Floppy iris syndrome associated with specific medication intake: A narrative review

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Intraoperative floppy iris syndrome (IFIS) is a cataract surgery complication that remains a challenge for eye surgeons. It is caused by the antagonism of alfa-1-adrenergic receptors within the dilator muscle of the iris, thus preventing the iris from dilation during a cataract surgery. The long-term blocking alfa-1 adrenergic receptors by the chronic use of a number of systemic medications may lead to permanent anatomical atrophy of the dilator muscle of the iris. The most common drugs associated with the development of IFIS are tamsulosin and other alpha-1 adrenergic receptor antagonists prescribed to patients with low urinary tract symptoms (LUTS). There are other systemic medications that have been reported to have increased risk for IFIS. It is crucial for the ophthalmologist to identify the high-risk patients prone to develop IFIS. Its presence may complicate the course of cataract surgery, ultimately negatively affecting visual outcome. Cataract surgery should be performed by an experienced eye surgeon using alternative pharmacological and surgical techniques. Interdisciplinary cooperation is essential to mitigate potential complications. Patients should be informed by their physicians about the need to report a medication history to their eye specialists, especially before cataract surgery.

Key words: intraoperative floppy iris syndrome, lower urinary tract symptoms, alpha-blockers, tamsulosin, iris

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INTRODUCTION

Cataract is the clouding of the eye lens and its capsule. The incidence of cataracts increases with age and affects 60–70% of patients over the age of 70 (ref.[1]). Nowadays, cataract is one of the main causes leading to vision impairment. Surgical extraction of a clouded lens and its replacement with an artificial lens is currently the only effective therapy to restore the central visual acuity[1]. Cataract extraction is one of the most frequently performed surgeries worldwide. The main prerequisite for a smooth surgical procedure is a sufficiently wide pupil and stability of the iris. Dilation of the pupil is achieved by the contraction of the dilator muscle of the iris, which has radially arranged muscle fibres at half the distance between the scleral spur and pupillary margin; it is innervated primarily by the sympathetic system through the release of noradrenalin[2].

Intraoperative floppy iris syndrome (IFIS) was first described by Chang and Campbell in 2005, who observed abnormal behaviour of the iris during cataract surgery in their patients using tamsulosin[3]. IFIS is a complication occurring during cataract surgery and is characterised by the following features: billowing of a floppy iris stroma that undulates depending on irrigation, progressive intraoperative miosis despite adequate use of mydriatics, and iris prolapse into the corneal incisions with the risk of its aspiration into the phacoemulsification probe[4,5]. The above-mentioned signs are used to classify IFIS into mild, moderate and severe grade (Table 1) (ref.[6]).

Table 1. The +grade of intraoperative floppy iris syndrome is determined by the presence of following signs.

Grade of intraoperative floppy iris syndrome	Signs
Mild	Billowing of a floppy iris stroma
Moderate	Billowing of a floppy iris stroma + progressive intraoperative miosis/iris prolapse into the corneal incisions
Severe	The presence of all three signs

IFIS is most commonly associated with chronic use of tamsulosin and other alpha-1 adrenergic receptor antagonists (α1-ARAs) in patients with lower urinary tract symptoms (LUTS) (ref.[3]). However, it has been reported in other systemic medication as well. This article is intended especially for urologists, ophthalmologists and internal medicine specialists, to review all the medication that can be associated with development of IFIS.

PATHOPHYSIOLOGY AND COMPLICATIONS OF IFIS

The main pathogenetic mechanism of IFIS is the inactivation of the α1-adrenergic receptors within the dilator muscle of the iris, leading to the decrease in the muscle tone and prevention of mydriasis[7]. Long-term use of α1-ARAs causing persistent pupil dilator atrophy[2,7-9]. There are a number of studies and clinical case reports that describe the development of IFIS during cataract surgery, even many years after tamsulosin discontinuation[4]. Therefore, ophthalmologists should ask not only about current α1-ARAs therapy, but also about its previous use[8]. Goseki et al. confirm the high binding affinity of selective α1-ARAs (tamsulosin and silodosin) for the α-receptors of the iris dilator. In addition, they also found that α1-ARAs interact with iris melanin, as demonstrated by microscopic changes of iris pigment epithelium, which is probably the other important mechanism of IFIS (ref.[10]).

