Intracameral Phenylephrine 1.5% for Prophylaxis against Intraoperative Floppy Iris Syndrome: Prospective, Randomized Fellow Eye Study

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Purpose: To evaluate the efficacy of intracameral phenylephrine (IPH) administered as prophylaxis against intraoperative floppy iris syndrome (IFIS) and to analyze the ability of IPH to reverse IFIS.

Design: Prospective, multicenter, randomized, comparative case series of fellow eyes.

Participants: Forty-two patients receiving tamsulosin who underwent cataract surgery between January and April 2011.

Methods: Phacoemulsification was performed by 2 experienced surgeons at 2 surgical sites (Complexo Hospitalario Universitario Orense and Complexo Hospitalario Universitario A Coruña). One eye of each patient was randomized to receive 0.6 ml of nonpreserved bisulfite-free IPH 1.5% (group 1) or balanced saline solution (group 2) at the start of surgery. If significant miosis or iris prolapse occurred, IPH was injected during phacoemulsification in group 2. No changes were performed in the surgeon’s standard fluidic parameters or viscoelastic preferences. Routine topical mydriatics were instilled before surgery. Intraoperative iris billowing and prolapse and pupil size were recorded and videotaped. Surgical complications; adverse events; pre- and postoperative pulse rate and blood pressure; and final best-corrected visual acuity (BCVA), intraocular pressure (IOP), and endothelial cell count (ECC) were recorded.

Main Outcome Measures: Incidence of IFIS and change in pupil size after IPH administration in those eyes of group 2 requiring IPH because of significant miosis or iris prolapse.

Results: Signs of IFIS were observed in 88.09% of eyes in group 2. No signs of IFIS were noted in group 1 (P < 0.001). Significant miosis, iris prolapse, or both occurred in 54.76% of eyes in group 2, although the condition was successfully reverted with IPH, with a significant increase in pupil size after IPH administration (from 4.77 ± 0.88 mm to 6.68 ± 0.93 mm; P = 0.000). No intraoperative complications occurred. No significant differences in ECC, BCVA, or IOP were detected between IPH-treated and nontreated eyes. Blood pressure/pulse rate did not differ significantly from preoperative values in IPH-treated cases.

Conclusions: Intracameral phenylephrine is a highly efficient measure for prophylaxis against IFIS. Moreover, the drug can reverse IFIS, restoring iris rigidity and causing the pupil to return to its preoperative size.

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Lundberg and Behndig\textsuperscript{17,18} reported intracameral xylocaine plus phenylephrine 1.5% to be safe in routine phacoemulsification surgery. Therefore, we hypothesized that intracameral phenylephrine (IPH) 1.5% could help prevent IFIS. After prospectively reviewing the efficacy of this approach in a large series of patients at risk of IFIS,\textsuperscript{19} we decided to evaluate the efficacy of IPH 1.5% as prophylaxis against tamsulosin-associated IFIS and to analyze its ability to reverse IFIS in a prospective randomized comparison of fellow eyes.

**Patients and Methods**

This study was a prospective randomized comparison of fellow eyes undergoing cataract surgery performed by 2 surgeons (R.L., V.R.) at 2 sites (Complexo Hospitalario Universitario Ourense and Complexo Hospitalario Universitario A Coruña). Patients receiving tamsulosin and scheduled to have routine phacoemulsification cataract surgery were included for study. Patients were excluded if there was a history of glaucoma, endothelial disease, media opacities other than cataract, ocular trauma, zonular dialysis, iridocyclitis, iris neovascularization, or prior iris surgery. Eyes with a preoperative pupil size less than 4.5 mm after topical mydriatics were not included in the study. Patients receiving treatment with any other $\alpha_1$-antagonist or other drugs associated with IFIS were excluded, because we intended to evaluate the efficacy of this prophylactic measure in those cases with the highest probability of experiencing the syndrome and in whom its manifestations were most severe.\textsuperscript{2,8} No patients discontinued the drug before surgery. The study was conducted in accordance with the tenets of the Declaration of Helsinki, and institutional review board approval was obtained at each center. All patients provided informed consent.

