Intraoperative Floppy Iris Syndrome (IFIS)

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IFIS is a recently identified condition, initially reported by Chang and Campbell, in the year 2005 associated with phacoemulsification in patients using systemic α1 antagonist drugs. It is a relatively common difficulty that can complicate an otherwise routine cataract surgery.

IFIS is characterized by a triad of intraoperative features. (1) A flaccid iris stroma that undulates and billows in response to ordinary intraocular fluid currents, (2) a propensity for the floppy iris stroma to prolapse toward the phaco and side port incisions despite proper wound construction and (3) progressive intraoperative miosis despite standard preoperative pharmacologic measures designed to prevent this (topical cyclopentolate, phenyl ephrine and topical nonsteroidal antiinflamatory drugs).

IFIS can be categorized as (1) Mild (good dilatation, some iris billowing without prolapse or constriction) (2) Moderate (iris billowing without prolapse but with constriction of a moderately dilated pupil and (3) Severe (Classic triad and poor preoperative dilation) (Table 1).

One of the most critical elements of safe cataract surgery is adequate pupillary dilation. Poor dilation leads to compromised visualization of the surgical field which not only impedes the complete removal of the cataractous lens but also significantly increases the risk of complications such as rupture of the posterior capsule. Other complications include iris stromal atrophy secondary to momentary aspiration of iris with phaco tip and capsulorhexis tear. The striking tendency toward progressive intraoperative miosis could be explained by prostaglandin release as a result of excessive mechanical iris stimulation. (eg, iris prolapse or billowing due to irrigation currents). Deficient iris dilator muscle tone also contributes to this tendency. Three characteristics of IFIS increase the risk for operative complications relative to other small pupil cases. These are the marked tendency for iris prolapse, the progressive and unexpected intraoperative miosis and the typical failure of sphincterotomies and mechanical stretching to maintain an adequate pupillary opening. In spite of routine administration of mydriatic agents, IFIS has been described in patients undergoing cataract surgery, with a suggested prevalence of 2%.

Although the prevalence is reported to be 2%, the actual number of patients using α1 AR antagonist drugs may be greater and prevalence of IFIS much higher.

Pharmacology

Understanding the role of adrenergic receptors (ARs) in iris biology is important in understanding IFIS. Adrenergic receptors bind the endogenous catecholamines, epinephrine and nor-epinephrine (NE) and are important targets in a wide range of diseases. Originally divided into α AR and β AR categories, nine total AR subtypes have been described – α1a, α1b, α1d, α2a, α2b, α2c, β1, β2 and β3. α1 receptors have been...
identified in the lower urinary tract as well as in the heart, liver and vascular and ocular smooth muscle. The \( \alpha_{1a} \) and \( \alpha_{1d} \) subtypes are present in the prostate and detrusor respectively. \( \alpha_{1a} \) receptor has been found to specifically mediate pupil dilation. Approximately 70% of \( \alpha_1 \) receptors in human prostate are the \( \alpha_{1a} \) subtype. Thus blockade of \( \alpha_{1a} \) AR results in relaxation of prostate smooth muscle as well as iris dilator smooth muscle. Stimulation of presynaptic \( \alpha_{2a} \) ARs inhibits release of NE from the nerve terminal, indirectly dampening the sympathetic tone. Nor-epinephrine released from the nerve terminal produces constriction of arterioles in the iris by activating \( \alpha_{1b} \) ARs.

**Signaling**

\( \alpha_1 \) ARs predominately couple to the pertussis toxin insensitive G protein, \( G_q \), resulting in hydrolysis of membrane phospholipids; subsequent activation of phospholipase C \( \beta \) generates the major second messengers inositol triphosphate and diacylglycerol. Inositol triphosphate binding to its receptor on intra cellular storage sites results in mobilization of calcium ultimately stimulating smooth muscle contraction.

**Role of \( \alpha_1 \) AR subtypes in BPH/LUTS**

Benign prostatic hyperplasia is a common enlargement of the prostate gland that may lead to bladder outlet obstruction, lower urinary tract symptoms (LUTS) and reduced quality of life. Approximately 50% of men >50 years of age and 90% of men beyond 85 years of age require treatment for LUTS. BPH consists of 2 components: Static (related to absolute size of the prostate gland) and dynamic (related to prostate smooth muscle contraction). \( \alpha_{1a} \) AR predominates and mediates contraction in human prostate, urethra and bladder neck. Blockade of \( \alpha_{1a} \) ARs results in relaxation of prostate smooth muscle and relief of bladder outflow obstruction. Hence \( \alpha_1 \) AR blockade is capable of modifying the dynamic component of BPH.

