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REVIEW

Intraoperative Floppy Iris Syndrome: Updated Perspectives

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Abstract: Almost fifteen years since its initial description, intraoperative floppy iris syndrome (IFIS) during phacoemulsification surgery remains a challenge for cataract surgeons in all its key aspects that include the stratification of the preoperative risk, preoperative prophylaxis treatment, surgery design and intraoperative management. Since its original association with tamsulosin intake, IFIS has been positively correlated with a plethora of risk factors which include: gender, age, hypertension, other a1-adrenergic receptor antagonists, finasteride, angiotensin II receptor inhibitors, benzodiazepines, antipsychotics, hypertension drugs and decreased dilated pupil diameter. The assessment and stratification of the preoperative risk is pivotal in screening patients prone to develop IFIS. For these patients, it is essential that preoperative prophylaxis, employment of necessary measures and surgical technique modifications are considered. A multidisciplinary approach of IFIS is a mandate, thus ophthalmologists, urologists and sometimes other specialties should cooperate to "educate" each other about the risks of their respective fields. They both must be aware of the joint statement on IFIS by the American Academy of Ophthalmology and the American Society of Cataract and Refractive Surgery which suggests either the initiation of tamsulosin after phacoemulsification or the use of a non-selective a1-ARA for benign prostatic hyperplasia treatment. In conclusion, awareness of the risk factors associated with IFIS and their detailed preoperative documentation is crucial in addressing IFIS. The lack of such an awareness can turn a routine, uneventful surgery into one with significant visual morbidity.

Keywords: intraoperative floppy iris syndrome, IFIS, risk factors, preoperative prophylaxis, intraoperative management

Introduction

Intraoperative floppy iris syndrome (IFIS) was primarily reported in 2005.[1] In their original article, Chang and Campbell defined IFIS as the presence of the following triad during phacoemulsification surgery: i. tendency of the iris to prolapse through corneal/limbal incisions; ii. a flaccid iris stroma that undulates and billows during surgery; and iii. a progressive intraoperative miosis. IFIS is classified based on the presence of the above signs as grade 0, 1 (mild), 2 (moderate) and 3 (severe).[2]

The overall reported prevalence of IFIS is 1.1–12.6%[1,3,4,] yet several risk factors are positively corelated with IFIS, thus significantly increasing the risk of its appearance. Beyond the original correlation with tamsulosin intake,[1] IFIS has been correlated with several risk factors which include: gender, age, hypertension, other a1- adrenergic receptor antagonists (a1-ARAs), finasteride, angiotensin II receptor inhibitors, benzodiazepines, antipsychotics, hypertension drugs and decreased dilated pupil diameter.[5–10] The careful preoperative assessment of these

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predisposing factors is essential in the stratification of the preoperative risk. As a matter of fact, IFIS is associated with higher rate of complications, that include increased ocular inflammation, posterior capsule rupture, anterior capsule tears, vitreous loss, iris trauma, cystoid macular edema and hyphema.[1,11,12] High-risk patients may be candidates for prophylaxis treatment and the employment of necessary measures and surgical technique modifications that will address the needs of IFIS management and minimize complications.

Almost fifteen years since its initial description, IFIS still remains a challenge for cataract surgeons in all its aspects. Our study aims to review the existing literature, address all these challenges and provide an updated perspective in the prophylaxis and management of IFIS. We, hereby, provide a comprehensive up-to-date review of the literature associated with intraoperative floppy iris syndrome. Eligible articles were identified by a search of the bibliographic database in PubMed using the following combination of search terms: (intraoperative floppy iris syndrome) OR (IFIS) OR (floppy iris AND cataract surgery) OR (floppy iris AND phacoemulsification). The end of the search date was December 18, 2019. We also checked all the references of relevant reviews and eligible articles that our search retrieved. Language restrictions were not used, and data were extracted from each eligible study by 2 investigators working independently (AT, CC). No restrictions were placed upon our search in terms of year of publication.

