias was not significantly different between medical and interventional (surgery or laser) studies. The prevalence of the bias was also not significantly different between the articles published in the first (2003 to 2007) and second 5-year (2008 to 2012) study

Received for publication October 29, 2014; accepted December 14, 2015.
From the *Department of Ophthalmology, Marmara University School of Medicine; and †Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey.
Disclosure: The authors declare no conflict of interest.
Reprints: Fehim Esen, MD, Department of Ophthalmology, Marmara Universitesi E. A. Hastanesi, Goz Hastaliklari Anabilim Dali, Pendik, 34899, Istanbul, Turkey (e-mail: fehimesen@yahoo.com).
Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Website, www.glaucomajournal.com.

DOI: 10.1097/IJG.0000000000000369

TABLE 1. The Included Journals and Number of Trials

Ophthalmology Journals	No. Trials
Progress in Retinal and Eye Research	0
Ophthalmology	27
American Journal of Ophthalmology	29
Ocular Surface	0
Archives of Ophthalmology	13
Investigative Ophthalmology & Visual Science	6
Journal of Vision	0
Experimental Eye Research	1
Survey of Ophthalmology	4
The British Journal of Ophthalmology	40
Retina	0
Current Opinion in Ophthalmology	0
Acta Ophthalmologica	9
Journal of Refractive Surgery	0
Vision Research	1

periods or higher-impact-factor journals (ranking 1 to 7) and lower-impact-factor journals (ranking 9 to 15) (Fig. 1B). A total of 27.6% of the articles (n = 36) had a biostatistician or epidemiologist among the authors and the prevalence of the double-organ bias was 11.1% in these studies, whereas the prevalence of the bias was 13.8% in the rest of the articles ($P = 0.68$, $\chi^2 = 0.169$).

DISCUSSION

The double-organ bias was present around 17/130 (13.1%) of the RCTs we surveyed. While designing this study, we had reasoned that the prevalence of this bias would be less in surgical studies or interventional studies as we usually do not do surgery on both eyes of the patient at the same day or there may not be an indication for surgery in the other eye. However, we observed that there was no statistically significant difference between the medical and interventional studies. We have also observed that there was no significant difference between the higher-impact-factor and lower-impact-factor journals for the presence of this bias. There was no trend for improvement by time in this kind of statistical miscalculations when we compared the first and second 5-year periods in our study. The presence of a biostatistician or epidemiologist among the authors did not have a significant effect on this statistical limitation. A relatively old study reported that this bias was present in 23% of the original articles published in *British Journal of Ophthalmology* in the first 6 months of 1995.[6] Our study only included a more strictly defined study type, RCTs, and therefore the bias might have been less in our work. Surely, the awareness of this bias might also have increased with time.

To overcome the double-organ bias, there are methods currently in practice. "One eye per individual" may be included in analysis.[8] In this case, we need a systematic selection process to avoid bias induced by selection and some statistical power is sacrificed for honest statistics requiring inclusion of more subjects. A second approach is using "overall summary of ocular findings per individual."[9] Although this approach is useful in representing clinical picture of a disease, one should be careful interpreting such data. Intraocular pressure (IOP) of 8 mm Hg in right eye and 28 mm Hg in left eye may not represent the same clinical picture as 17 mm Hg in right eye and 19 mm Hg in the left eye, while both conditions will be represented with an average IOP of 18 mm Hg. This approach also causes similar loss of statistical power. A third option is to make a "paired eye comparison" where fellow eye is used as control group in bilateral disease.[10] With this approach the allocation of eyes should be systematic to avoid bias (in case of asymmetrical disease) and the systemic effect of the local treatment should not be able to affect the other eye. A unique advantage of this study design is that both groups share the same genetic background, which is hardly possible in other types of human studies.[11] When we do the analysis at "ocular level," we experience the above-mentioned double-organ bias and an unjustified overestimation of statistical power yielding incorrect *P*-values.[12] Alternatively, the right and the left eyes in each patient can be reported on separately which might be the simplest way to address the issue. We could not find an example of such a case in our study. The last option is to include data from both eyes in the same data set and correct the statistical error with a regression model. This approach is a relatively new way of handling data in studies that treat the eye as unit of analysis and has the advantage of increasing statistical power compared with the above-mentioned approaches while yielding valid *P*-values.[13]