### \( \alpha_1 \) AR antagonists drugs

Four \( \alpha_1 \) AR antagonists are currently available in the United States \(^3\). Tamsulosin (\( \alpha_{1a} \) and \( \alpha_{1d} \) AR subtype selective) (Flomax), and three non subtype selective \( \alpha_1 \) AR antagonists. Alfuzosin (Uroxatral), Doxazosin (Cardura) and Terazosin (Hytrin). They block \( \alpha_{1b} \) ARs also. In treating lower urinary tract symptoms, \( \alpha_{1a} \) and \( \alpha_{1d} \) receptors are targeted because these receptors are prevalent in bladder neck smooth muscle. IFIS is associated with all these \( \alpha_1 \) AR antagonists, although it is much more common with tamsulosin which is highly specific for the \( \alpha_{1a} \) receptor. The subtype \( \alpha_{1b} \) is vasoconstrictive; thus nonspecific \( \alpha_1 \) antagonists such as prazosin and doxazosin may produce clinically significant hypotension in some patients. The \( \alpha_{1a} \) and \( \alpha_{1d} \) subtypes, present in prostate and detrusor are selectively antagonized by tamsulosin which was

<table>
<thead>
<tr>
<th>( \alpha_1 ) AR Antagonist</th>
<th>( \alpha_1 ) AR Subtype Binding</th>
<th>Decreases Incr BP?</th>
<th>Usual Dose (mg)</th>
<th>Regimen (doses/day)</th>
<th>Half-life (hours)</th>
<th>Side-Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terazosin (Hytrin)</td>
<td>( \alpha_{1a} = \alpha_{1b} = \alpha_{1d} )</td>
<td>Y</td>
<td>1-10</td>
<td>1</td>
<td>12</td>
<td>Asthenia, dizziness, somnolence, hypotension, nasal congestion/rhinitis, impotence</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>( \alpha_{1a} = \alpha_{1b} = \alpha_{1d} )</td>
<td>Y</td>
<td>1-8</td>
<td>1</td>
<td>22</td>
<td>Dizziness, fatigue, edema, dyspnoea, hypotension</td>
</tr>
<tr>
<td>Alfuzosin (Uroxatral)</td>
<td>( \alpha_{1a} = \alpha_{1b} = \alpha_{1d} )</td>
<td>(Y)</td>
<td>7.5 - 10</td>
<td>1-3</td>
<td>10</td>
<td>Dizziness, headache, nausea, dry mouth, diarrhea, hypotension</td>
</tr>
<tr>
<td>Tamsulosin (Flomax)</td>
<td>( \alpha_{1a} = ) prostate and UB &gt;( \alpha_{1b} )</td>
<td>N</td>
<td>0.4</td>
<td>1</td>
<td>14-15</td>
<td>Abnormal ejaculation, dizziness, infection, headache, flu-like symptoms</td>
</tr>
</tbody>
</table>
developed to overcome possible hypotensive side effects seen with nonspecific \( \alpha_1 \) antagonists \(^8\). Contraction of iris dilator muscle is mediated via \( \alpha_{1a} \) receptors which explains why tamsulosin in particular is associated with IFIS. Summary of the characteristics of \( \alpha_1 \) AR antagonists used to treat BPH/LUTS is given in table 1. All the four currently available drugs are competitive antagonists, therefore, their binding and clinical effects can be competed off by administering agonists such as nor epinephrine, epinephrine and phenyl ephrine.

Alpha agonist drugs are used to decrease intraocular pressure in patients with glaucoma by increasing conventional and uveoscleral outflow. These topical drugs include dipivefrine (Propine), a prodrug as well as \( \alpha_2 \) agonists such as apraclonidine and brimonidine. They do not have significant effect on the iris. However the direct acting \( \alpha_1 \) AR selective agonist, phenyl ephrine is capable of constricting iris dilator smooth muscle and therefore mediates mydriasis.

### Conditions which Predispose to IFIS

Drugs which cause iris dilator relaxation like \( \alpha_1 \) AR antagonists, Endothelin A antagonists, angiotension antagonists and nitric oxide donors (nitrates) can predispose to IFIS if not discontinued. Systemic diseases associated with endothelial dysregulation like congestive cardiac failure, diabetes and hypertension also predispose to IFIS \(^8\).

### Management and Prevention of IFIS

Pre operative recognition of patients at risk for IFIS is the key to reducing cataract surgery complications in these patients. It is most commonly linked to the use of tamsulosin which is the most common and effective drug prescribed for lower urinary tract symptoms in elderly males \(^2\). Rather than being a rare, unexpected, unpredictable syndrome, due to one drug, possible IFIS predisposition should be able to be predicted via a careful medical history designed to elicit whether the patient has concurrent diseases known to be associated with endothelial dysfunction eg, congestive cardiac failure, diabetes, hypertension or drugs that mediate expected iris dilator smooth muscle relaxation eg, \( \alpha_1 \) AR antagonists, Endothelin A antagonists, angiotensin antagonists and nitric oxide donors such as nitrates \(^8\).

