Prospective Masked Comparison of Intraoperative Floppy Iris Syndrome Severity with Tamsulosin versus Alfuzosin

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Objective: To determine whether severe intraoperative floppy iris syndrome (IFIS) is more or equally likely with tamsulosin or alfuzosin.

Design: Prospective, masked, multicenter, cross-sectional study.

Participants and Controls: Consecutive patients taking systemic tamsulosin or alfuzosin and scheduled for routine cataract surgery (case group) and patients with no history of systemic α1-antagonists scheduled for routine cataract surgery (control group).

Methods: Phacoemulsification with intraocular lens implantation was performed and recorded on video. Intracameral phenylephrine or epinephrine, either by direct injection or placement in the irrigation bottle, was not permitted. Every surgical video subsequently was reviewed remotely by 2 masked investigators who diagnosed the presence or absence of IFIS and graded the severity of IFIS as follows: none, mild (billowing only), moderate (billowing and either iris prolapse or ≥2 mm of pupil constriction), or severe (billowing accompanied by iris prolapse and ≥2 mm of pupil constriction).

Main Outcome Measures: Rate and severity of IFIS and surgical complication rate.

Results: A total of 226 eyes (70 in the tamsulosin group, 43 in the alfuzosin group, and 113 in the control group) were enrolled. Severe IFIS was noted in 34.3% (24/70) of the tamsulosin eyes and in 16.3% (7/43) of the alfuzosin eyes compared with 4.4% (5/113) of the control eyes. The differences between each of the 3 groups were statistically significant. In the absence of epinephrine in the irrigation bottle, 12.4% of control eyes had moderate to severe IFIS. There were no instances of posterior capsular rupture or significant surgical complications in either the case or control groups.

Conclusions: Moderate to severe IFIS can occur in low-risk eyes when epinephrine is omitted from the irrigation bottle. Although both tamsulosin and alfuzosin significantly increase the risk of IFIS compared with patients without prior α1-antagonist intake, severe IFIS statistically was more likely with tamsulosin than with alfuzosin (P = 0.036). Patients with symptomatic benign prostatic hyperplasia and cataracts requiring a uroselective α1-antagonist may consider trying alfuzosin first. Ophthalmology 2014;121:829-834 © 2014 by the American Academy of Ophthalmology.

Supplemental material is available at www.aaojournal.org.
Methods

Main Study

Alfuzosin is manufactured by the French pharmaceutical company Sanofi Aventis. A French population of cataract patients was selected for the study because of the relatively higher prescribing rate of alfuzosin in France compared with the United States. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board; informed consent was obtained from all study patients. A total of 4 different study sites were used, and 1 to 3 surgeons at each site participated in the study (listed in the Study Surgeon Group). During a 2-year period from January 2009 through January 2011, we prospectively enrolled all consecutive eligible patients taking either tamsulosin or alfuzosin who were scheduled for routine cataract surgery (case group). For enrollment, the tamsulosin patients were required to have a minimum 3-month history of taking tamsulosin, without a history of taking other systemic α1-antagonists. The same requirements applied to the alfuzosin patients. Each time that a tamsulosin or alfuzosin patient was enrolled, the study surgeon enrolled a male control patient of a similar age (control group). For enrollment, the tamsulosin patients were required to have a minimum 3-month history of taking tamsulosin, without a history of taking other systemic α1-antagonists. The same requirements applied to the alfuzosin patients. Each time that a tamsulosin or alfuzosin patient was enrolled, the study surgeon enrolled a male control patient of a similar age (control group). All control patients had no history of taking other systemic α1-antagonist medication use and were scheduled to undergo cataract surgery on the same day by the same surgeon. Any eyes with posterior synechiae, prior topical miotic use, or anatomic iris abnormalities were excluded.

A complete medication history and medical history were obtained for all study subjects. For the case group, the duration of α1-antagonist intake was recorded in months. The systemic α1-antagonist was not discontinued before surgery in any study patient and preoperative atropine was not permitted. All study eyes were dilated for surgery with 2.5% phenylephrine and either 1% tropicamide or 1% cyclopentolate according to the surgeon’s preference. The surgeon was instructed to record the pupil diameter measured with calipers immediately before and at the conclusion of cataract surgery.

Topical anesthesia and clear corneal incisions were used for all procedures. We sought to avoid surgical strategies that might mask clinical signs of IFIS. Therefore, the surgeon was allowed to use any ophthalmic viscosurgical device except for Healon 5 (Advanced Medical Optics, Santa Ana, CA). Intracameral phenylephrine or epinephrine, either by direct injection or placement in the irrigation bottle, was not permitted. Surgeons were allowed to use iris retractors or other mechanical expansion devices at their discretion. All surgery was performed with coaxial phacoemulsification instrumentation using the surgeon’s preferred technique.

