

Association between Tamsulosin and Intraoperative “Floppy-Iris” Syndrome

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ABSTRACT: Intraoperative “floppy-iris” syndrome is a novel entity that was initially described in 2005 by Chang and Campbell who encountered it during cataract surgery. The manifestations include a triad of the following intraoperative findings: a) flaccid iris stroma leading to fluttering and bellowing of the iris, b) prolapse of the iris through the surgical incisions, and c) progressive pupil constriction. IFIS has been associated with increased surgical difficulty and, as a result, with increased morbidity including retinal detachment and loss of vision. Since the initial publication of IFIS in 2005, there have been several reports of a possible association between the use of tamsulosin for symptomatic prostate hyperplasia and IFIS. Consequently, in 2005 the U.S. Food and Drug Administration issued an alert recommending ophthalmic examination prior to treatment with tamsulosin. In this review we present evidence of the association between tamsulosin and IFIS. We conducted a Medline search using the key words tamsulosin or alpha-blockers and retrieved English written reports and data on the prevalence of treatment with alpha-blockers in general and specifically tamsulosin among patients undergoing cataract surgery, the prevalence of IFIS among treated versus non-treated patients, and the resulting surgical complications. Of the 19 publications on this topic only 7 were patient series providing data on IFIS and treatment with tamsulosin. The prevalence of men receiving tamsulosin for BPH among the patients operated for cataract was 1–3%, the occurrence of IFIS was reported in 2–3% of the patients, and 57–100% of the patients receiving tamsulosin had at least one manifestation of IFIS. The occurrence of IFIS among men receiving other alpha-blockers or in non-treated patients was rare. An association between preoperative treatment with tamsulosin and IFIS is probable. This observation warrants further research to establish causality. Meanwhile, it seems prudent to perform an ophthalmic examination prior to prescribing tamsulosin.

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Intraoperative floppy-iris syndrome is a new entity occurring during cataract surgery that was originally described in 2005 by Chang and Campbell [1]. IFIS consists of a triad of flaccid and billowing iris, iris prolapse through the surgical incisions and progressive pupil constriction. Adequate pupil dilation and a normal iris are key factors for the safety of cataract surgery. Failure to achieve these conditions renders the operation more technically difficult and therefore may lead to significant complications including posterior capsular tear, leakage of the vitreous fluid, and ultimately decreased postoperative visual acuity. Typically, patients affected by IFIS do not respond to standard pharmacological measures aimed at pupil dilatation and, consequently, IFIS has been associated with the above risks.

In their series, Chang and Campbell [2] reported an association between IFIS and ongoing treatment with tamsulosin for benign prostate hyperplasia-related symptoms, and this association was further corroborated in other studies [3–6]. Due to its higher selectivity tamsulosin has been associated with fewer cardiovascular side effects as compared with other non-selective alpha-blockers, and as a result has become the most frequently used medication for symptomatic BPH in the United States [7]. Because both cataract disease and BPH are prevalent problems in aging men, it is important to analyze the evidence of the putative link between tamsulosin and IFIS. Practicing urologists, ophthalmologists as well as primary care physicians need to be aware of this possible association.

We conducted a Medline search using the key words IFIS or intraoperative floppy-iris syndrome and tamsulosin or alpha-blockers. All publications were retrieved and only large prospective or retrospective series were included, omitting individual case reports. Data were collected on the frequency of tamsulosin use among patients undergoing cataract surgery, the reported occurrence rate of IFIS among patients who had been exposed to tamsulosin or other alpha-blockers versus patients who had not been exposed to such medications, and the resultant surgical complications related to IFIS. We analyzed the design of those studies, aiming to detect possible confounders and bias.