One eye of each patient was randomized to receive 0.6 ml of nonpreserved bisulfite-free IPH 1.5% (group 1) or balanced saline solution (BSS) (group 2) at the start of surgery. Randomization was performed using computer-generated random numbers so that 1 eye was randomized to group 1, with the second eye automatically assigned to group 2. In the case of significant miosis or prolapse that could compromise the safety of surgery, IPH was injected during phacoemulsification in group 2 (group 2 IPH). Our previous retrospective study provided evidence that IPH was not only efficient for prophylaxis against IFIS but also able to reverse IFIS once it occurred.\textsuperscript{15} Thus, we considered it would have been unethical not to use it in group 2 if required. Topical mydriatics (tropicamide 1%, phenylephrine 10%) and topical diclofenac were administrated with a noncomparative, prospective study; thus, for the purpose of sample estimation in the current study, a lower efficacy of IPH was considered in the bilateral approach. Thus, by assuming that IPH was expected to reduce IFIS occurrence in at least 50%, versus an incidence of 90% in eyes without IPH, with $\alpha=0.05$ and a statistical power of 90% ($\beta=0.10$), with a bilateral approach, then a sample of 26 eyes in each group would be required. Thus, our sample of 42 eyes in each group allowed us to estimate these differences with $\alpha=0.05$ and a statistical power >90%.

Statistical analysis was performed using SPSS software (SPSS Inc, Chicago, IL). Visual acuity was converted to the logarithm of the minimum angle of resolution for statistical analysis. Paired or unpaired $t$ tests were used to compare mean pupil sizes. The paired $t$ test was used to compare pupil size between different intervals during surgery in the same group. The unpaired $t$ test was used to compare pupil size at each interval between groups. The Mann–Whitney test was used to compare ECC, BCVA, and IOP between IPH-treated and nontreated eyes. Nontreated eyes were those eyes in group 2 that did not receive IPH. The ECC, BCVA, and IOP were compared between those eyes and fellow treated eyes. Treated fellow eyes in group 2 IPH were not included in this comparison. The paired $t$ test was used to compare preoperative and postoperative MAP and pulse rate. The Wilcoxon rank-sum test was used to compare pupil size between different time intervals in group 2 IPH eyes. The chi-square test was used to compare occurrence of IFIS between groups 1 and 2. $P<0.05$ was considered statistically significant.
Results

Forty-two patients (84 eyes) were enrolled in the study from January 2011 to April 2011. Two patients were excluded because of a preoperative dilated pupil size (<4.5 mm). Baseline characteristics are shown in Table 1. Vertical phaco-chop was performed in 19 eyes in group 1 and 17 eyes in group 2; divide-and-conquer was performed in 23 eyes in group 1 and 25 eyes in group 2. All patients completed the minimum follow-up of 3 months.

The incidence of IFIS was significantly higher in group 2 (P < 0.001). No signs of IFIS were noted in group 1 (Video 1, available at http://aaojournal.org), whereas 37 of 42 eyes (88.09%) in group 2 showed some sign of IFIS. Of these, IFIS was graded as 1 in 4 cases (9.5%), as 2 in 7 cases (16.6%), and as 3 in 26 cases (61.9%), with 83% of eyes presenting iris billowing, 76.19% of eyes presenting iris prolapse, and 69% of eyes presenting miosis (Table 2). In group 2, 23 eyes (54.76%) required IPH during surgery because of significant miosis or iris prolapse (group 2 IPH), in 1 case after hydrodissection and in the remaining cases during phacoemulsification. In all these cases, the use of IPH restored iris rigidity, thus stopping the tendency of the iris to prolapse, and caused the pupil to dilate almost back to its preoperative size (Video 2, available at http://aaojournal.org). No eyes required placement of iris hooks or any additional maneuvers.

