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Average versus Highest Intraocular Pressure Analyses in Glaucoma Clinical Trials

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Key Words

Intraocular pressure · Glaucoma · Average intraocular pressure analysis · Highest intraocular pressure analysis

Abstract

Purpose: To evaluate methods which account for both eyes as a single, independent variable in glaucoma clinical trials. ***Methods:*** A review of clinical trial articles published between January 1995 and April 2011 evaluating currently used topical glaucoma medications. ***Results:*** This analysis included 17 articles with 36 treatment arms of which 14 were prostaglandins, 13 β-blockers, 6 topical carbonic anhydrase inhibitors and 3 α-agonists. Twenty-four articles used average intraocular pressure (IOP) analysis, 12 used the highest IOP analysis and none utilized the randomized eye method. At untreated baseline, there was a difference in the IOP between average IOP and highest baseline IOP analyses at 8 a.m. ($p = 0.001$) and for the diurnal curve ($p = 0.02$) as well as specifically for β-blockers ($p = 0.002$) at 8 a.m. and β-blockers for the diurnal curve ($p = 0.01$). ***Conclusions:*** This study suggests that the highest IOP analysis method generally provides slightly higher IOPs at baseline than the average IOP analysis method.

Introduction

The proper design of clinical trials to evaluate new glaucoma medications is important to be able to determine how they can most effectively and safely be used with our patients. One issue in designing glaucoma clinical trials is how to account for the intraocular pressure (IOP) data acquired from two separate eyes that are not independent variables [1, 2]. The statistical analysis should be performed by either an average IOP analysis (the mean value of IOP averaged between both eyes), choosing the highest IOP value between eyes, or choosing one randomly selected eye.

The potential advantage of choosing the average IOP analysis is that it uses all of the data available to the study sponsor to evaluate the IOP. In contrast, the highest IOP analysis has the advantage of analyzing the eye that is potentially 'most stressed' by the IOP and so provides the medication a greater chance to demonstrate efficacy. The randomized eye method has the advantage of being unbiased. Unfortunately, little data are available evaluating the advantages, disadvantages and results acquired by these three data analysis methods.

The purpose of this study was to evaluate methods which account for both eyes as a single, independent variable in glaucoma clinical trials.

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Materials and Methods

Inclusion Criteria

A database was created from articles evaluating clinical trials of currently used glaucoma medicines dated from January 1995 to April 2011 found on PubMed (www.pubmed.gov) using the following search terms: primary open-angle glaucoma, ocular hypertension, IOP, diurnal, monotherapy, baseline, reduction, β-blockers, carbonic anhydrase inhibitors, α-agonists, prostaglandins (PTGs) and combination therapy. Brand names of single and fixed combination agents were also used as search terms.

Complete articles were retrieved and studies were accepted into the database if they were: randomized, prospective, parallel, single or double-masked, active-controlled, monotherapy comparisons with at least 60 patients per treatment arm and 6 weeks of treatment. Only subjects with ocular hypertension or primary open-angle glaucoma were included. Exfoliation and pigment dispersion glaucoma patients were included if they each comprised <10% of the total patient sample size.

Studies must have had both baseline and treated diurnal curve IOP measurements consisting of at least 3 time points. The morning IOP must have been measured between 07:00 and 09:30 and at least 1 measurement should have taken place in the afternoon. The baseline IOP should have been ≥21 mm Hg. IOPs must have been measured with Goldmann applanation tonometry. Each article was evaluated independently by 2 of the authors (D.L.D., L.A.N.) to assure that it met the inclusion criteria specified above. All articles meeting the above criteria were used in the analysis.

Procedures

The following was recorded in an Excel spreadsheet for each article: citation, medicine class, medicine name, baseline a.m. IOP, baseline diurnal (average of available time points) IOP, treated a.m. IOP, treated diurnal IOP, percent reduction in a.m. IOP and percent reduction in diurnal IOP. Also, specifically for the current analysis it was noted whether the IOP was analyzed by: the average IOP analysis, the highest IOP between eyes or one randomly selected eye. Quality assurance was performed on 10% of the entries.

Statistics

PRN Pharmaceutical Research Network, LLC, analyzed the data. The level to declare significance was 0.05 and all analyses were two-way. Mean IOP values for the morning IOP and diurnal curve were analyzed between analysis methods [for the average IOP analysis and highest IOP value between eyes (there were no studies using one randomly selected eye)] by a one-way ANOVA test [3]. Because of multiple comparisons, we used a modified Bonferroni correction (α/2).

Results

The database included 17 articles with 36 treatment arms. Originally 88 studies were chosen to be considered for the database of which 71 were rejected (most common reasons: 21 studies having <60 patients per treatment arm and 20 studies having less than 3 diurnal IOP measurements).