IFIS = intraoperative floppy-iris syndrome
BPH = benign prostate hyperplasia

ASSOCIATION OF TAMSULOSIN AND IFIS

A total of six reports including seven patient series with more than 5000 patients and 6995 operated eyes have been published [Table 1]. In their initial report, Chang and Campbell [1] included two separate patient series. The first study consisted of a retrospective analysis of 511 patients (706 eyes) who underwent cataract operation in a single clinic. Of 16 patients (2.2%) who had been taking tamsulosin, 10 developed the full-blown manifestation of IFIS. The syndrome was not observed among non-treated patients. These findings prompted the authors to explore the correlation between tamsulosin and IFIS prospectively in another series of 741 patients (900 eyes) [1]. IFIS occurred in 16 patients of whom 14 were taking tamsulosin before surgery and another had stopped it a year before surgery. Among the non-exposed patients only 1 of 726 patients had features of IFIS, which the authors attributed to diabetes. In another study from Britain of 1768 cataract patients, 72 had been taking various alpha-blockers including 21 who had taken tamsulosin [3]. A total of 29 patients were noted to have IFIS either as the full-blown syndrome (11 patients) or milder and partial forms (18 patients). Twelve of the 21 patients who had been taking tamsulosin and 1 patient who had been taking doxazosin developed IFIS. The syndrome was uncommon among patients who had not been exposed to alpha-blockers (17 of 1696 patients). In another large patient series of 2390 operated eyes, IFIS occurred in 11 of 15 patients (65%) who had taken tamsulosin prior to the operation [2].

Urologists need to be aware of this association and either send their patients to an ophthalmologic consultation prior to prescribing tamsulosin or consider another medication

Although IFIS has been typically associated with the preoperative use of tamsulosin, it has also been reported anecdotally in association with other alpha-blockers including doxazosin and terazosin [3]. Blouin et al. [5] prospectively compared the occurrence rate of IFIS in 64 men who had received either tamsulosin or afluzosin before cataract surgery. IFIS affected 86.4% of the men who had taken tamsulosin but only 15.6% of those taking afluzosin.

SURGICAL COMPLICATIONS OF IFIS

In the original report by Chang and Campbell [1], 27 of the 40 patients who had been taking an alpha-blocker had poor pupil dilatation but frank IFIS was observed only in patients who had taken tamsulosin. In the patients with IFIS who were operated on both eyes IFIS occurred bilaterally except in one patient. Of the 16 patients with IFIS, posterior capsular tear and vitreous loss were found in 2 and an abrupt increase in intraocular

pressure was noted in 4 others on the first postoperative day. Significant permanent decrease in visual acuity was noted in two patients. Transient intraocular pressure elevation was noted in two patients in the prospective arm of the study. No other significant complications were reported in the prospective cohort. However, two of the IFIS patients had their cataract operation in the fellow eye performed elsewhere, another two had irregular pupil shape as the result of iris prolapse and one had a posterior capsular tear. In the report by Chandha and co-authors [3] a posterior capsular tear was noted in a single patient aged 29 who had IFIS.

Cheung et al. [2] noted that despite various degrees of IFIS the operation proceeded uneventfully in 94% of the patients who had taken tamsulosin and resulted in zonular dehiscence in one patient only. No vitreous loss occurred. These authors concluded that although exposure to tamsulosin renders cataract surgery more technically difficult, major complications can usually be avoided if the surgeon is aware of IFIS. In patients undergoing surgery on both eyes, tamsulosin was discontinued for 3 weeks after the first operation; however, milder degrees of IFIS were still apparent during the surgery on the contralateral eye. Likewise, in the prospective arm of Chang's study, one of the patients with IFIS had discontinued tamsulosin one year before surgery [1].