All significant intraoperative complications such as posterior capsule rupture, vitreous loss, or zonular dialysis were recorded. All patients were examined and followed up for a minimum of 1 month after surgery. In addition to recording the best-corrected visual acuity (BCVA) at the final postoperative visit, any significant postoperative complications also were reported.

Every operation was videotaped with a digital operating microscope camera. The digital video files each were labeled with alphanumeric codes to identify the study eye, the surgeon, and whether the patient was taking tamsulosin or alfuzosin or was a control patient. Remote review of every surgical video was performed by 2 masked investigators (D.F.C., J.R.C.). For this remote masked review, the digital video files were arranged randomly and were assigned new numbers by the study coordinator before sending them to the reviewers. The study coordinator kept track of which new numerical label corresponded to which original alphanumeric code. As a result, the study coordinator did know the identity of the cataract surgeon or the patient’s medication history for every video case, but the reviewers did not.

The 2 reviewers graded each video case for the presence or absence of IFIS using the following scoring system: 0, stable normal iris; 1, mild IFIS (noticeable iris billowing without significant miosis or iris prolapse); 2, moderate IFIS (iris billowing accompanied by either iris prolapse or 2 mm or more of pupil diameter reduction); 3, severe IFIS (iris billowing accompanied by iris prolapse and ≥2 mm of pupil diameter reduction). After separately grading all of the study videos, the 2 masked reviewers compared scores. Where there was disagreement, the videos were re-reviewed by both masked investigators together and a consensus score was determined.

The IFIS association with age, duration of α1-antagonist intake, and a variety of different medical conditions and systemic and topical medications was analyzed separately. The systemic conditions included hypertension, diabetes, coronary artery disease, dyslipidemia, asthma or chronic obstructive pulmonary disease, depression, and neurodegenerative disease. Systemic medications analyzed included statins, digitalis, allopurinol, oral corticosteroids, oral diabetic medication, antidepressants, antianxiety medication, and chronic pain medication. The topical medications analyzed were prostaglandin analogs, β-blockers, carbonic anhydrase inhibitors, and α2-agonists. Finally, the association of severe IFIS with preoperative and postoperative pupil size also was analyzed.

Substudy

Preliminary IFIS score analysis revealed that IFIS with all degrees of severity had occurred in the control group. This was also the impression of the study surgeons, who had not been masked. One investigator (D.F.C.) decided to evaluate the rate and severity of IFIS independently and prospectively in a series of consecutive routine cataract surgeries performed without any intracameral epinephrine in the irrigation bottle. A period during which bisulfite-free and bisulfite-containing epinephrine were back-ordered and unavailable was selected for the study, and separate institutional review board approval was obtained. Patients with small pupils determined before surgery, those currently using or with a history of using systemic α1-antagonists, and those deemed to have higher-risk eyes (e.g., mature cataracts, trauma, pseudoxefoliation) were excluded. Routine phacoemulsification surgery was performed and the presence or absence of IFIS was recorded according to the same scoring system used in the main study. The study complied with the Health Insurance Portability and Accountability Act.

Statistical Analysis

Statistical analysis was performed using SAS software version 9.2 (SAS, Inc., Cary, NC). Continuous variables were described with means and standard deviations and were compared with the Student t test. Categorical variables were described with frequencies and percentages and were compared with the chi-square test; if the theoretical number was fewer than 5, the Fisher test was used. Odds ratios and 95% confidence intervals were estimated with simple logistic regressions. Statistical significance was defined as \( P < 0.05 \).

Results

A total of 226 eyes from 215 patients were enrolled in the main study. The 113 eyes in the case group included 43 alfuzosin eyes and 70 tamsulosin eyes. A total of 113 control patients undergoing routine cataract surgery were enrolled. Iris retractors or pupil expansion rings were not used in any of the study cases. The mean
of patients who were not taking systemic α1-antagonists: the substudy group and the main study control group. For the substudy, 127 patients were enrolled consecutively. The results are similar and show that between 4% and 5% of these eyes experienced severe IFIS.

The analysis of IFIS risk and association with a variety of different medical conditions and systemic or topical medications is listed in Tables 6 and 7 (available at www.aaojournal.org). Intraoperative floppy iris syndrome was statistically more likely to occur in patients taking oral corticosteroids. Besides tamsulosin and alfuzosin, no other medication or medical condition was a statistical risk factor for IFIS. The duration of systemic α1-antagonist intake did not make a difference in IFIS rate or severity.

Within the tamsulosin group, smaller presurgical pupil diameter correlated with increased risk of severe IFIS (Table 8). For pupils less than 8.0 mm in diameter, there was a nearly 4-fold increased risk of severe IFIS compared with eyes with larger pupils. There were no significant intraoperative complications, such as posterior capsule rupture or vitreous loss, reported in any study patient. No significant postoperative complications were reported.