Pathogenetic Mechanism

The appearance of intraoperative floppy iris syndrome has been shown to be affected by many reasons and various systemic medications.[5–10] However, IFIS came in the spotlight when the therapeutic algorithm for the treatment of benign prostatic hyperplasia (BPH) suggested the intake of a1-ARA as the first line treatment, substituting surgical intervention.[13] Three subtypes of a1- adrenergic receptors (a1- AR) have been identified so far: $a1_A$, $a1_B$ and $a1_D$. $a1_A$ AR is the main regulator of smooth muscle tone in the human urinary system and dominates also the musculus dilatator pupillae.[14] $a1_B$ subtype regulates blood pressure through arterial muscle relaxation.[14] The choroid as a highly vascularized layer is rich in $a1_B$ ARs, thus all $a1_B$-ARAs have potential effects on the choroidal blood flow. $a1_D$ is associated with contraction of the bladder muscle and sacral spinal cord innervation.[14] In the early stages of a1-ARAs intake, they antagonize the a1-receptors within the dilator muscle of the iris, thus preventing the iris from fully dilating during cataract phacoemulsification.[1]

The discontinuation of a1-ARAs and/or the use of epinephrine which displaces a1-ARAs may theoretically lead to an increase of the iris tone and a decrease of IFIS incidence. However, cases of severe IFIS do not benefit significantly from either measure which implies a different mechanism through which a1-ARAs act upon the iris.[15,16] It is proposed that the long-term intake of a1-ARAs leads to permanent anatomical variations, which are incompletely resolved after treatment interruptions and are not affected by the use of mydriatic agents.[17] In addition, the drug-melanin interaction causes further dilator muscle atrophy that contributes to the development of IFIS.[16]

Other systemic medication such as benzodiazepines, antipsychotics and hypertension drugs may have a similar effect on the iris, although the exact pathophysiological mechanism has not been fully understood and the correlation with IFIS incidence does not seem to be as strong as with tamsulosin.[4,5,7] Cataract surgery is one of the most frequently performed surgeries worldwide.[18] Similarly, BHP is present in almost 50% of men by the age of 50 years and 75% of men by the age of 80 years.[19] Therefore, it is only natural, that with the life expectancy elongation, men with BHP on a1-ARAs treatment requiring cataract phacoemulsification surgery or vice versa, would be the norm.

Risk Factors

Medication

Tamsulosin

The positive correlation of tamsulosin and IFIS is well established since the initial description of this phenomenon.[1] Along with alfuzosin, they are the most commonly prescribed ARAs.[20] Tamsulosin blocks equally $a1_A$ and $a1_D$ ARs with an affinity ten times greater than other a1-ARAs,[21] thus tamsulosin has the higher odds ratio (OR=206.5) and relative risk ratio (RR=99.3) for IFIS development among a1-ARAs.[22] The recommended daily dosage in Japan is 0.2mg while in Europe and the US is 0.4mg.[23] It is of note, that studies originating from Japan report lower IFIS incidence among men on tamsulosin than the incidence reported in Europe and the U.S.[23] Therefore, IFIS development for patients on tamsulosin is probably positively corelated with its cumulative dosage. However, development of IFIS has been reported even after 48 hrs of tamsulosin intake.[24]

The discontinuation of tamsulosin 4–7 days prior to surgery might be beneficial, although it does not prevent IFIS completely.[1,13] Due to its high OR and RR for IFIS, it is recommended that urologists inform their patients for the risk of IFIS before prescribing tamsulosin. Ideally, the ophthalmologist of the patient should be notified.[25] Patients requiring cataract surgery, could be scheduled for surgery before the initiation of tamsulosin. Alternatively, a non-selective a1-ARA can be considered.

Other a1-Antagonists

Alfuzosin, doxazosin and terazosin block equally all three a1-AR subtypes.[21] Due to their decreased affinity for the $a1_A$-AR, they have lower ORs and RRs for the development of IFIS compared to tamsulosin.[2] Their increased affinity for the $a1_B$-ARs (located in the blood vessels) causes hypotension.[26–28] Therefore, these non-selective a1-ARAs could be used when BPH and hypertension coexist. In men with symptomatic BPH and cataract, the initiation of alfuzosin is considered by many physicians as the first-line treatment as its risk of causing IFIS is up to 30 times smaller than with tamsulosin.[2] In a study which compared the effect that systemic alfuzosin or tamsulosin intake has on choroidal thicknesses (CT) and pupil diameter size (PD), alfuzosin was found to significantly decrease both CT and PD.[29] Tamsulosin on the other hand, did not affect CT, which makes sense since it does not antagonize the $a1_B$ AR. Considering PD, the alfuzosin group showed significantly smaller pupils than the tamsulosin group. The authors proposed that alfuzosin leads to IFIS due to its a1-AR blockage while tamsulosin causes additional atrophy of the iris dilator muscle.[29]