In the study comparing the risk of IFIS between patients taking tamsulosin versus afluzosin, the former alpha-blocker was significantly more frequently implicated in IFIS [5]. Of 92 eyes exposed to either alpha-blocker, 61 (66%) developed IFIS. The overall complication rate was 49% (30/61) in patients with IFIS as compared to 9.7% (3/31) in eyes with-

Table 1. Occurrence of IFIS among patients exposed to tamsulosin and among those not exposed

n	Design	Patients exposed to tamsulosin	Attack rate in exposed patients (%)	Attack rate in non-exposed patients (%)	P	Reference
511	Retrospective	16	10/16 (63)	0/495 (0)	< 0.01	Chang [1]
741	Prospective	15	15/15 (100)	1/726 (0.1)	< 0.01	Chang [1]
1768	Retrospective	21	12/21 (57)	17/1747 (0.1)	< 0.01	Chadha [3]
2390*	Retrospective	15**	11/17 (65)	NA	NA	Cheung [2]
64	Prospective	22	19/22 (86)	2/42 (5)	< 0.01	Blouin [5]
135	Prospective	135	151/167 (90)***	NA	NA	Chang [4]
774	Prospective	18	14/18 (78)	NA	NA	Takmaz [6]

* In this study the number of eyes operated was provided rather than the number of patients
 ** 15 patients (17 eyes) had been taking tamsulosin
 *** 151 of 167 exposed eyes expressed the outcome of IFIS at various severity degrees.
 n (number of patients reported in series); attack rate = the ratio between the number of patients who had IFIS and the number of patients exposed or not exposed to tamsulosin.
 NA = not available

out IFIS [5]. Major complications were noted in 15% of the patients with IFIS and included iris laceration, iris dialysis, iris hemorrhage, posterior capsular tear with vitreous loss, zonular dehiscence and others.

In a prospective multicenter study on tamsulosin and IFIS, the syndrome was considered moderate or severe in 73% of the affected eyes, and posterior capsular tear with vitreous loss was noted in one patient (0.6%) [4]. In a series from Turkey posterior capsular tear occurred in a single patient aged 14 who developed IFIS [6].

Since the recognition of IFIS, the ophthalmologic literature has reported various intraoperative measures devised to cope better with the difficulties associated with IFIS and to reduce complications. These include the use of iris hooks and pharmacological interventions [8-11].

TAMSULOSIN AND IFIS – A PUTATIVE MECHANISM

Although IFIS has been anecdotally reported in association with other alpha-blockers, exposure to tamsulosin was the typical underlying factor in IFIS. Contemporary studies have shown that the iris is a very complex organ composed of two distinct regions – the dilator plate and sphincter region, each with separate innervation and blood supply that are independently responsible for pupil constriction and dilation. The balance between pupil constriction and dilation is maintained by an interplay between alpha and beta-adrenergic receptors and the cholinergic system [12]. The neural control on the iris is mediated through adrenergic receptors and it was recently found that the alpha-1a receptor is the most abundant receptor in the iris that mediates pupil dilation [12] [Figure 1]. In addition, the alpha-1a receptor is the most widespread adrenergic receptor in small iris arterioles. Likewise, more than 70% of the adrenergic receptor population in the bladder neck and prostate are alpha-1a receptors. However, there is scarce distribution of this particular receptor outside the urinary tract and the iris. As a result, tamsulosin, a super-selective alpha-1a receptor competitive antagonist, is associated with fewer cardiovascular side effects as compared with other alpha-blockers, and consequently it has become the most commonly used medication for symptomatic BPH in the USA [7].

Because of its selective antagonism, tamsulosin has an effect on the iris, and the relaxation ability and pupillary dilation are impaired. Although these effects are associated with other non-selective alpha-blockers, the effect of tamsulosin on the eye is more pronounced. It has been suggested that long-term tamsulosin administration leads to disuse atrophy of the muscular plate responsible for pupil dilata-

tion. Such atrophic changes may explain the flaccid nature of this tissue as found during cataract surgery, as well as other findings such as progressive constriction that is not adequately opposed by effective relaxation. With significant atrophic changes, the muscle function is impaired and the response to mydriatic drugs is dull. This can also explain why IFIS occurs not only with concurrent tamsulosin treatment but also in those who had been exposed to this medication in the past and had discontinued the drug some time before surgery. Since there are only scarce reports on such patients who had IFIS despite previous cessation of tamsulosin, the exact extent of this phenomenon as well as the duration between the cessation of tamsulosin treatment and full recovery of the eye are still unknown and demand further investigation.

