REVIEW ARTICLE

Cataract Surgery in Patients Taking Alpha-1 Antagonists

Know the Risks, Avoid the Complications

Daniel M. Handzel, Sebastian Briesen, Steffen Rausch, Tilman Kälble

SUMMARY

Background: The growing use of alpha-1 receptor antagonists in the treatment of benign prostatic hyperplasia (BPH) has created a new problem in ophthalmic surgery, the so-called intraoperative floppy iris syndrome (IFIS). This consists of a billowing iris, insufficient pupillary dilation with progressive intraoperative miosis, and protrusion of iris tissue through the tunnel and side port incision that are made for access to the anterior chamber during surgery. IFIS presents particular difficulties in cataract surgery which is carried out through the pupil with manipulations in the immediate vicinity of the iris. The complications range from poor visibility of the operative field to iris damage with the surgical instruments and to rupture of the posterior capsule, with loss of lens material into the vitreous body.

Methods: Selective literature review.

Results: Alpha-blockers have a direct effect on the alpha-receptors of the iris but also induce ultrastructural changes in the iridial stroma, leading to IFIS. The most important factor in avoiding complications of IFIS seems to be the ophthalmic surgeon's knowledge that the patient is taking an alpha-1 receptor antagonist.

Conclusion: A thorough medical history and an optimized information flow among all physicians treating the patient—the urologist, the family physician, and the ophthalmic surgeon—are essential for safe cataract surgery.

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The growing use of alpha-1 receptor antagonists in the treatment of disorders of the urinary tract, especially benign prostatic hyperplasia (BPH), has created a new problem in ophthalmic surgery. The so-called intraoperative floppy iris syndrome (IFIS) describes an intraoperative situation with a "billowing" iris, which starts fluttering as a result of mild intraocular fluid currents in spite of medication induced mydriasis, progressive intraoperative miosis in spite of sufficient administration of mydriatic medications, and a tendency to spontaneous protrusion of iris tissue through the tunnel and side port incisions that are made during surgery for access to the anterior chamber during surgery (*Figure 1*). This is particularly important in the context of cataract surgery, which is carried out through the pupil, with manipulations in the immediate vicinity of the iris. The complications range from poor visibility of the operative field to iris damage with the surgical instruments and to rupture of the posterior capsule, with loss of lens material into the vitreous body. This change is often explained with the large number of alpha receptors in the muscles and vasculature of the iris, which also respond to the alpha-1 receptor antagonists. Pupillary dilation, which is mediated by the alpha receptors, among others, is severely restricted; furthermore, ultrastructural changes have been observed after long-term use.

This review article explains the problems to an interdisciplinary readership, since interdisciplinary collaboration—especially the exchange of information regarding relevant medication—seems to represent the most important prophylactic measure.

Methods

What follows is a review summarizing the current evidence on the pathomechanism, management of complications, and interdisciplinary collaboration in solving the problem on the basis of a selective literature search in PubMed (IFIS, intraoperative floppy iris syndrome, alpha-1 receptor antagonists, tamsulosin).

Alpha-1 antagonists in BPH

Systemic alpha blockers are used to treat benign prostatic hyperplasia (BPH) (1, e1). Their effect is due to the relaxation of smooth muscles in the prostate and

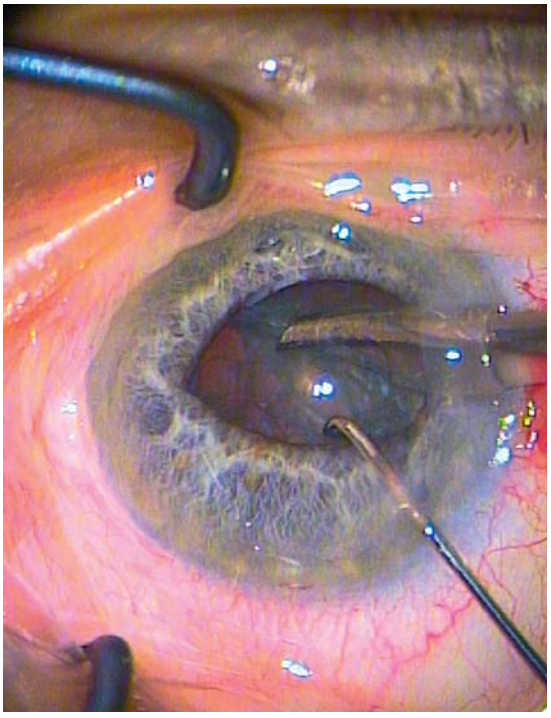

Figure 1: Full-blown IFIS: The iris seems to be ballooning and contracts at an early stage of the surgery. The tissue has an increased tendency to prolapse through the accesses. (With permission from D F Chang, MD, Los Altos, CA, USA)

urinary bladder neck. The prevalence of histological BPH is 40% in men in the 5th decade of life and 90% in the 9th decade, although not every aging man reports problems with micturition (e2). In Germany, the proportion of men older than 50 with lower urinary tract symptoms (LUTS) requiring treatment is 40.5% (e3).

