

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

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Purpose: To evaluate published, randomized, prospective, parallel clinical trials utilizing currently approved glaucoma medications to determine what influence, if any, pigment dispersion (PD) or exfoliation glaucoma (XFG) patients had on the intraocular pressure.

Methods: A review of clinical trial articles evaluating currently used topical glaucoma medicines. Articles were published between January 1995 and April 2011. If the articles met the inclusion/exclusion criteria, they were analyzed for PD and XFG.

Results: Twenty-four articles were included, containing 49 treatment arms that included PD or XFG patients. The range of PD patients was 0% to 4.5%, with a mean of $1.5 \pm 0.9\%$, and for XFG patients 0% to 6.3%, with a mean of $2.2 \pm 2.1\%$. The treatment arms with PD showed a difference in the intraocular pressures (IOPs), for all studies analyzed together, for the baseline IOPs between clinical trials that did and did not include PD patients (8 AM IOPs: with PD 26.5 ± 0.9 mm Hg and without PD 25.8 ± 1.3 mm Hg, $P = 0.024$; and diurnal curve mean IOPs: with PD 25.3 ± 1.1 mm Hg and without PD 24.5 ± 1.3 mm Hg, $P = 0.024$). The XFG treatment arms showed that there was a difference in the IOPs for all studies analyzed together for diurnal baseline IOPs between clinical trials that did and did not include XFG patients (with XFG 25.2 ± 1.2 mm Hg and without XFG 24.3 ± 1.0 mm Hg, $P = 0.016$).

Conclusions: Trial designs for prospective, parallel, glaucoma clinical studies that are performed in the United States generally can include PD and XFG patients with only a small impact on the IOP and a low number of such subjects enrolled.

Key Words: pigment dispersion, exfoliation glaucoma, intraocular pressure, clinical trials, primary open-angle glaucoma, ocular hypertension

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The design of glaucoma clinical trials must be carefully constructed to provide inclusion criteria that allow for examination of a pure population sample, usually the most

common variety, primary open-angle glaucoma.^{1–3} Such a design should assist in providing valid results regarding efficacy and safety. However, ease of recruitment must also be considered when creating inclusion criteria to complete the clinical trial in a timely and cost-efficient manner.

Several secondary forms of glaucoma, pigment dispersion (PD) and exfoliation syndrome, are of the open-angle type and demonstrate similar, although potentially higher, intraocular pressures (IOP) than does primary open-angle glaucoma.^{1,2} Nonetheless, stepwise therapy for these secondary forms is similar to the primary form.^{1,2} Consequently, clinical trial designs sometimes include PD and exfoliation syndrome to ease recruitment. Some protocols, however, exclude these forms of secondary glaucoma because they could potentially distort the IOP findings from a pure primary open-angle glaucoma group and limit the conclusions of the study. This occurs despite the probability of only a small number of these subjects being enrolled, at least in the United States. This is not the case in Europe, where the percentage of exfoliation is much higher in some countries.^{2,4} Unfortunately, little information exists that specifically evaluates the influence of including PD and exfoliation syndrome patients in clinical trials composed primarily of primary open-angle glaucoma patients.

The purpose of this study is to evaluate published, randomized, prospective, parallel clinical trials utilizing currently approved glaucoma medications to determine what influence, if any, PD or exfoliation patients had on the intraocular pressure.