IS THERE ENOUGH EVIDENCE OF A CAUSATIVE RELATIONSHIP BETWEEN TAMSULOSIN AND IFIS?

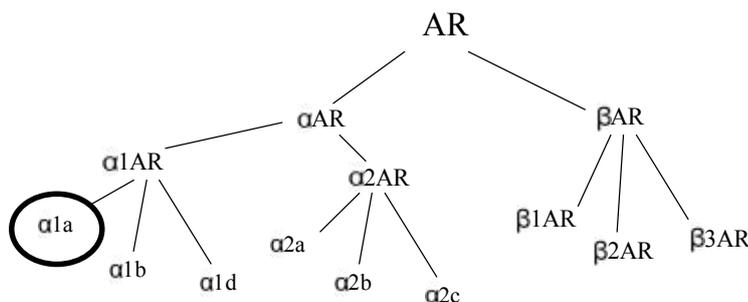
The establishment of an association between exposure to an effector and a clinical result is a major epidemiological challenge. Nevertheless, understanding how the exposure to a risk factor is associated with the resultant disease is a key factor in preventive medicine.

A highly significant association between exposure and event, and, in parallel, a paucity of cases among non-exposed individuals, suggests a possible clinical association between effector and disease. Such associations are typically determined by case-control studies where the exposure to the putative risk factor is retrospectively compared between individuals who have the disease and controls who do not.

The resultant difference in exposures is expressed by the odds ratio. Alternatively, a prospective cohort study may allow the involved patients to be exposed to the risk factor and determination of the relative risk of developing the disease in time. While these study designs can outline a clinical

Ophthalmologists should ask their patients whether they had been exposed to this drug prior to cataract surgery

Figure 1. Classification of adrenergic receptors (AR). Encircled is the most abundant AR in the prostate and in the iris.



association between exposure and disease event, they are not enough to prove causality and as such they are perceived as observational. Significant bias in the selection of cases, in matching controls or in the definition and measurement of the exposure may be misleading in defining the association. Confounders may further blur the picture as the association is made with the wrong factor.

In addition to a strong well-documented association between exposure and event, causality requires a reasonable biological mechanism that could explain how the resultant disease is provoked by the exposure.

IS THE PERTINENT EVIDENCE ON TAMUSOLIN AND IFIS SUFFICIENT TO DETERMINE CAUSALITY?

Seven relatively large studies have shown a strong association between exposure to tamsulosin and the observation of IFIS. None of these was designed as a case-control study. Thus, cases that were observed with IFIS during surgery were not matched by age, ethnicity, smoking history, co-morbidity or iris color, with controls who did not have IFIS. Rather, the cases were compared to all the other patients who had cataract surgery. Confounders such as other medications, and concurrent disease such as diabetes mellitus were not carefully assessed and controlled for. Furthermore, despite the clear definition of IFIS as a triad of flaccid iris,

prolapse and progressive miosis, Cheung and others [2,3] observed milder or incomplete forms of IFIS in some of their patients. This could have led to over-reporting of IFIS. Similarly with regard to patients who were operated on both eyes, although blinding of the ophthalmologist to the data on exposure to tamsulosin was undertaken in some of the studies, the physician became well aware of the patient's condition and previous exposure to tamsulosin once IFIS was noted in the first operated eye. The extent of exposure to tamsulosin was not well defined. The duration of treatment and the time span between discontinuation of tamsulosin and cataract surgery were not well documented and consequently it remains unclear how long before cataract surgery tamsulosin treatment should be discontinued and if such discontinuation is effective in preventing IFIS.