Prudent preoperative discontinuation of \( \alpha_1 \) antagonist drugs in collaboration with the urologists definitely lessens the likelihood of IFIS, although it does not prevent it entirely \(^8\). Half lives of the four \( \alpha_1 \) AR antagonist drugs are similar, ranging from 10 to 22 hours. Chronic use of these drugs lead to disuse atrophy of the dilator smooth muscle. Recent recommendations by urologists are to not change prescribing practices, encourage patients to inform their ophthalmologists that they are taking the drug and stop using it one week before surgery, to minimize its effects \(^8\).

**Intracameral injection of phenyl ephrine:** Phenyl ephrine hydrochloride, a direct acting sympathomimetic, acts predominantly on the \( \alpha_1 \) AR of the iris. It acts directly on the \( \alpha_1 \) receptors and provides maximum stimulation that causes the pupil to dilate or at least increases the tone of the dilator muscle and prevents iris billowing \(^4\). Intracameral phenyl ephrine is prepared using 0.25 ml of unpreserved phenyl ephrine 2.5 \% diluted with 2ml of BSS in a 2ml syringe. The PH of intracameral phenyl ephrine is 6.4. When used during surgery, atleast 30 seconds should be allowed to ensure maximum effect before the agent is washed out.

Preoperative use of atropine 1\% when used twice daily for 10 days effectively decreases the incidence of IFIS \(^5\). The pre operative use of atropine appears to be as effective as intracameral phenyl ephrine without the increased risk for toxic anterior segment syndrome that any intracameral drug possesses. However this strategy alone is often ineffective for moderate to severe IFIS. Combined preoperative topical atropine sulfate 1 \% and intracameral non preserved epinephrine hydrochloride 1:2500 has also been studied and found to bring down significantly the incidence of IFIS \(^4\). Atropine sulfate, as the strongest available pupiloplegic agent, helps dilate the pupil. Super stimulation of the dilator by intracameral epinephrine combined with atropine pupiloplegia provides powerful synergism. It is also important that patients suffering from benign prostatic hyperplasia do not stop using an \( \alpha_1a \) blocker, especially when preoperative atropine is used, as acute urinary retention may ensue.

In tamsulosin patients, particular attention should be paid to proper incision construction and to avoiding excessive hydrodissection. A viscoadaptive agent such
as sodium hyaluronate 2.3 % (Healon 5) when properly positioned over the iris, may mechanically expand the pupil and block the iris from prolapsing to the incisions (due to its maximally cohesive properties). Iris prolapse can be caused by poor incision construction or by excessive injection of Ophthalmic Viscosurgical Devices (OVDS) or hydrodissection fluid. Other conditions such as diabetes can be associated with progressive intraoperative miosis 3. However IFIS is distinguishable by the characteristic bellowing of iris stroma that accompanies the iris prolapse and pupil constriction.

Two additional characteristics often accompany IFIS-poor preoperative pupil dilation and elasticity of the pupil margin. Partial thickness sphincterotomies and mechanical stretching of the pupil which creates microscopic sphincter tears is usually ineffective in IFIS because the iris pupil margin remains elastic 8. Unlike with non elastic miotic pupils, IFIS pupil immediately snaps back to its original size following attempts at stretching it. Because mechanical pupil restraining devices are difficult to safely insert after the capsulorhexis is completed, the ability to anticipate and recognize IFIS is important for strategizing small pupil management. Iris hooks or iris expansion rings should be employed prior to capsulorhexis.

Disposable pupil expansion rings are costly but 100 % effective 8. Both the Morcher 5S Pupil Ring and the Milvella Perfect Pupil are grooved PMMA rings that are threaded alongside the pupillary margin using metal injectors. A disposable plastic injector is used to insert Vision’s Graether Silicone Eagle pupil expansion ring. All these rings are difficult to position if the pupil is less than 4 mm wide or if the anterior chamber is shallow 3.

Iris retractors are another 100 % reliable strategy for pupil expansion with IFIS 8. One mm limbal paracenteses are made in each quadrant, including a separate stab incision made just posterior to the temporal clear corneal incision. Placement of hooks in this diamond configuration has several significant advantages. The sub incisional hook retracts the iris downward and out of the path of the phaco tip. This maximizes exposure in front of the phaco tip while the nasal hook facilitates chopper placement.

Bimanual microincisional phacoemulsification may represent a useful strategy in IFIS patients. A maximally water tight seal minimizes the strong tendency for the iris to prolapse to the phaco or side port incision 8. This is the case with bimanual microincisional phaco instrumentation around which the incisions are deliberately sized for a maximally tight fluidic seal. A separate front irrigating chopper also provides a better opportunity to keep irrigation flow circulating anterior to the iris, which can minimize the billowing. Irrigation/aspiration should be accomplished with lower flow and vacuum setting.