Two additional new a1-ARAs have been recently released, silodosin and naftopidil. Similarly to tamsulosin, they are not supposed to cause hypotension. Silodosin has the following affinity for a1-ARs: $a1_A > a1_D > a1_B$ and a high affinity for melanin,[16,21] while naftopidil has the following affinity: $a1_D = a1_A > a1_B$.[21] Silodosin has already been characterized as the causative agent in some cases with IFIS.[16,30,31] Further prospective randomized studies are expected to quantify the exact risk of developing IFIS with these newer medications.

Other Drugs

Except from a1-ARAs, several other drugs have been corelated with IFIS. Finasteride inhibits the type II and III isoenzyme of 5a-reductase enzyme, thus decreasing the levels of the serum dihydrotestosterone.[32] It is commonly used in BHP treatment and it has been linked with cases of anterior subcapsular cataracts and IFIS.[6,32] Therefore, some authors propose its discontinuation prior to cataract surgery.[6,32] Angiotensin II receptor inhibitors have also been implicated as a main predisposing factor for IFIS, particularly in women, although it has not been established yet whether particular medication or arterial hypertension itself could be the main contributing factor to the development of floppy iris.[8]

In addition, several neuromodulators including benzodiazepines, donepezil and duloxetine have been associated with IFIS by several studies.[5,7,33,34] In a large retrospective study, Chatziralli et al reported an increased incidence of IFIS in patients receiving benzodiazepines, an association that was confirmed in a univariate analysis by Kaczmarek et al.[5,7] In 2007 Papadopoulos et al reported IFIS in a patient with long history (8 years) of donepezil intake for Alzheimer's disease, while recently González-Martín -Moro et al published a case of IFIS in a patient receiving duloxetine as antidepressant for 3 years.[33,34] The increased incidence of IFIS in patients treated with the above-mentioned medications might be either causative or coincidental. Although cholinergic medications are known to oppose mydriasis, the exact pathogenetic mechanism through which these drugs contribute to IFIS development is less clear and remains subject for future studies. Nonetheless, it is advisable that patients are always preoperatively asked regarding intake of these medications and surgeons should be aware of the possibility of IFIS.

Regarding antipsychotics, typical and atypical antipsychotics, including quetiapine, chlorpromazine, zuclopenthixol, aripiprazole and risperidone have been associated with IFIS.[5,35–39] These reported cases responded well to the use of intracameral epinephrine, this suggesting that the a1-antagonism was probably the causative mechanism.[36–39]

Gender and Age

Regarding gender, a strong positive correlation has been found between IFIS and male sex.[5,7,9,40] The significantly higher prevalence of IFIS among men, can obviously be attributed to the intake of a1- ARAs for BHP treatment. IFIS however, occurs in females too, although less commonly than in males, thus women are unfortunately often overlooked as high-risk candidates for IFIS development.[9] Notably, IFIS in women has been correlated with a higher incidence of intraoperative complications than in men, including posterior capsule rupture, vitreous loss, nucleus drop and endothelial cell loss, leading in a significantly

worse final visual outcome.[9] Clinicians should not forget that females, although less frequently than men, are also prescribed a1- ARAs for outlet obstruction and detrusor underactivity, as well as other drugs that are related to IFIS such as benzodiazepines, angiotensin receptor inhibitors and antipsychotics. All these predisposing factors should be clearly documented during preoperative visits in order to avoid unanticipated IFIS that could have a detrimental effect to the surgical outcome.