Pupil size is summarized in Tables 3 and 4 and illustrated in Figure 1. There were no significant differences in preoperative pupil size between eyes in group 1 and group 2 (P = 0.356). There were no significant differences between preoperative and postoperative pupil size in eyes in group 1 (P = 0.105) (Table 3). No significant changes in pupil size were observed after administration of IPH or BSS at the beginning of surgery. However, in group 2 IPH, pupil size at the end of surgery was significantly larger than pupil size at administration of IPH (P = 0.000), although it was still significantly smaller than the preoperative pupil size of the same eyes (P = 0.000) (Table 4). Compared with before surgery, a significant decrease in pupil size was detected at each step of surgery after hydrodissection in group 2 (P = 0.000) (Table 3). At the end of surgery, pupil size was significantly larger in group 1 than in group 2 (P = 0.001), and that of eyes in group 2 showed a statistically significant decrease at the end of surgery compared with before surgery (P = 0.000). Pupil size after hydrodissection and phacoemulsification was significantly larger in group 1 than in group 2 (P = 0.000) (Table 3; Fig 1).

No intraoperative complications occurred, and no adverse events were detected. Areas of mild iris atrophy were observed in 7 eyes of group 2 in which iris prolapse had occurred, whereas no sign of iris transillumination defect was detected in group 1. No statistically significant differences in BCVA (P = 0.651), IOP (P = 0.464), or ECC (P = 0.805) were noted between IPH-treated and nontreated eyes (Table 5). Postoperative MAP and pulse rate did not differ significantly from preoperative values in group 1 (MAP P = 0.492; pulse rate P = 0.791) (Table 6).

Discussion

The present study compared fellow eyes of patients requiring cataract surgery who were taking tamsulosin and were randomized to receive IPH or BSS at the beginning of surgery as a measure to prevent IFIS. We evaluated the incidence and grade of IFIS. No signs of IFIS were observed in group 1, whereas 88.09% of eyes in group 2 presented some sign of IFIS, which was scored as grade 3 in 61.9% of cases. This finding demonstrates the success of IPH in preventing IFIS; the efficacy of this solution is underscored by its ability to reverse IFIS once it occurred in 54.76% of eyes in group 2, in which significant miosis or prolapse were noted. The results of the current study support the conclusion of our previous investigation.19

We included only patients taking tamsulosin, because tamsulosin leads to more common and severe IFIS than other nonselective α1-blockers,1,2,4–8 and we wanted to evaluate the efficacy of phenylephrine in the worst possible scenario. Tamsulosin was taken by 3.2% of patients undergoing cataract surgery in our previous study,19 this percentage is consistent with the findings of previous studies in the United States,1 lower than findings reported in Japan,7 and higher than findings reported in the United Kingdom.20
It is difficult to conclude whether one IFIS management technique is superior to another without a randomized prospective trial, because the severity of IFIS varies widely between patients. The current study was designed not only as a randomized and prospective trial but also as a comparison of fellow eyes to prevent any variations in the individual tendency to develop the syndrome from inducing bias in the results. To our knowledge, this is the first investigation in which a strategy to prevent or to manage IFIS has been evaluated in a prospective, randomized, comparative paired-eye study. The incidence of IFIS—considered as the occurrence of any sign of IFIS—was 88.09% in group 2. This rate is higher than the incidence of 65% found by Cheung et al and similar to the rate of 90% published in the multicenter refractive surgery study. One-third of respondents said they routinely used multiple strategies for IFIS. Furthermore, staged protocols allowing progressive addition of new measures according to severity have been recommended. Among the many pharmacologic methods advocated to directly stimulate the iris dilator smooth muscle receptors, intracameral α1-receptor agonists such as phenylephrine or epinephrine have proven useful for preventing IFIS. These agents not only induce pupil dilatation but also restore iris rigidity by increasing dilator smooth muscle tone, thus markedly reducing the tendency toward iris prolapse and billowing.

Shugar described successful prevention of IFIS using intracameral epinephrine, a finding that was confirmed by Schulze and Masket and Belani also combined epinephrine with preoperative atropine for management of IFIS and found that intracameral epinephrine was less effective than the combined regimen. Moreover, contrary to Shugar’s experience, it did not reverse established IFIS. Chen et al recently reported that prophylactic intracameral lidocaine-epinephrine did not reduce the incidence of IFIS, although the authors hypothesized that this result could be biased by the confounding effect of preoperative dilated pupil size.