Table 1. IOP measurement technique – average versus highest

	All treatment arms	Prostaglandins	β-Blockers
IOP number of studies			
Highest	12	5	6
Average	24	9	7
Baseline IOP at 8 a.m.			
Highest, mm Hg, ± SD	26.8 ± 0.5	26.8 ± 0.6	26.9 ± 0.6
Average, mm Hg, ± SD	25.8 ± 0.9	25.9 ± 0.8	25.3 ± 0.8
p value	0.001	0.03	0.002
Baseline IOP diurnal			
Highest, mm Hg, ± SD	25.6 ± 0.8	25.5 ± 0.9	25.6 ± 0.9
Average, mm Hg, ± SD	24.6 ± 1.2	24.5 ± 1.2	24.1 ± 1.0
p value	0.02	0.14	0.01
ATV IOP at 8 a.m.			
Highest, mm Hg, ± SD	19.8 ± 1.0	19.1 ± 1.0	20.2 ± 0.8
Average, mm Hg, ± SD	19.7 ± 2.0	17.9 ± 1.0	19.4 ± 0.8
p value	0.91	0.05	0.1
ATV IOP diurnal			
Highest, mm Hg, ± SD	19.2 ± 1.1	18.3 ± 0.9	19.7 ± 0.6
Average, mm Hg, ± SD	18.9 ± 1.6	17.4 ± 1.0	18.7 ± 0.7
p value	0.47	0.11	0.03
IOP reduction at 8 a.m.			
Highest, mm Hg, ± SD	7.1 ± 0.9	7.7 ± 0.7	6.7 ± 0.7
Average, mm Hg, ± SD	6.1 ± 1.8	8.0 ± 1.0	5.8 ± 0.8
p value	0.09	0.64	0.08
IOP reduction diurnal			
Highest, mm Hg, ± SD	6.3 ± 1.1	7.2 ± 0.6	5.9 ± 0.8
Average, mm Hg, ± SD	5.8 ± 1.3	7.1 ± 0.8	5.4 ± 0.6
p value	0.22	0.84	0.21

ATV = Active treatment visit; SD = standard deviation.

The results of the study are shown in table 1. Of the 36 treatment arms, 14 were PTGs, 13 β-blockers, 6 topical carbonic anhydrase inhibitors and 3 α-agonists. Twenty-four articles used the average IOP, 12 used the highest IOP analysis and none utilized the randomized eye method.

At untreated baseline, after the modified Bonferroni correction, there was a difference in the IOP between average IOP and highest IOP baseline analyses at 8 a.m. ($p = 0.001$) and for the diurnal curve ($p = 0.02$) as well as specifically for β-blockers ($p = 0.002$) at 8 a.m. and for the diurnal curve ($p = 0.01$). For the last active treatment visit and for reductions from baseline, following the Bonferroni correction, no significant values were found.

Discussion

The results of this paper show that using a highest IOP analysis provides, on average, a higher IOP than the average IOP analysis at untreated baseline among currently available glaucoma medications. This was shown at 8 a.m. and for the diurnal curve for all glaucoma products together and shown specifically at 8 a.m. for PTGs and at 8 a.m. and for the diurnal curve for β-blockers. The extent of the difference at baseline among the two methods was approximately 1.0–1.5 mm Hg.

These results are not surprising in that often there is a difference between the IOP measurements of 2 eyes despite their lack of independence [1]. Consequently, if the highest IOP between eyes was routinely chosen, we could expect a slightly higher IOP than using an average IOP analysis.

However, when the active treatment visits were analyzed among all medicines pooled together, and for PTGs and β-blockers specifically, the IOPs were statistically comparable between the highest IOP and the average IOP methods with differences of 0.1–0.3 mm Hg. Further, when the reduction in IOPs was considered among all medicines pooled together, and for PTGs and β-blockers specifically, the IOPs were statistically comparable between the highest IOP and the average IOP methods, at both 8 a.m. and for the diurnal curve, with a difference of 0.5–1.0 mm Hg.

What does this analysis mean clinically? At baseline, the highest IOP method provides a slightly greater IOP than the average IOP evaluation. Subsequently, the statistical differences between techniques are lost with treatment indicating a greater decrease in the eye with the highest IOP but the reductions in IOPs between groups are small and probably clinically inconsequential.

However, our results should be interpreted with caution. Carbonic anhydrase inhibitors and α-agonists were not evaluated separately because of a fewer number of studies available. The use of all studies together must also be interpreted with caution because of the different classes of medicine used in the results. Also, there were not enough studies to evaluate direct treatment comparisons to determine if two medicines were better differentiated by one of the methods. Further, the randomized eye method was not able to be evaluated in this analysis.

This study suggests that the highest IOP method generally provides slightly higher IOPs at baseline than the average IOP method. These differences disappear following monotherapy treatment. Nonetheless, the differences in reduction of IOP between groups are small and probably are not helpful in separating efficacy effects between medicines.

Disclosure Statement

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