As far as patient age is concerned, IFIS has been positively correlated in a recent prospective study with advanced age, yielding a proposed adjusted OR for each 1-year increase in age, 1.09 (95% CI 1.03–1.16, P=0.006).[7] Pathogenetically, the potency of norepinephrine is proportional to the receptor reserve in the iris dilator muscle which is altered with aging.[41] In addition, a study which used the incidence of fluorescein leakage as an iris vasculature dysfunction indicator, suggested a positive correlation between aging and vasculature dysfunction.[42]

Hypertension

The impact of hypertension in the development of IFIS remains controversial. The proposed pathogenetic mechanism suggests that systemic diseases cause endothelial dysregulation that lead to increased resistance of the iris dilator muscle to adrenergic agonists.[43] Using immunochemistry, it has been confirmed that $a1_A$-ARs are located in the human iris arteriolar muscularis in addition to the iris dilator muscle.[44] However, the existing literature is unclear with several studies reporting no correlation between hypertension and IFIS development[7,45] and other studies reporting statistical significance.[5,45] Therefore, it is unclear whether the increased risk in the development of IFIS should be attributed to hypertension as an independent risk factor or whether it is associated with specific antihypertensive drugs.

Dilated Pupil Diameter

Decreased preoperative dilated pupil diameter has been proposed as an independent risk for the development of IFIS regardless of a1-ARAs intake.[10,46] Several cut-off values have been proposed ranging from 6.5–8mm.[2,10,46,47] It has been reported that a dilated pupil of 7.0mm or smaller had 73% sensitivity and 95% specificity for predicting IFIS in patients being treated with a1- ARAs.[46] Since pupil and cornea sizes are different among races and individuals,[48] the dilated pupil to limbal diameter ratio was proposed as a more objective measurement for IFIS development prediction.[47] A ratio less than 0.6 was found positively corelated with the development of IFIS.[47]

Preoperative Assessment and Prophylaxis

Even though numerous studies have investigated several risk factors, a unified risk stratification system that evaluates all risk factors and predicts with high sensitivity and specificity the chance of IFIS development, is absent. Until such a clinical tool is available, it is strongly recommended that a detailed medical history is taken that thoroughly evaluated all risk factors which have been associated with IFIS. As mentioned above, specific medication intake (tamsulosin, other a1- ARAs, antipsychotics, benzodiazepines, anti-hypertensive drugs) should always be documented in the preoperative control and further clinical data including arterial hypertension, advanced patient age and small dilated pupil size should also be recorded.

The discontinuation of drugs with a causative relationship to IFIS such as tamsulosin does not seem to fully eliminate the risk of developing IFIS although it might be helpful sometimes.[1,13] In their initial description, Chang et al concluded that withdrawal of tamsulosin 4–7 days prior cataract surgery might prevent IFIS in some cases but not completely.[1] Tamsulosin has a relatively long half-life and can irreversibly block a1 adrenoceptors or induce permanent iris atrophy. Therefore, a discontinuation period of several days might be insufficient. Although many surgeons anecdotally tend to withdraw, when possible, tamsulosin and alfuzosin prior to cataract surgery, there is no strong evidence in the literature that such a withdrawal can be of help.[40]

In addition, to date, there is no consensus on a definitive preventive strategy for the development of IFIS in high-risk patients. It is therefore up to the ophthalmologist to stratify the risk for each patient and decide the patients for whom a preoperative prophylaxis and surgical technique modifications are needed. Preoperative use of topical atropine as a parasympatholytic agent with or without the use of intracameral epinephrine reduces the incidence of IFIS in high-risk patients.[17,49,50] A recent study proposed that atropine sulfate 1% instillation at 40 and 20 mins prior to surgery significantly reduces IFIS incidence and especially its mild forms.[17] It is of note that many surgeons favour the use of pre-operative topical non-steroidal anti–inflammatory drugs (NSAIDs) such as

ketorolac to facilitate pupillary mydriasis during cataract surgery, as these drugs block cyclo-oxygenase and inhibit prostaglandins from causing pupillary miosis intraoperatively. A relevant study which investigated the use of topical NSAIDs in high risk patients (dilated pupil<5mm), found that the need for iris fixation ring insertion to maintain pupil dilation or to control IFIS was reduced from 50% in the control group (epinephrine) to 0% in the study group (epinephrine/ketorolac, p=0.0034).[51] Mean surgical time was also significantly shorter in the study group (p=0.0068).