Ophthalmic viscosurgical devices (OVD) can be designed and used to construct any physical environment in the anterior chamber that may be desired, simplifying and facilitating the surgery 6. The best known and most frequently used of these techniques are the Soft Shell Technique (SST) and the Ultimate Soft Shell Technique (USST), described by Steve Arshinoff 7.

After the side port incision and the primary clear corneal phaco incision are fashioned, the anterior chamber is filled through the phaco incision with sodium hyaluronate 3 %- chondroitin sulfate 4 % (Viscoat) until the anterior chamber is 75 % to 81 % full. Healon 5 (Sodium hyaluronate 2.3 %) is then injected into the surface of the anterior capsule, in the centre of the anterior chamber and pushes the viscoat upward and outward until the pupil stops dilating. It is important that the boundary of the Healon 5 Viscoat be at the pupil margin. This will later serve as a fracture boundary and will help to keep the iris stable and the pupil dilated throughout the surgery. At this point the anterior chamber should be over 90 % full of OVD. Balanced salt solution (BSS) or nonpreserved lidocaine (enhances dilation of pupil) is then injected slowly under the Healon 5 layer on the surface of the lens capsule. This elevates the OVD soft shell off the lens surface and creates a water pocket on the lenticular surface, confined to the lenticular surface and not spilling over the iris surface. A routine capsulorhexis is then performed keeping the diameter of the rhexis smaller than the pupillary diameter. This will later act to confine fluid flow into an area smaller than the pupil, preventing turbulence from impacting the iris and the Viscoat layer, which would permit the pupil to constrict. During hydrodissection, the BSS should be able to circulate around the lens and flow out of the eye, beneath the OVD shell, without disturbing the shell.
Table 1. IFIS GRADING

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tbody>
<tr>
<td>Iris billowing</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pupillary dilation</td>
<td>Good</td>
<td>Constriction</td>
</tr>
<tr>
<td>Iris Prolapse</td>
<td>_</td>
<td>_</td>
</tr>
</tbody>
</table>

Table 2. MANAGEMENT

A. PROPHYLACTIC
- Preoperative Recognition and Prediction
- Careful Medical History
  - Systemic Diseases
  - Drugs
- Stopping Drugs Preoperatively (1Week) In Collaboration With Urologist

B. PHARMACOLOGIC
- Preop Atropine (1% Tid x 2 Days)
  - Maximise Cycloplegia
  - No Risk of TASS
- Intracameral Phenyl Ephrine / Adrenaline
  - Competitive Antagonist
  - Direct Action on α1 Receptors
  - Prepn - .25 ml Unpreserved Phe.eph 2.5% + 2 ml BSS (30 Sec)
- Combined Preop Atropine + Intracameral Phenyl ephrine

C. THERAPEUTIC
- Proper Incision Construction
- Gentle and Slow Hydrodissection
- Ophthalmic Visco Surgical Devices
  - Healon 5 - Ideal Viscomydriasis
    - Blocks Prolapse
- Low I/A Flow Parameters
- Bimanual MICS- Tighter Incision

D. MECHANICAL DILATATION
- Pupil Stretching - Not effective
  - Elastic Pupil
- Pupil Expansion Rings
- Iris Retractors

Phaco emulsification is performed keeping the phaco tip at or below the capsulorhexis and confining fluid flow into the capsular bag.

Because of the rigid inferior surface of the OVD soft shell, formed by Healon 5 and the tamponade of the iris, achieved by the Viscoat, iris is seen to be completely stable throughout the procedure. Irrigation / aspiration should be accomplished with lower flow and vacuum settings.

The main advantage of this OVD technique is that it can be instituted safely and effectively at any time during surgery, unlike mechanical pupil dilators. The peripheral OVD ring is made with Viscoat because it is the best lower viscosity dispersive OVD available which tends to make it highly retentive despite the presence of moderate fluid turbulence. The viscoadaptive central layer of Healon 5 adds rigidity to the OVD structure to keep the iris from moving and keeping Viscoat in place. The BSS layer provides working space while the phaco is being done. It is important to have a viscoadaptive central layer above the BSS layer to avoid excessive mixing that would occur with Viscoat use alone (Table 2).

In conclusion, progressive intraoperative miosis, significantly increases the risk for complications in cataract surgery. Common pupil stretching techniques are usually ineffective in these eyes and the use of iris hooks or expansion rings before initiating the capsulorhexis may be preferable. Therefore, knowledge, anticipation and recognition of this syndrome may lead to a lower incidence of surgical complications in these patients.

References