IFIS may represent a source of difficult operating conditions for eye surgeons. It is associated with higher rate of complications, such as increased intraocular pressure, posterior capsule rupture, iris trauma, zonula dehiscence, hyphema or prolapse of the vitreous into the anterior chamber that may occur during phacoemulsification and other surgical steps[2,5,11,12]. Storr-Paulsen et al. measured the number of corneal endothelial cells three months after cataract surgery. In the group of men using tamsulosin, who developed IFIS, there was a significantly reduced number of endothelial cells compared to the control group (12% versus 3%) (ref.[13]). According to the study, a higher loss of endothelial cells can be associated with a more complicated course of cataract surgery due to billowing iris[13].The development of IFIS can lead to postoperative complications as well, including permanent iris damage, pupil distortion with glare and photophobia, cystoid macular edema and postoperative ocular inflammation[3,4,14].

SURGICAL TECHNIQUE MODIFICATION

The ophthalmic surgeon must be informed about the risk group of patients to be able to prevent the development of a severe IFIS by modifying the surgical technique[11,15,16.] During the surgery, it is generally recommended to minimize in-and-out movements through corneal incisions, use low-flow irrigation/aspiration parameters, perform gentle hydrodissection, and keep the irrigation flow above the iris plateau[5,17]. An often preferred and reliable technique is the instillation of phenylephrine or epinephrine into the anterior chamber at the beginning and during the surgery[16], Lorente et al. confirmed the ability of phenylephrine to induce more pronounced mydriasis and restore iris rigidity[18]. An alternative – 1% atropine drops twice a day for one week – can be chosen in the preoperative period[19]. Mydriasis and iris stability can also be supported by viscoelastic material with a high sodium hyaluronate content in combination with soft-shell technique. Viscoelastic material is a protective film against incarceration of the iris into the corneal incisions[20,21]. Iris hooks dilate the pupil mechanically into the resulting square shape. A disadvantage is the need for four separate incisions to introduce the hooks into the anterior chamber, which increases the risk of postoperative inflammation[14]. Another option is pupil expanders introduced into the anterior chamber using injectors. Unlike iris hooks, expanders do not require a separate incision and are able to stabilize the pupil throughout the surgery, thus minimizing its deformation[11].

MEDICATIONS ASSOCIATED WITH IFIS

Alpha-blockers in the treatment of LUTS

Epidemiological data show that LUTS occurs in 50–60% of patients older than 60 years. The incidence increases with age and LUTS is diagnosed in 80–90% of the male population between 70–80 years of age[22]. Alpha-blockers are used as first-line treatment in patients with moderate to severe LUTS due to their rapid onset of action[2]. Alpha-blockers decrease the tonus of the smooth muscle of the prostate and the bladder neck, reducing the obstruction of prostatic part of the urethra and thus the accompanying symptoms of the lower urinary tract[23]. There are three subtypes of α_1-adrenergic receptors – A, B and D, subtypes A and D are dominant in hyperplastic prostate tissue[22-23]. α_{1A}-receptors are also found in the dilator pupillae muscle[24] contrary to α_{1B}-receptors in the smooth muscle of arteries[2]. There are selective (tamsulosin, silodosin) and non-selective (alfuzosin, doxazosin, terazosin, prazosin) alpha-blockers[2]. Non-selective alpha-blockers are also indicated in the management of hypertension[23]. An overview of alpha-blockers in LUTS with their recommended daily dose is shown in the Table 2.

Selective alpha-blockers

Tamsulosin is one of the most commonly used alpha-blockers in men in LUTS pharmacotherapy in benign prostatic hyperplasia (BPH) (ref.[2]). It is often the drug of first choice due to its rapid onset of action[2]. It is also used as an antihypertensive (currently to a limited extent), and its effectiveness in the treatment of LUTS in women has also been reported[16,25]. Tamsulosin has recently been used in expulsive pharmacotherapy in distal ureterolithiasis, increasing the probability of the stone passing spontaneously by relaxing the tone of the smooth muscle of the ureter[26].