Surgical Management of IFIS

Surgical Design

Beyond preoperative prophylaxis, for patients associated with a high risk to develop IFIS, protocols should ensure that the hazard is highlighted before surgery and necessary measures and surgical technique modifications are employed. Primarily, these patients should be assigned to the most senior members of the surgical team.[9,10] Then, careful incision location and construction along with the use of less aggressive, low-flow phacoemulsification fluidic parameters are effective in controlling iris behavior and lead to milder cases of IFIS.[9,13] Further slight modifications such as gentle hydrodissection, minimization of in-and-out movements and keeping the irrigation flow above the iris plane could be helpful.[22] In addition, the use of anterior elongated corneal incisions has been reported to reduce the incidence and severity of IFIS for dilated pupils no less than 4.5mm.[52]

Intraoperative Management

Maintenance of an adequately dilated pupil is crucial for optimal and accurate visualization,[53] thus during a surgery that is complicated with an unanticipated IFIS, the enlargement of the pupil using pupil expansion rings or iris hooks can be considered.[54] Mechanical pupil stretching or partial sphincterotomy are generally not advisable in cases of anticipated IFIS as they may induce further miosis due to irritation of a partially atrophic iris and its abnormal elasticity.[1] Furthermore, controlling the iris mechanically, although sometimes effective, requires additional surgical time and increases the postoperative billowing.[53,55] Consequently, in cases at high-risk for IFIS, such as male population on tamsulosin with a poor mydriasis, pupil expansion devices are preferably used as a preventive measure from the beginning of surgery rather than after IFIS develops to avoid jeopardizing the integrity of the capsulorrhexis.

Iris retractors, although time consuming, are sometimes preferred by cataract surgeons over pupil expanders due their significantly lower cost and better safety profile in cases with a shallow anterior chamber. When applied, one of the retractors should be located directly beneath the main incision forming a diamond-shape pupil, thus pulling the iris away from the phaco tip and decreasing the risk of iatrogenic iris trauma. In this case, a clear cornea incision is preferred in order to provide adequate space for the sub-incisional retractor tunnel.[55] On the other hand, pupil expansion devices are in most cases much easier to use, require less operating time, do not require extra incisions and provide a stable pupil during surgery minimizing postoperative pupil deformity and anterior chamber inflammation.[53–55]

Healon5® OVD (Johnson & Johnson Vision, Santa Ana, CA) and other viscoadaptive/dispersive ophthalmic viscosurgical devices (OVDs) have been used as a mean for maintaining the pupil dilated intraoperatively.[47] Healon5 is generally preferred in cases where low fluidics are used as it can be aspirated easily. Alternatively, in cases where high flow parameters are needed, a dispersive OVD can be used on top of Healon5 in a modified soft-shell technique to ensure better stability of viscomydriasis.[56] A sub-tenon injection of 2.5mL of lidocaine 2.5% has also been reported to reduce all features of IFIS in mild-to-moderate cases.[57]

Intracameral epinephrine and phenylephrine promote pupillary dilation and reduce iris floppiness.[58,59] They can be used either at the beginning of surgery for poorly dilated pupils (<4,5mm) or intraoperatively during progressive miosis where they can yield an additional 1mm of dilation.[60] The use of intracameral epinephrine has been reported to decrease IFIS incidence in patients receiving a1- ARAs.[17] A poorly dilated pupil at the beginning of the surgery after an intracameral epinephrine injection is an early sign of potential IFIS.[49] Epinephrine (1:1000) should be adequately diluted before intracameral use in order to avoid corneal endothelial damage. The most common dilution used is 1:3 with Balanced Salt Solution (BSS), resulting in a 1:4000 epinephrine solution.[55]