Phenylephrine hydrochloride acts predominantly on the α1-receptors of the iris. Intracameral phenylephrine 1.5% provides adequate intraoperative dilatation in routine phacoemulsification surgery. Manvikar and Allen and Gurbaxani and Packard found that IPH 0.3125% and 0.625% prevented iris prolapse and billowing and further pupil constriction in patients with medium-to-small pupils before surgery in 22 eyes and 7 eyes, respectively. Manvikar and Allen found that IPH, unlike intracameral epinephrine, was effective for reversing pupil constriction. Bäckström and Behndig also showed IPH to be effective in redilating constricting pupils during routine phacoemulsification. Our results confirm these findings, because IPH successfully reverted miosis and iris prolapse in 23 eyes in group 2, thus restoring iris rigidity and inducing a significant increase in pupil size that allowed surgery to conclude without intraoperative complications in all cases.

Table 4. Mean Pupil Diameter in Group 2 Eyes Requiring Intracameral Phenylephrine for Significant Pupil Miosis or Iris Prolapse: Preoperatively, Pre–Intracameral Phenylephrine Administration, and Postoperatively

<table>
<thead>
<tr>
<th>Stage of surgery during which IPH was administered</th>
<th>Preoperatively</th>
<th>Pre–IPH Administration</th>
<th>Postoperatively</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2 IPH</td>
<td>7.15±1</td>
<td>4.77±0.88</td>
<td>6.68±0.93</td>
</tr>
<tr>
<td>After hydrodissection</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>During phacoemulsification</td>
<td></td>
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IPH = intracameral phenylephrine.

Figure 1. Mean pupil size (mm) in group 1, in group 2 as a whole, in the subgroup of eyes of group 2 that required intracameral phenylephrine (IPH) administration during surgery (group 2 IPH), and in the subgroup of eyes of group 2 that did not require IPH administration (group 2 w/IPH) at different intervals during surgery: preoperatively, after hydrodissection, after phacoemulsification, and at the conclusion of surgery.

Table 5. Mean Postoperative Endothelial Cell Count, Intraocular Pressure, and Best-corrected Visual Acuity in Intracameral Phenylephrine–treated and Nontreated Eyes

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2 w/IPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECC (cells/mm²)</td>
<td>2445.71±291.18</td>
</tr>
<tr>
<td>IOP (mmHg)</td>
<td>13.35±2.4</td>
</tr>
<tr>
<td>BCVA (logMAR)</td>
<td>0.029±0.07</td>
</tr>
</tbody>
</table>

BCVA = best-corrected visual acuity; ECC = endothelial cell count; IOP = intraocular pressure; IPH = intracameral phenylephrine; logMAR = logarithm of the minimum angle of resolution; w/IPH: eyes in group 2 that did not require IPH administration.
Table 6. Mean Preoperative and Postoperative Blood Pressure and Pulse Rate in Group 1

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>104.46±10.03</td>
<td>105.44±10.12</td>
<td>0.492</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>65.40±11.51</td>
<td>65.04±10.81</td>
<td>0.791</td>
</tr>
</tbody>
</table>

Manvikar and Allen\textsuperscript{13} limited administration of IPH because of safety concerns in patients with miosis or in those with small or mid-dilated pupils before surgery. Lundberg and Behndig,\textsuperscript{17} however, found no statistically significantly different rates of endothelial cell loss among patients who had received intracameral mydriatics including IPH 1.5%. The ECC in the present study is consistent with previously reported data. No adverse events were detected in any of the 65 eyes that received IPH, either at the beginning of or during surgery, and no significant differences in BCVA or IOP were detected between IPH-treated and nontreated eyes. A larger sample, however, would be required to rule out unexpected rare adverse events. In regard to systemic side effects, despite 1 report of a hypertensive episode related to intracameral α-agonists,\textsuperscript{24} the risk of systemic adverse reactions seems to be low, because MAP and heart rate did not differ significantly from preoperative values in our study or a previous report on the subject.\textsuperscript{17} In addition, although IPH can reverse IFIS, our results clearly show that preoperative administration of IPH is more advantageous than administration when IFIS occurs. Two findings support this statement: firstly, postoperative pupil size in group 1 was not statistically different from preoperative pupil size, whereas postoperative pupil size in group 2 overall or even in group 2 IPH was significantly smaller than preoperative pupil size. Secondly, mild areas of iris atrophy were noted only in group 2, whereas no eyes in group 1 showed any signs of iris atrophy, because no eyes in group 1 presented iris prolapse. Therefore, we think that IPH should be used as routine prophylaxis at the beginning of surgery in any patient receiving tamsulosin.