Tamsulosin has 10 times greater affinity for α_{1A}- and α_{1D}-adrenergic receptors than non-selective alpha-blockers[17]. IFIS risk in patients treated with tamsulosin is 57–100% (ref.[27]). Chang et al. retrospectively analysed 706 operated eyes – iris instability and prolapse developed in 10 of 16 patients treated with tamsulosin. In their prospective study, they report that IFIS developed in 16 of 741 patients during cataract surgery, 14 of whom confirmed concomitant use of tamsulosin. One patient who developed IFIS had discontinued tamsulosin more than a year prior to the surgery. Another patient with signs of an unstable iris pointing to IFIS stated that he had never

used tamsulosin in the past[3,7]. A retrospective study by Santaello et al. investigated the anatomical proportions of 51 cadaveric eyes at the level of the dilator pupillae muscle, comparing 14 patients with tamsulosin use (Flomax) and a control group of 13 patients of the same age category. The study found a statistically significant difference in the thickness of the pupil dilator between the observed groups (6.53 ± 1.99 μm versus 8.50 ± 1.61 μm) (ref.[7]). At the same time, they found no correlation between iris atrophy and the duration of tamsulosin use[7]. In contrast, an experimental study by Popescu et. al. confirms the association between pupil dilator thinning and duration of tamsulosin use. At the same time, they found that the duration of alpha-blocker use was closely related to the degree of IFIS (ref.[28]). Shtein et al. in their study they investigated the vascular morphology of the iris affected by the use of tamsulosin under the assumption of permanent blockade of α1-adrenergic receptors, which are part of the iris arterioles. The vasculature of the iris was visualized using fluorescence angiography in 20 patients with current or previous use of tamsulosin and the results were compared with a control group of 10 patients without therapy. No dysregulation of iris vascular structures was confirmed in patients on tamsulosin therapy[29].

Silodosin was introduced in 2008 as a highly selective alpha-blocker for lower urinary tract symptoms intended for the treatment of LUTS with minimal side effects[8,30]. The first report of IFIS in association with the use of silodosin was published by Ipekci in 2015. The article discusses a 60-year-old patient diagnosed with BHP after a two-month therapy with silodosin at a dose of 8 mg/day. He underwent cataract surgery in his left eye 45 days after discontinuing the alpha-blocker. During the surgery, he developed all the signs of IFIS in the left eye, requiring the modification of the surgical technique[31]. The first bilateral occurrence of IFIS in association with the use of silodosin for one month is described in a case report by Ozcur et al. in a 63-year-old man[8]. Christou et al. investigated the incidence of IFIS in a group of 350 patients using tamsulosin, alfuzosin, and silodosin. They report that IFIS developed in 37.2% of patients treated with silodosin. In conclusion, studies indicate that silodosin is considered a significant risk factor for the development of IFIS (ref.[32]). Umut et al. confirmed a statistically significant difference in pupil width and stability between a group of 74 men treated with silodosin and a control group of 30 healthy men. They demonstrated a narrower pupil under both photopic and scotopic conditions, a longer time to induce mydriasis, and a shorter duration of mydriasis in patients with silodosin therapy[33].

Naftopidil exhibits high affinity for α_{1D}- and α_{1A}-adrenergic receptors. With its antagonistic effects, it mainly suppresses the micturition symptoms of LUTS (delay in the start of urination, weak and intermittent stream of urine, difficult urination, terminal dribbling) and nocturia[34]. Naftopidil was approved for the treatment of LUTS by the Japanese Ministry of Health, Labour and Welfare in 1996 based on a randomized prazosin-controlled trial and another double-blind placebo-controlled trial. It is currently only used in countries outside the European Union (Japan, China, Korea) (ref.[35]). Oshika et al. describe an association between the use of naftopidil and the development of IFIS. They noted IFIS in four of 21 eyes of patients with naftopidil therapy (19%) (ref.[35]).