MATERIALS AND METHODS

Study Criteria

Articles evaluated in this analysis were extracted from a database, created by the authors, of clinical trials evaluating currently used topical glaucoma medicines. The database was created from articles dated between January 1995 and April 2011 found on PubMed (<http://www.pubmed.gov>) using the following search terms: primary open-angle glaucoma, ocular hypertension, IOP, diurnal, monotherapy, baseline, reduction, beta-blockers (timolol, timolol gel forming solution, betaxolol, carteolol, levobunolol), carbonic anhydrase inhibitors (dorzolamide, brinzolamide), alpha-agonists (brimonidine, brimonidine polyquaternium-1, brimonidine purite, apraclonidine), prostaglandins (latanoprost, travoprost, bimatoprost), and combination therapy (brinzolamide/timolol, dorzolamide/timolol, latanoprost/timolol, travoprost/timolol, brimonidine/timolol, bimatoprost/timolol). Brand names of single and fixed combination

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agents were also used as search terms. Search terms linked were the individual medicine names and different combinations of the terms randomized, parallel, glaucoma and/or ocular hypertension, clinical trial, and Phase III/IV.

Complete articles were retrieved and studies were included in the database if they were monotherapy, 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 patients were included if they each comprised < 10% of the total patient sample size. Studies must have had both baseline and treated diurnal 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 in the afternoon. The morning IOP was analyzed specifically because it is typically the time point of the highest daily pressure and it is commonly evaluated in clinical trials. The baseline pretreatment IOP between 07:00 and 09:30 must 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 ensure that it met the study criteria specified above. The authors had to be in complete agreement that the article fulfilled the criteria as marked in an Excel spreadsheet and concur on what studies should be excluded. All articles meeting the above criteria were used in the analysis. No specific exclusion criteria were defined for the study.

Procedures

Data from articles meeting the study criteria data were entered into an Excel spreadsheet for each treatment: citation, medicine class, average age \pm SD, age range, medicine name, percentage of patients with PD and/or exfoliation glaucoma (XFG), baseline morning IOP, baseline mean diurnal (average of available time points) IOP, treated morning IOP, treated diurnal IOP, percentage reduction in morning IOP, percentage reduction in diurnal IOP, name and incidence of side effects, number and cause of serious adverse events, and number and cause of deaths.

For this analysis, published study reports including PD and/or XFG patients were compared specifically with those that did not include these patients. Only

studies conducted in the United States were used. Quality assurance was performed on 10% of the entries, in which a separate Excel spreadsheet was created and compared with the original to ensure that there were no mistakes. The results of the quality assurance analysis showed no data entry errors.

Statistics

PRN Pharmaceutical Research Network, LLC, analyzed the data. All analyses were two sided and unpaired and a value of 0.05 was selected to determine statistical significance.

The mean IOP values for the morning IOP and diurnal curve, both including and excluding patients with PD and XFG, were analyzed using the Student *t* test.⁵ Because of multiple comparisons we used a modified Bonferroni correction ($\alpha/2$). All diagnoses were analyzed together and then β -blockers and prostaglandins specifically because sufficient studies were available to analyze these 2 important medicine classes specifically.

RESULTS

Initially, 88 studies were chosen to be considered for the database, of which 64 were rejected for the following reasons: < 60 patients per treatment arm (25 articles), < 3 IOP measurements during the day (23 articles), morning IOP was not reported (4 articles), run-in with glaucoma medication before randomization (8 articles), no breakdown of the number of exfoliation or PD patients included (2 articles), and data were presented as percentage reduction only, rather than specific IOP (2 articles).

For this specific analysis, the 24 published studies from the database contained 49 treatment arms that included PD or exfoliation patients (all 24 studies allowed both types). Of these, 4 XFG studies including 8 treatment arms were rejected because part, or all, of the study was carried out in Europe.⁶⁻²⁹

In studies allowing PD and XFG, the range of PD patients was 0% to 4.5%, with a mean of $1.5 \pm 0.9\%$, and for exfoliation patients 0% to 6.3%, with a mean of $2.2 \pm 2.1\%$. In these studies, 5 treatment arms did not enroll any PD patients but enrolled exfoliation patients. In contrast, 4 treatment arms did not admit any exfoliation patients but enrolled PD patients. No study that allowed PD and XFG patients failed to enroll at least 1 subject who was diagnosed with 1 of these 2 conditions.