It is preferable to use preservative- and bisulfite-free epinephrine and phenylephrine intracamerally. However, these solutions are not always available in the surgical setting and a recent study that was designed to evaluate the intracameral phenylephrine preparations protocols for dosage accuracy, concluded that current protocols are inaccurate and inconsistent, thus the concentration of

phenylephrine delivered intracamerally is low and highly variable.[61] The use of commercial intracameral phenylephrine products would address this problem.[61] FDA recently approved a combination of phenylephrine 1% and ketorolac 0.3% for intraocular use during cataract surgery to prevent intraoperative miosis and iris flaccidity and to decrease postoperative pain.[52,62,63] Specifically, Donnenfeld et al designed a randomized clinical trial where patients were randomized administrated with either vehicle or phenylephrine or ketorolac or the study drug containing phenylephrine and ketorolac intracamerally during surgery. Regarding the maintenance of mydriasis, the percentages of patients with an intraoperative pupil diameter <6mm were 47.2% for the vehicle, 22.4% for the phenylephrine, 34.6% for the ketorolac and 6.1% for the study drug.[63] These results of the fixed combination are promising so far, as it is shown to reduce the incidence of IFIS in patients receiving tamsulosin and maintain intraoperative mydriasis, either injected intracamerally or being added to the irrigation solution during cataract surgery.[62,63]

Although pupil constriction minimizing surgical visibility is the main concern of cataract surgeons in IFIS patients, iris prolapse can also be a major intraoperative issue leading to complications such as wound dehiscence, iatrogenic iris injury, postoperative endophthalmitis etc.[11,12] In order to deal with iris prolapse, several tricks have been described such as lowering intraocular pressure followed by "milking" the iris back into the anterior chamber.[64,65] The key in management is to equalize the pressure gradient by releasing fluid from behind the iris. Additional OVD can also be placed in front of the iris to help in this regard.[66] Furthermore, when iris prolapse occurs towards the completion of surgery after IOL implantation, the intracameral injection of miotic agents such as acetylcholine (Miochol-E, Bausch+Lomb) or carbachol (Miostat, Alcon Laboratories) can be of benefit.[67]

Complications

Considering complications, their incidence is significantly higher in an unanticipated IFIS.[9,55] Complications related to IFIS may vary from mild and transient to detrimental including posterior capsule rupture, vitreous prolapse, retained lens fragments, iris trauma, wound dehiscence, nuclear drop, postoperative inflammation and intraocular hypertension among others. Fortunately, in verified high-risk patients where preventive measures are employed, complication rates return to their baseline values.[54] Specifically, posterior capsule rupture rates in unanticipated IFIS range from 7–12%, where adequate awareness and preventive measures could reduce this rate to almost zero.[68]

Notably complication rates were found significantly higher in females, where IFIS was not expected as opposed to men receiving a1- ARAs highlighting the need for better preoperative documentation and the establishment of a new stratification system.[9] In addition, Campbell et al, in a recent study, descripted that the rates of complications associated with IFIS in their centre, steadily decrease year by year due to the increased awareness for IFIS.[69] The long-term consequences of a cataract surgery complicated with IFIS include permanent pupil deformity and vision loss secondary to endophthalmitis, macular edema or retinal detachment.[55]

Conclusion

This review highlights the pivotal role of preoperative assessment as the key in addressing IFIS. Preoperative prophylaxis and the employment of necessary measures turn the risks of complications back to their baseline.[54] The need to apply such measures is dictated by increased prevalence of IFIS among high-risk groups. Unanticipated IFIS is still corelated with high rates of complications.[9] There are several limitations of this review. The retrospective character of some of the studies included and the small sample size of case series analyzed, especially when it comes to subgroups analysis, raises doubts about the conclusiveness of their findings. Further prospective randomized clinical trials are needed to draw safe conclusions. Such studies could lead to the development of a unified preoperative assessment clinical tool that will stratify the potential risk and predict IFIS with high sensitivity and specificity.

The fact that along with life expectancy elongation more and more patients with BHP on ARAs intake would require cataract surgery, dictates that urologists, ophthalmologists and general practitioners should cooperate to address this tendency. They must all be aware of the joint statement on IFIS by the American Academy of Ophthalmology and the American Society of Cataract and Refractive Surgery which suggests either the initiation of tamsulosin after phacoemulsification or the use of a non-selective a1-ARA for BPH treatment.[70] In conclusion, proper identification of predisposing factors related to the development of IFIS and thorough preoperative documentation is crucial in managing IFIS and avoiding associated complications that could significantly increase visual morbidity.

Disclosure

The authors report no conflicts of interest in this work.

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