Non-selective alpha-blockers

Alfuzosin has a lower affinity for the α_{1A}-receptor compared to tamsulosin. A statistically significant difference in the probability of IFIS between the group using tamsulosin and alfuzosin was reported by Chang et al. examining 226 eyes. 34.3% of tamsulosin-treated eyes and 16.3% of alfuzosin-treated eyes showed signs of IFIS during cataract surgery[6]. Similar results were reported in a retrospective study by Blouin et al. from 2007, where 86% of tamsulosin-treated patients and only 15% of alfuzosin-treated patients developed IFIS during cataract surgery[36]. As for alpha-blockers, alfuzosin is recommended as the drug of first choice preferred to tamsulosin in men diagnosed with cataracts and LUTS (ref.[2,6]).

Terazosin, doxazosin and prazosin are non-selective alpha-blockers indicated for the treatment of arterial hypertension, among others. They can be used alone in the therapy of hypertension or in combination with other antihypertensive drugs, if the therapeutic response is insufficient. Another indication is the symptomatic treatment of LUTS (ref.[2,5]). Their association with the development of IFIS was retrospectively investigated by Chang et al. – 11 patients (15 eyes) used these non-selective alpha-blockers. None of these patients developed IFIS during surgery[3]. A similar conclusion is retrospectively reported in patients on terazosin and prazosin therapy by Oshika et al., where none of these patients developed IFIS (ref.[35]). The first case of IFIS during five years of terazosin use was reported in 2006 by Venkatesh et al. in a 72-year-old man with primary open-angle glaucoma who underwent a combined procedure (nuclear cataract extraction and trabeculectomy) (ref.[37]). Haridas et al. compared the incidence of IFIS and the rate of intraoperative complications in patients using tamsulosin and doxazosin. They state a significantly higher incidence of IFIS in patients using tamsulosin compared to the group treated with doxazosin (48% of eyes versus 16% of eyes) (ref.[38]). At the same time, more perioperative complications were detected in individuals treated with tamsulosin than in the doxazosin group (13.5% of eyes versus 1.9%) (ref.[38]).

The discontinuation of α1-ARAs prior to cataract surgery appears to be a reasonable step. However, a prospective study by Chang et al. from 2007 demonstrates that preoperative discontinuation of tamsulosin cannot fully prevent or reduce the severity of IFIS (ref.[16,39]). In addition, this approach can lead to significant patient discomfort associated with micturition problems[11,12,65].

5alpha-reductase inhibitors

5alpha-reductase inhibitors (5ARi) are another very frequently prescribed group of drugs for LUTS patients in urology. The enzyme 5alpha-reductase converts testosterone (TST) to its more effective form dihydrotestosterone

Table 2. Overview of alpha-blockers in the treatment of lower urinary tract symptoms.

Alpha-blocker	Selectivity	RDD (mg)*
Alfuzosin	no	10
Doxazosin	no	4–8
Terazosin	no	5–10
Prazosin	no	1–5
Tamsulosin	α_{1A}, α_{1D}	0.4
Silodosin	α_{1A}	4–8
Naftopidil+	α_{1A}, α_{1D}	50–75

*RDD, recommended daily dose; list of forms with controlled release of the active substance; use once a day; +available outside EU countries

(DHT) – a substance with a key role in the development and growth of the prostate. There are two isoforms of 5ARi – type 1 and 2; type 2 has greater activity in the prostate. Two 5ARi are available for clinical use – finasteride and dutasteride. Finasteride inhibits only type 2 enzyme, while dutasteride inhibits both types. 5ARi induce apoptosis of prostatic epithelial cells, leading to the reduction in prostate volume (by 15–25% on average) and circulating prostate-specific antigen (PSA) levels by up to 50% after 6–12 months of treatment[23]. 5ARi relieve urination problems. Unlike alpha-blockers, long-term use of 5ARi significantly reduces acute urinary retention, reduces the risk of further prostatic tissue growth and the need for LUTS-related surgery[40].

In their 2007 paper, Issa & Dagres discuss the case reports of two men using finasteride due to LUTS who underwent cataract surgery in both eyes and developed IFIS bilaterally[41]. A similar IFIS case in a patient with subcapsular cataracts in both eyes is described by Wong and Mak, a 47-year-old man with a four-year history of finasteride therapy for alopecia[42]. The authors draw attention to the possible association of IFIS and the use of finasteride. Horvath et al. also reached similar results[43]. The mechanism of action of finasteride on IFIS development remains unclear[44]. There are no published IFIS reports of concomitant use of dutasteride.