TABLE 1. Pigment Dispersion Versus no Pigment Dispersion

	All Treatment Arms	Prostaglandins	β -blockers
No. studies with PD treatment arms	28	13	9
No. studies without PD treatment arms	21	7	8
With PD baseline IOP at 8 AM	26.5 \pm 0.9	26.4 \pm 0.8	26.8 \pm 1.2
Without PD baseline IOP at 8 AM	25.8 \pm 1.3	26.1 \pm 1.8	25.6 \pm 1.1
<i>P</i>	0.024	0.61	0.044
With PD baseline IOP diurnal	25.3 \pm 1.1	25.1 \pm 1.2	25.6 \pm 1.2
Without PD baseline IOP diurnal	24.5 \pm 1.3	24.7 \pm 1.7	24.3 \pm 1.1
<i>P</i>	0.024	0.49	0.032
With PD-active treatment visit IOP at 8 AM	19.4 \pm 1.5	18.3 \pm 1.1	19.8 \pm 1.1
Without PD-active treatment visit IOP at 8 AM	19.8 \pm 1.6	18.5 \pm 1.2	19.6 \pm 0.9
<i>P</i>	0.51	0.72	0.64
With PD-active treatment visit IOP diurnal	18.6 \pm 1.4	17.7 \pm 1.0	19.3 \pm 1.1
Without PD-active treatment visit IOP diurnal	19.0 \pm 1.4	17.9 \pm 1.1	18.9 \pm 0.9
<i>P</i>	0.60	0.76	0.38

IOP indicates intraocular pressure; PD, pigment dispersion.

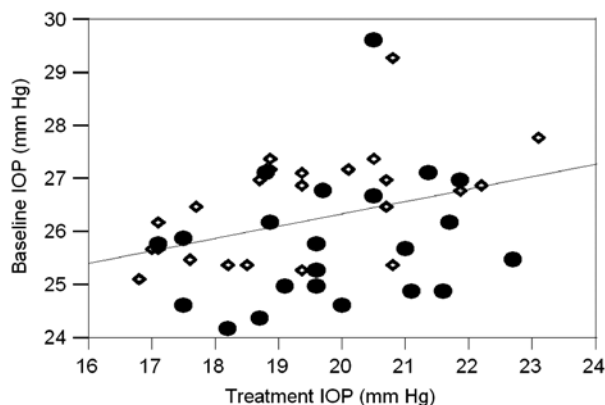


FIGURE 1. A scatter plot demonstrating the comparison between baseline and treated intraocular pressure in patients with (diamonds) and without (circles) pigment dispersion.

The results of the PD analyses are shown in Table 1. After a modified correction for multiple comparisons, there was a difference in the IOPs, for all studies analyzed together, for the baseline IOPs between clinical trials that did and did not include PD patients. This was true for both the 8 AM ($P = 0.024$) and the diurnal curve mean IOPs ($P = 0.024$). However, no differences were observed at baseline for prostaglandin or β -blocker studies specifically or at the last active treatment visit for all comparisons ($P > 0.025$). The comparison between baseline and treated IOP in patients with and without PD can be seen in the scatter plot (Fig. 1).

The results of the exfoliation syndrome analyses are shown in Table 2. After a modified correction for multiple comparisons, there was a difference in the IOPs, for all studies analyzed together for diurnal baseline IOPs between clinical trials that did and did not include exfoliation patients ($P = 0.016$). However, no differences were observed at baseline for prostaglandins or β -blockers alone or at the last active treatment visit for all comparisons ($P > 0.025$).

DISCUSSION

What does this study mean clinically? This analysis implies that, when designing a clinical trial for the United States, significant differences at untreated baseline IOP

between studies that did and did not include PD and exfoliation syndrome patients may be expected. However, the differences between groups are small, typically < 1.0 mm Hg, and so may be of little clinical relevance. Further, differences between these 2 groups typically disappeared after initiation of monotherapy treatment. This suggests that the reduction of IOP might be slightly greater in studies that included PD and exfoliation syndrome patients as might be expected generally when the baseline IOPs are higher.³⁰ The differences in pressure were not explained by higher IOP entry criteria in studies allowing PD and XFG patients.