### Discussion

The original report by 2 of the authors (D.F.C., J.R.C.) describing IFIS listed the triad of signs that we now consider to characterize severe IFIS (iris prolapse and billowing, along with progressive intraoperative miosis). A subsequent large, prospective, unmasked study of 167 consecutive tamsulosin patients was the first to classify IFIS according to severity. What we currently define as severe (grade 3) IFIS was present in 43% of these tamsulosin eyes, whereas 10% showed no evidence of IFIS. Because IFIS is a

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**Table 1. Rate and Severity of Intraoperative Floppy Iris Syndrome between Case and Control Groups**

<table>
<thead>
<tr>
<th>Intraoperative Floppy Iris Syndrome</th>
<th>Controls (n = 113)</th>
<th>Cases (n = 113)</th>
<th>P Value, Control vs. Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (n = 126)</td>
<td>85 (75.2%)</td>
<td>41 (36.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All grades (n = 100)</td>
<td>28 (24.8%)</td>
<td>72 (63.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 1 (n = 30)</td>
<td>14 (12.4%)</td>
<td>16 (14.2%)</td>
<td>0.697</td>
</tr>
<tr>
<td>Grade 2 (n = 34)</td>
<td>9 (8.0%)</td>
<td>25 (22.1%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Grade 3 (n = 36)</td>
<td>4 (4.4%)</td>
<td>31 (27.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grades 2 and 3 (n = 70)</td>
<td>14 (12.4%)</td>
<td>56 (49.5%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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**Table 2. Rate and Severity of Intraoperative Floppy Iris Syndrome between Tamsulosin and Control Groups**

<table>
<thead>
<tr>
<th>Intraoperative Floppy Iris Syndrome</th>
<th>Controls (n = 113)</th>
<th>Tamsulosin (n = 70)</th>
<th>P Value, Control vs. Tamsulosin</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (n = 126)</td>
<td>85 (75.2%)</td>
<td>28 (40.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All grades (n = 100)</td>
<td>28 (24.8%)</td>
<td>42 (60.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 1 (n = 30)</td>
<td>14 (12.4%)</td>
<td>3 (4.3%)</td>
<td>0.067</td>
</tr>
<tr>
<td>Grade 2 (n = 34)</td>
<td>9 (8.0%)</td>
<td>15 (21.4%)</td>
<td>0.089</td>
</tr>
<tr>
<td>Grade 3 (n = 36)</td>
<td>4 (4.4%)</td>
<td>24 (34.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grades 2 and 3 (n = 70)</td>
<td>14 (12.4%)</td>
<td>39 (55.7%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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**Table 3. Rate and Severity of Intraoperative Floppy Iris Syndrome between Alfuzosin and Control Groups**

<table>
<thead>
<tr>
<th>Intraoperative Floppy Iris Syndrome</th>
<th>Controls (n = 113)</th>
<th>Alfuzosin (n = 43)</th>
<th>P Value, Control vs. Alfuzosin</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (n = 126)</td>
<td>85 (75.2%)</td>
<td>13 (30.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All grades (n = 100)</td>
<td>28 (24.8%)</td>
<td>30 (69.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 1 (n = 30)</td>
<td>14 (12.4%)</td>
<td>13 (30.2%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Grade 2 (n = 34)</td>
<td>9 (8.0%)</td>
<td>10 (23.3%)</td>
<td>0.029</td>
</tr>
<tr>
<td>Grade 3 (n = 36)</td>
<td>4 (4.4%)</td>
<td>7 (16.3%)</td>
<td>0.113</td>
</tr>
<tr>
<td>Grades 2 and 3 (n = 70)</td>
<td>14 (12.4%)</td>
<td>17 (39.5%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
To test this hypothesis, a small adjunct study was performed by one of the investigators (D.F.C.) in a consecutive series of 127 patients for whom no epinephrine was placed in the irrigation bottle. This prospective, nonmasked trial confirmed that moderate and severe IFIS are more likely to occur in low-risk eyes when no intracameral epinephrine is used, and the rate of grade 2 IFIS or higher was 13.4%. Intraoperative floppy iris syndrome rates and severity scores in patients not receiving a systemic α1-antagonist were similar in both the main study control group and the sub-study group. These shared the same reviewer (D.F.C.), who was masked in one trial but not the other. Based on 240 total non–α1-antagonist eyes in our main and adjunct study, the rate of moderate and severe IFIS is between 12% and 14% when epinephrine is not added to the irrigation bottle in low-risk patients.