Phytotherapy

Some plant extracts are also used in the treatment of LUTS. Their mechanism of action lies in the inhibition of fibroblasts, which stimulate the proliferation of prostate tissue. The most widely used plant extract is an extract from Seronea repens known as Saw Palmetto, which relieves micturition symptoms[22,23]. It has been shown to have an α-adrenergic effect[45]. Neff et al. report Saw palmetto as a possible risk factor for the development of IFIS, although the results are not statistically significant[46]. Due to its nature of an herbal medicine, it is often overlooked in patient's pharmacological history[47].

Antipsychotics

Chlorpromazine is the first discovered antipsychotic of the phenothiazine group. It has an inhibitory effect on α1-adrenergic receptors, leading to a number of side effects, such as orthostatic hypotension, tachycardia, etc. (ref.[48]). Unal et al. present a case report of a 48-year-old woman with the history of 29-year chlorpromazine therapy for schizophrenia. She developed IFIS in both eyes during nuclear cataract surgery. The authors assume that the antagonistic effect of chlorpromazine on α 1-adrenergic receptors is responsible for the inhibition of mydriasis and disruption of the stability of the iris[49]. Of the other first-generation antipsychotics, zuclopenthixol is also associated with IFIS, as reported by Pringle et al. in their case report of a male patient with schizophrenia[50]. As for second-generation antipsychotics, IFIS was observed in a 59-year-old woman using quetiapine for dementia-related psychosis[51]. Ford et al. provide a similar report on three eyes of two patients using risperidone[52]. Matsuo et al. point to the risk of IFIS with any class of antipsychotics, despite their previous use[53].

Anxiolytic agents

Chatzialli et al. report a retrospective statistically significant association between the development of IFIS and the use of benzodiazepines[44]. The positive correlation is also confirmed by a prospective study by the same author in another group of patients[15]. Using autoradiography, Zarbin and Anholt detected benzodiazepine receptors in several ocular tissues, such as the epithelium and endothelium of the cornea, the iris, the ciliary body, and the retina with its vascular bed[54].

Cognitive agents

Acetylcholinesterase inhibitors (donepezil, rivastigmine), slowing the progression of Alzheimer's disease, are also reported as a risk factor of IFIS (ref.[55,56]). Their cholinergic action on the iris sphincter prevents mydriasis. However, the exact mechanism is unknown and remains under investigation[5,55,56].

Antidepressants

González-Martin-Moro et al. reported severe IFIS in a patient with a 3-year history of 60 mg duloxetine use for major depressive disorder[57]. Ugarte at. al. published a case report of a 68-year-old woman using mianserin for 20 years for the treatment of depression. She developed IFIS during cataract surgery, which damaged the iris subsequently leading to glare effect[58]. Imipramine is one of the main representatives of tricyclic antidepressants. Gupta and Srinivasan described three cases of patients with a history of imipramine use who developed IFIS during cataract surgery. Two of these patients discontinued imipramine several months before surgery. Neither of them used an alpha-blocker[59].

Other drugs

A number of articles have been published indicating the association of IFIS with some other drugs, such as metformin, aspirin, losartan[55], ropinirole[60] or labetalol[61]. However, the association of these drugs with IFIS requires further investigation[55].

An overview of all drugs possibly associated with IFIS syndrome is shown in the Table 3.

OTHER CONDITIONS ASSOCIATED WITH THE OCCURRENCE OF IFIS

Chatziralli et al. focused on other risk factors – the univariate analysis detected a significant association with possible IFIS in case of short axial bulb length. A positive IFIS risk correlation was also found in hypertension[44,62]. In contrast, Altan-Yaycioglu et al. refute hypertension as a cofactor in the development of IFIS in their cohort of 500 patients[63]. Kaczmarek et al. report male sex (related to the occurrence of LUTS and the use of alpha-blockers) and older age as risk factors. Aging is a risk factor for the development of IFIS due to the increased prevalence of cataract in the elderly population[13,24]. In contrast, diabetes mellitus, glaucoma and pseudoexfoliation syndrome were not found to be IFIS risk factors[24]. According to Tint et al., other risk factors of IFIS include iris configuration, anterior chamber depth, and location of corneal incisions. The mechanism of IFIS development is explained by Bernoulli's principle – the fluid flow rate in the anterior chamber changes depending on the position of the iris[64].