Manvikar and Allen\textsuperscript{13} reported increased pupil size after intracameral injection of phenylephrine in some cases, whereas in others it remained unchanged. However, in all the patients who received IPH for miosis, pupil size returned to its preoperative value.\textsuperscript{13} Our previous study\textsuperscript{19} and the current study support these findings. Therefore, when the pupil is previously dilated with routine topical mydriatics, IPH has no significant effect on pupil size, and its administration does not change the convenience or limitations of surgical maneuvers. Consequently, eyes with a preoperative pupil size <4.5 mm after topical mydriatics were excluded from the study, because no further increase in pupil size is expected after administration of IPH and mechanical pupil expansion devices are required from the beginning of surgery. The comfort level and proficiency of operating through small pupils vary greatly according to individual surgeon skill and experience, and thus, mechanical retractors could be useful even with preoperative pupils >4.5 mm for less-experienced surgeons. In those cases in which the drug was omitted and miosis occurred, IPH was able to restore the pupil to near its preoperative size, thus allowing surgery to conclude uneventfully.

Intracameral drug solutions must be prepared carefully. Toxic anterior segment syndrome has been associated with several ocular medications and may be due to the chemical composition, concentration, pH, or osmolality of the solution, or whether preservatives or additives are included. Particular emphasis must be given to pH and osmolality, whose impact on the functions of corneal endothelial cells means that they have to be within ranges compatible with tissue preservation.\textsuperscript{25} González et al compared the pH and osmolality of 3 different solutions of IPH 1.5% (using distilled water, saline 0.9%, or BSS as solvent) (González N, Pena I, González-Barcia M, Chuclá MT. Assay of stability of phenylephrine hydrochloride 1.5% in different conditions of elaboration. Poster presented at: the Spanish Society of Hospital Pharmacology, September 23, 2009). Although drug stability did not differ significantly between the different solutions, the pH and osmolality values of the BSS solution were found to be the most compatible with those recommended for intracameral administration, that is, a pH of between 6.5 and 8.5\textsuperscript{26} and osmolality of between 200 and 400 mOsm/kg,\textsuperscript{27} which explains our use of BSS as a solvent. Care must also be taken to ensure that the solution is preservative- and sulfite-free, because preservative agents are potentially toxic to the corneal endothelium.\textsuperscript{28}

Surgery in eyes with IFIS has been associated with a higher rate of complications than routine cases, especially when the condition is not recognized or anticipated.\textsuperscript{1,2,5} Conversely, and not surprisingly, because no eyes developed IFIS in group 1 and IFIS appearing in group 2 was successfully reverted, no intraoperative complications occurred in the current series. It is therefore of paramount importance to question patients with cataract before surgery about current or previous use of α\textsubscript{1}-agonists. Preoperative recognition of patients at risk for IFIS allows preventive measures to be taken.

Intracameral phenylephrine presents several advantages over other agents considered for IFIS prophylaxis.\textsuperscript{2} It is simpler, less traumatic, and quicker than placing iris hooks. The solution is easy to prepare and can be stored for up to 2 months at room temperature in the operating room. Our study is limited in that we did not evaluate whether the lower concentration of phenylephrine used in previous studies would be as effective as IPH 1.5%.

In conclusion, the absence of IFIS manifestations in the group of eyes receiving phenylephrine at the beginning of surgery and the ability of phenylephrine to reverse IFIS once it occurred demonstrate that IPH 1.5% is a simple, efficient measure for prophylaxis and management of IFIS.

References


Footnotes and Financial Disclosures

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