Single-versus double-masking in glaucoma clinical trials

Sir,
The parallel, randomized, double-masked, active-controlled trial is generally thought to be the best design to compare two glaucoma medicines.[1,2] Double-masking is typically done using identical bottles prepared with labels designed for a trial. This technique hides the appearance of the actives, so they cannot be identified by the patient, investigator, or medical personnel. Double-masking is commonly used for Phase III regulatory trials, but it is time consuming and expensive. In contrast, Phase IV marketing trials often use single-investigator masking techniques.

For this study, we reviewed randomized, prospective, parallel, single- or double-masked, active-controlled, monotherapy clinical trials with >60 patients/treatment arm and at least 6 weeks of treatment. Subjects with ocular hypertension or primary open-angle glaucoma were included (exfoliation/pigment dispersion patients included if they comprised <10% of the patient sample).

Studies had both baseline and treated diurnal intraocular pressure (IOP) measurements with >3 time points. Further, the morning IOP was measured between 07:00-09:30 and demonstrated an intraocular pressure ≥21 mm Hg. In addition, included studies had at least one afternoon pressure measurement. IOPs were measured by Goldmann applanation tonometry.

This study included 18 treatment arms from 13 studies of which 7 arms were single-masked and 11 double-masked. All treatment arms were prostaglandin-related compounds because other classes of medicines did not have sufficient treatment arms to provide a valuable comparison. The complete results are shown in Table 1.

This review showed studies utilizing double-masking demonstrated statistically higher baseline morning and diurnal IOPs. However, at the last active treatment visit, the statistical difference was lost although approximately 50% of the original baseline difference was preserved after initiating treatment.

This finding is surprising and has no clear explanation. Prior research has shown study entry criteria may affect baseline IOPs including the inclusion of pigment dispersion/exfoliation glaucoma or higher minimum or maximum entry IOPs.[3,4] However, in this database, none of these confounding variables differed between groups.

Interestingly, all Phase III regulatory trials were double-masked, and all Phase IV were single-masked. Phase III trials differ from Phase IV in that they may be better controlled regarding inclusion/exclusion criteria as well as monitoring procedures since they are conducted for regulatory purposes. Consequently, perhaps physicians chose better-qualified patients for studies that might have been under higher scrutiny, possibly allowing for the higher baseline IOPs.

These data might be used clinically by government or private sponsors designing trials when considering better controls for the study or the higher quality patient to be recruited for the trial. Such a patient might provide higher baseline IOPs.

Regarding the greater reduction in IOP from baseline in the double-masked group, the reason also remains unclear. The greater IOP reduction might have occurred because of the higher baseline IOP in the double-masked group. However, the existence of greater IOP reductions from higher baselines remains controversial.[5] Future research with a larger sample size could further clarify this issue.

This study suggests that double-masking provides higher baseline IOPs than single-masking in well-controlled, parallel, multi-center studies.

### Table 1: Intraocular pressures (mm Hg)

|                      | Single-masked | Double-masked | P    |
|----------------------|---------------|---------------|------|
| Number of treatment arms | 7             | 11            |      |
| Morning - before treatment | 25.5 ± 0.9    | 26.9 ± 1.1    | 0.02 |
| Diurnal - before treatment | 23.8 ± 0.8    | 25.6 ± 1.1    | 0.002|
| Morning - active treatment visit | 18.0 ± 1.0    | 18.7 ± 1.2    | 0.22 |
| Diurnal - active treatment visit | 17.4 ± 0.9    | 18.0 ± 1.0    | 0.19 |
| Morning - reduction | 7.4 ± 1.3     | 8.1 ± 0.8     | 0.17 |
| Diurnal - reduction | 6.5 ± 0.8     | 7.6 ± 0.7     | 0.007|

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### Conflicts of interest
There are no conflicts of interest.

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Letter to Editor

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REFERENCES

1. McDonald MB, Protzko EE, Brunner LS, Morris TW, Haas W, Paterno MR, et al. Efficacy and safety of besifloxacin ophthalmic suspension 0.6% compared with moxifloxacin ophthalmic solution 0.5% for treating bacterial conjunctivitis. Ophthalmology 2009;116:1615‑23.e1.
2. Holló G, Chiselita D, Petkova N, Cvenkel B, Liehneova I, Izgi B, et al. The efficacy and safety of timolol maleate versus brinzolamide each given twice daily added to travoprost in patients with ocular hypertension or primary open-angle glaucoma. Eur J Ophthalmol 2006;16:816‑23.
3. Stewart WC, DeMill DL, Wirostko BM, Nelson LA, Stewart JA. Review of the influence of pigment dispersion and exfoliation glaucoma diagnosis on intraocular pressure in clinical trials evaluating primary open-angle glaucoma and ocular hypertension. J Glaucoma 2013;22:506‑9.
4. DeMill DL, Wirostko BM, Nelson LA, Stewart WC. Upper limits of intraocular pressure in glaucoma clinical trials. Clin Experiment Ophthalmol 2015;43:84‑5.
5. Stewart WC, Limtong AC, Magrath GN, Rembold JC, Nelson LA, Stewart JA. Lower limits of intraocular pressure in glaucoma clinical trials. J Glaucoma 2014;23:e105‑7.

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