CONCLUSIONS

IFIS is a substantial complication to the surgical process of cataract extraction. It is associated with a risk of irreversible damage to the intraocular tissues with a negative impact on the vision. The rising life expectancy and the number of chronically used drugs lead to the increase of IFIS occurrence. An ophthalmologist must carefully research the patient's medication history before planning the cataract surgery. Weak mydriasis of the patient already in the preoperative period may alert the ophthalmologist about the possible association with chronically used α-adrenergic receptor inhibitors. It is necessary to inform the eye surgeon about the risk group of patients in advance to prevent possible intraoperative complications.

Of the above-mentioned drugs, tamsulosin is substantially associated with IFIS risk. However, it is also necessary to consider other alpha-blockers and other groups of drugs with the risk of iris atrophy and IFIS. A multidis-

Table 3. Overview of drugs associated with Intraoperative floppy iris syndrome.

Drugs associated with the development of intraoperative floppy iris syndrome		
Treatment of low urinary tract symptoms	Tamsulosin Silodosin Naftopidyl	Selective α_1-adrenergic receptor antagonists
Treatment of low urinary tract symptoms Treatment of hypertension	Alfuzosin Doxazosin Terazosin Prazosin	Non-selective α_1-adrenergic receptor antagonists
Treatment of low urinary tract symptoms	Finasteride	5alpha-reductase inhibitors
Supportive treatment of low urinary tract symptoms	Saw Palmetto	Phytopharmaceutical
Antipsychotics	Chlorpromazine	Antagonist of dopamine, cholinergic, α_1-adrenergic, histamine H_1, serotonin receptors
	Zuclopenthixol	Antagonist of dopamine D_1 and D_2, serotonin 5-HT_2, α1-adrenergic receptors
	Quetiapine	Antagonist of serotonin 5-HT_2, dopamine D_1 and D_2, histamine, α1-adrenergic receptors
	Risperidone	Antagonist of serotonin 5-HT_2, dopamine D_2, α1-adrenergic, histamine H_1, α_2-adrenergic receptors
Anxiolytic agents	Benzodiazepines	Anxiolytic, increase in GABAergic neurotransmission
Cognitive agents	Donepezil	Acetylcholinesterase inhibitor
	Rivastigmine	Acetylcholinesterase inhibitor
Antidepressants	Duloxetine	Serotonin 5-HT and noradrenaline reuptake inhibitor
	Mianserin	Antagonist of α_1- and α_2-adrenergic, serotonin, histamine receptors
	Imipramine	Noradrenaline and serotonin reuptake inhibitor, histamine, muscarinic, dopamine, α-adrenergic receptor antagonist
Others	Metformin	Oral antidiabetic drug
	Losartan	Antihypertensive, angiotensin II receptor antagonist
	Aspirin	Antiplatelet agent, nonsteroidal antiinflammatory drug
	Ropinirole	Treatment of Parkinson's disease, D_2/D_3 receptor agonist
	Labetalol	Antihypertensive agent, antagonist of α-/β-adrenergic receptors

ciplinary collaboration aims to deepen awareness of the adverse effects of these drugs and thus improve the level of provided care.

Search strategy and selection criteria

Our goal was to unify all possible drugs that can potentially lead to development of IFIS. We obtained the relevant information by the search of reliable articles in peer-reviewed journals and professional literature. We verified the data from several sources. We worked, among other things, with the PubMed and ScienceDirect database. The following keywords were used: "Intraoperative floppy iris syndrome", "IFIS associated with alpha antagonists", "IFIS associated with medication intake", "Surgical strategies of IFIS", "Risk factors for IFIS".

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