Our findings further imply that when PD and exfoliation syndrome patients are allowed in a study to assist recruiting, the number of such patients enrolled should be anticipated generally to be small, perhaps on average about 4% of the sample population for both of these glaucomas together. Consequently, even if these types of secondary glaucoma patients do demonstrate a higher baseline pressure, the opportunity to affect the overall mean of a large sample would likely be small.

In Europe, the number of PD patients expected in clinical trials and the effect on intraocular pressure would probably be anticipated to be similar as in the United States, but neither topic has been specifically studied. In our study, there was an average of $0.5 \pm 0.6\%$ PD patients in the 8 European treatment arms that were excluded. The reason for this finding remains unclear. In contrast, allowing exfoliation patients in a clinical trial in Europe might have a profound impact on baseline and treatment IOPs because this type of glaucoma is known to have higher baseline and monotherapy IOPs, with an incidence as high as 25% to 75% of all glaucomas, in a number of European countries.^{31,32} In our study, there was an average of $2.2 \pm 2.4\%$ exfoliation patients in the 8 excluded European treatment arms. Exfoliation incidence varies widely in incidence in the European Union depending on the country; it may be that the sponsor chose sites in low-incidence countries to assist recruiting.

This study suggests that trial design for prospective parallel glaucoma clinical studies, performed in the United States, can generally include PD and exfoliation syndrome patients with only a small impact on the IOP and a low number of such subjects enrolled.

TABLE 2. Exfoliation Glaucoma Versus no Exfoliation Glaucoma

	All Treatments Arms	Prostaglandins	β -blockers
No. studies with XFG treatment arms	23	11	7
No. studies without XFG treatment arms	18	7	5
With XFG baseline IOP at 8 AM	26.5 ± 1.2	26.5 ± 1.3	26.8 ± 1.4
Without XFG baseline IOP at 8 AM	25.8 ± 0.9	25.7 ± 1.0	25.7 ± 0.7
<i>P</i>	0.048	0.22	0.13
With XFG baseline IOP diurnal	25.2 ± 1.2	25.1 ± 1.3	25.5 ± 1.3
Without XFG baseline IOP diurnal	24.3 ± 1.0	24.1 ± 1.0	24.2 ± 1.1
<i>P</i>	0.016	0.11	0.12
With XFG-active treatment visit IOP at 8 AM	19.5 ± 1.7	18.5 ± 1.3	19.7 ± 1.2
Without XFG-active treatment visit IOP at 8 AM	19.6 ± 1.6	18.1 ± 0.9	19.6 ± 0.7
<i>P</i>	0.89	0.55	0.81
With XFG-active treatment visit IOP diurnal	18.7 ± 1.4	17.8 ± 1.1	19.2 ± 1.2
Without XFG-active treatment visit IOP diurnal	18.8 ± 1.5	17.4 ± 0.8	18.9 ± 0.7
<i>P</i>	0.83	0.41	0.55

IOP indicates intraocular pressure; XFG, exfoliation glaucoma.

Caution is warranted in interpreting these results, given the relatively small number of studies, especially with the use of a modified correction for multiple comparisons because of the multiple questions asked. In addition, newer glaucoma medicines, especially those currently in regulatory trials that focus more on conventional outflow mechanisms, might be more influenced by exfoliation or PD patients where the site of pathology is the conventional meshwork. This study did not evaluate the influence of these patients on study comparators, but only intragroup IOP levels, as the numbers of qualified studies were too small for such an analysis. More research is needed to fully understand the effects of the inclusion and exclusion of exfoliation syndrome and PD patients in general glaucoma primary open-angle clinical studies.

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