We included only relatively recent RCTs in our survey. RCTs are generally considered to be more meticulous in design and analysis, and conforming to the Consolidated Standards of Reporting Trials (CONSORT) checklist[14] is required by most of the journals when they assess RCTs for publication. In contrast, the unique issue of the double-organ bias is not included in the CONSORT statement.[14]

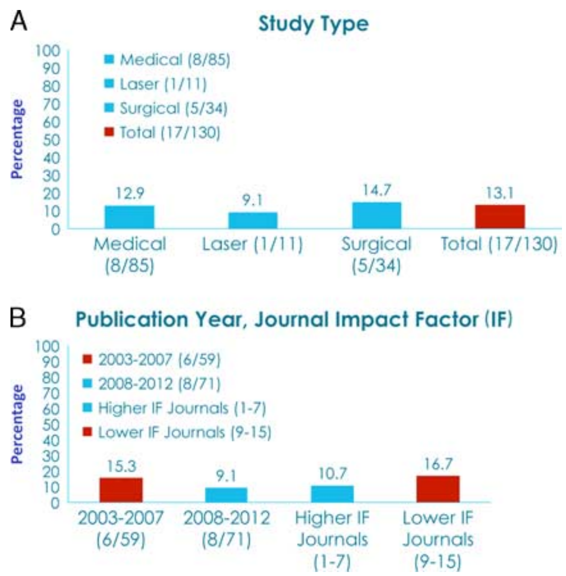

FIGURE 1. Prevalence of double organ bias according to study type, publication year, and impact factor. A, Medical versus interventional: $P = 0.950$ ($\chi^2 = 0.004$); B, First 5 years versus second 5 years: $P = 0.502$ ($\chi^2 = 0.451$); higher IF (first 7) versus lower IF (lower 7): $P = 0.320$ ($\chi^2 = 0.988$). IF indicates impact factor. Figure 1 can be viewed in color online at http://www.glaucomajournal.com.

ACKNOWLEDGMENTS

The authors thank Professor Hasan Yazici for his valuable advice and critical reading of this manuscript.

REFERENCES

1. Patton N, Aslam T, Murray G. Statistical strategies to assess reliability in ophthalmology. *Eye*. 2006;20:749–754.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

2. Bunce C, Patel KV, Xing W, et al. Ophthalmic statistics note 1: unit of analysis. *Br J Ophthalmol*. 2014;98:408–412.
3. Ederer F. Shall we count numbers of eyes or numbers of subjects? *Arch Ophthalmol*. 1973;89:1–2.
4. Ederer F. Methodological problems in eye disease epidemiology. *Epidemiol Rev*. 1983;5:51–66.
5. Newcombe RG, Duff GR. Eyes or patients? Traps for the unwary in the statistical analysis of ophthalmological studies. *Br J Ophthalmol*. 1987;71:645–646.
6. Murdoch IE, Morris SS, Cousens SN. People and eyes: statistical approaches in ophthalmology. *Br J Ophthalmol*. 1998;82:971–973.
7. Holopigian K, Bach M. A primer on common statistical errors in clinical ophthalmology. *Doc Opthalmol*. 2010;121:215–222.
8. Konstas AG, Holló G, Mikropoulos D, et al. Twenty-four-hour intraocular pressure control with bimatoprost and the bimatoprost/timolol fixed combination administered in the morning, or evening in exfoliative glaucoma. *Br J Ophthalmol*. 2010;94:209–213.
9. Parrish RK, Palmberg P, Sheu WP. XLT Study Group. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. *Am J Ophthalmol*. 2003;135:688–703.
10. Maul EA, Friedman DS, Quigley HA, et al. Impact of eyelid closure on the intraocular pressure lowering effect of prostaglandins: a randomised controlled trial. *Br J Ophthalmol*. 2012; 96:250–253.
11. Glassman AR, Melia M. Randomizing 1 eye or 2 eyes: a missed opportunity. *JAMA Ophthalmol*. 2015;133:9–10.
12. Nilforushan N, Yadgari M, Kish SK, et al. Subconjunctival bevacizumab versus mitomycin C adjunctive to trabeculectomy. *Am J Ophthalmol*. 2012;153:352–357.
13. Glynn RJ, Rosner B. Regression methods when the eye is the unit of analysis. *Ophthalmic Epidemiol*. 2012;19:159–165.
14. Schulz KF, Altman DG, Moher D. for the CONSORT group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *PLoS Med*. 2010;7:e100025.