Like other studies published before ours, we found no other correlation between systemic medications, systemic disease, eye color, or eye medication and the risk of IFIS, with the possible exception of oral corticosteroids. We did find that a preoperative pupil diameter smaller than 8.0 mm increased the risk of severe IFIS in tamsulosin patients. This was consistent with another prospective study of tamsulosin patients by Casuccio et al. In those eyes, a dilated pupil of 7.0 mm or smaller was highly predictive of IFIS.

Systemic α1-antagonists continue to be the most commonly prescribed pharmacologic treatment for BPH.
Uroselective α1-antagonists often are prescribed because of a theoretical decrease in side effects, such as orthostatic hypotension.14,15 No direct comparative study has demonstrated superior efficacy of one particular α1-antagonist over another for the treatment of BPH.15 Because of the increasing prevalence of cataract and BPH worldwide, knowing which uroselective α1-antagonist is least likely to cause severe IFIS would be of importance to BPH patients with cataracts and their prescribing physicians.

Several other studies support our conclusion that severe IFIS is more likely with tamsulosin than with nonselective α1-antagonists.5–13 Among retrospective studies, one large Canadian trial reported that tamsulosin significantly increased the rate of severe postoperative complications, but that nonselective α1-antagonists did not.5 A second Canadian retrospective study found that IFIS developed in 86% of patients taking tamsulosin compared with only 15% of patients taking alfuzosin.9 A more recent retrospective trial found IFIS to be more common in patients taking tamsulosin compared with those taking doxazosin.13 Finally, in the 2008 American Society of Cataract and Refractive Surgery survey, 90% of respondents with sufficient experience believed that IFIS was more common with tamsulosin than with nonselective α1-antagonists.12

Among published prospective studies, a trial of 1786 cataract surgeries by Chadha et al7 found that IFIS occurred in 57% of patients taking tamsulosin but in only 2% of patients taking nonselective α1-antagonists. In a prospective study of 1968 cataract surgeries, Oshika et al8 found the incidence of IFIS to be 43% in patients taking tamsulosin compared with 19% in patients taking naftopidil, a nonselective α1-antagonist. In another prospective study, Herd5 reported a 37% incidence of IFIS among doxazosin patients compared with 83% among tamsulosin patients. Casuccio et al,11 in a prospective, single-surgeon, masked trial comparing phacoemulsiﬁcation in patients taking tamsulosin versus nonselective α1-antagonists, and the authors of a large 2011 meta-analysis of the literature both concluded that IFIS is more common and severe with tamsulosin.12

The stronger association of IFIS with tamsulosin compared with nonselective α1-antagonists suggests a more complex mechanism than simple blockade of the α1A-receptor. In 2012, Goseki et al25 published in vitro and histologic rabbit studies showing that tamsulosin binds strongly to pigment granules in the iris in addition to the smooth muscle α1-receptors. Iris pigment epithelial cells share nuclei with the adjacent smooth muscle cells, and this unique morphologic feature may explain the histopathologic finding of iris dilator muscle atrophy in tamsulosin-treated rabbits. They postulated that IFIS results from a combination of pharmacologic inhibition of iris smooth muscle contraction and longer-term smooth muscle degeneration relating to drug accumulation in adjacent iris pigment epithelial cells. These permanent structural changes could explain the well-documented occurrence of IFIS long after tamsulosin cessation and the postmortem finding of iris dilator muscle atrophy in patients taking this drug.26

A 2008 in vitro rabbit dilator muscle study found tamsulosin to be a more powerful antagonist of rabbit iris dilator muscle contraction than alfuzosin.27 Interestingly, the Schild plot dose-response curves led the authors to hypothesize that iris dilator muscle contraction could be mediated by a hypothetical second non–α1A-receptor; this would explain the observed in vitro difference in iris dilator muscle antagonistic potency between the 2 drugs. Therefore, independent of the α1A-receptors, stronger binding affinity of tamsulosin to iris pigment granules may explain its greater propensity to cause IFIS compared with alfuzosin.

Regardless of the mechanism, it is unlikely that complication rates are increased by mild IFIS, as characterized by iris billowing without prolapse or pupillary constriction during surgery. However, increased surgical risk with sudden pupil constriction and iris prolapse is well accepted. Our prospective controlled and masked study confirms that both tamsulosin and alfuzosin significantly increase the risk of severe or moderately severe IFIS compared with patients not taking any α1-antagonist. More important, our study provides the strongest evidence to date that tamsulosin is more likely to cause severe IFIS compared with alfuzosin. Patients with symptomatic BPH and cataracts needing a uroselective α1-antagonist therefore may wish to try alfuzosin first. Finally, we recommend that α1-agonists should be added to the irrigation bottle or injected directly intracamerally to reduce the rate of IFIS in all eyes.

References


Footnotes and Financial Disclosures

Originally received: August 18, 2013.
Final revision: October 22, 2013.
Accepted: October 22, 2013.
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Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article.
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