The reported prevalence of tamsulosin therapy among patients undergoing cataract surgery is 2–3%. This is a surprisingly low rate as cataract disease and BPH seem to affect the same age group, and since tamsulosin is currently the most widely distributed alpha-blocker in many countries. It would be expected that among aging men who require cataract surgery the frequency of use of alpha-blockers to control BPH-related symptoms would be higher [13]. Possibly,

the low number of patients taking any alpha-blockers and specifically tamsulosin in these studies stems from the retrospective nature of chart review and the incompleteness and inaccuracy of data collection with regard to medication history at the time the patient chart was written. If this bias is real it is possible that the risk of IFIS among tamsulosin takers is actually lower than reported. Patients who experienced a severe unexpected untoward effect during surgery are probably questioned about their health state and medication history more than patients in whom the operation proceeded in a standard manner. The history of previous or concurrent exposure to tamsulosin might therefore have been overlooked in some of the patients, who despite this treatment did well during cataract surgery.

The surgical complications and permanent sequelae from IFIS are not yet well documented. It appears that the amount of awareness on the part of the ophthalmologist to IFIS and its putative association with tamsulosin can make a difference in patient outcome. Primary prevention in the form of discontinuation of tamsulosin with time before surgery may decrease the risk of IFIS or present it in a milder form.

Specific surgical and pharmacological interventions may contribute by providing secondary prevention where IFIS has already occurred, but measures are taken to prevent injury. The current ophthalmologic literature expands on

measures to be taken during and before surgery to minimize the complications associated with IFIS.

Our understanding of the biological mechanism explaining the association between tamsulosin and IFIS needs additional enhancement by animal and clinical studies. The association between cause and effect needs further corroboration with molecular and histological findings and the theory of muscle atrophy in the iris needs additional support.

Despite these shortcomings, one cannot ignore the initial impression that tamsulosin treatment is significantly associated with factors that tend to complicate and endanger an otherwise straightforward common surgical procedure. In this line is the alert issued by the U.S. Food and Drug Administration with regard to the possible association between tamsulosin and IFIS [<http://www.fda.gov/med-watch/safety/2005/safety05.htm#Flowmax>]. Although the earliest reports on IFIS were made in 2005, the vast majority of the pertinent literature since then was published in ophthalmologic journals. Consequently, urologists and primary care physicians who may not read ophthalmologic journals routinely are not aware of this possible untoward effect of tamsulosin. Preventive medicine aims at decreasing the risks of an expected negative event by taking measures to

Concurrent therapy with tamsulosin for symptomatic prostate hyperplasia seems to be associated with an increased risk for Intraoperative floppy-iris syndrome during cataract surgery

avoid the event (primary prevention), to minimize its effects (secondary prevention), and to treat the resultant damage thereby avoiding further complications (tertiary prevention). Although not a well-accepted term, we have previously suggested "quaternary prevention" [14] as yet another level of preventive medicine where relevant knowledge and lessons learned from previous untoward events are published, thereby improving the awareness and capacity to engage in the three standard levels of prevention among practicing clinicians. We believe that this review will serve this purpose.

SUGGESTED RECOMMENDATIONS

Until the much needed additional studies are published and the causative relation between tamsulosin and IFIS can be established or disputed, some clinical measures are necessary to protect patients. We suggest that urologists and primary care practitioners ask their patients about possible eye problems and suggest an ophthalmologic consultation prior to prescribing tamsulosin and possibly other alpha-blockers. Theoretically, if the patient is a candidate for cataract surgery it may be best to defer treatment with tamsulosin until after the surgery. Likewise, ophthalmologists are encouraged to obtain a full medication history from patients who are candidates for cataract surgery with particular attention given to tamsulosin, much like the standard questioning on the use of anticoagulants. Early discontinuation of tamsulosin before surgery may be beneficial although further study is required to prove it.

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The greatest tragedy in mankind's entire history may be the hijacking of morality by religion"

Arthur C. Clarke (1917-2008), British science-fiction writer