BPH and LUTS affect the lower urinary tract (prostate, urethra, and bladder), where primarily alpha-1a and alpha-1d receptors are located, although all alpha-1 adrenergic receptors are present. For this reason, alpha blockers are suitable for alleviating symptoms caused by BPH. The effect of the alpha-1 receptor blockade is due only to a minimal extent to a reduction in urodynamic voiding resistance (2). To date, a minimum of nine adrenergic receptors (alpha-1 and alpha-2 receptors and their subtypes) have been identified (e4, e5). *Table 1* provides an overview of the relative binding affinity of several widely used alpha-1 blockers.

TABLE 1

Overview of the relative binding affinity of different alpha-1 blockers

Substance	Affinity to alpha receptors
Tamsulosin	alpha 1a = alpha 1d > alpha 1b
Terazosin	alpha 1a = alpha 1d = alpha 1b
Doxazosin	alpha 1a = alpha 1d = alpha 1b
Alfuzosin	alpha 1a = alpha 1d = alpha 1b

Among the alpha-1 blockers mentioned earlier, tamsulosin has the greatest relative binding affinity to the alpha-1a receptor compared with the other substances (e6). More than 80% of patients with BPH in the United States are being treated with tamsulosin, because this preparation is assumed to have a low side effect profile, for example, a lesser risk of orthostatic hypotension. However, this potential advantage remains scarcely documented (3).

Tamsulosin is available only on prescription in Germany. In some EU countries, it is freely available over the counter without the need for a prescription (for example, in the United Kingdom). It is therefore quite possible (for example, by means of ordering over the internet) that patients are taking alpha-1 antagonists without their primary care physician being aware of this.

In a database analysis of more than 96 000 men who had been referred for a cataract operation in 2002 to 2007, 3.7% of patients had been treated with tamsulosin within a fortnight preceding the surgery, and 7.7% with other alpha blockers. A significant increase in the risk for IFIS was noted for patients treated with tamsulosin, but this did not apply to other alpha blockers (e7, e8). In general, use of an alpha-1 blocker is recommended in uncomplicated LUTS according to the European guideline for the treatment of BPH; in patients with mild symptoms, a combination of watchful waiting and behavioral advice to improve micturition is an option (4). According to a meta-analysis, the therapeutic potential of the alpha-1 blockers is alleviation of symptoms in 30% to 40% and improvements to the flow rate in 20% to 25% (1). Whether individual patients with LUTS are likely to respond to treatment with alpha-1 blockers can currently not be predicted but is based on observation of the therapeutic success. If the treatment has not been successful within eight weeks, a change in medication is recommended (e9). This represents a relevant difference to pharmacotherapy with 5-alpha reductase inhibitors, which significantly affect the size of the prostate on the one hand but whose effect sets in notably later (4). In this context it is worth mentioning the side effect profile of the medications, with a possible effect on sexual functioning in the sense of erectile dysfunction, loss of libido, ejaculatory disorders, or gynecomastia.

In women, alpha-1 blockers are rarely used, except in the context of medical expulsive therapy (medication treatment to help expel calculi) in ureteric calculi or to treat urinary retention (1, 5).

Effects of alpha-1 blockers on the iris

Of the three subtypes of alpha-1 receptors (a, b, and d), the alpha-1a receptor dominates in the musculus dilatator pupillae (the iris dilator muscle) as well as in

the smooth muscles of the prostate tissue. Of the currently used alpha-1 antagonists that are given to treat BPH, only tamsulosin is subtype specific and has the greatest affinity to the alpha-1a receptor. All alpha-1 antagonists can impede pupillary dilation, but the frequency and severity of pathological changes to the iris in patients taking tamsulosin is higher than in patients taking non-selective alpha-1 antagonists (6–8, e7, e10–e12). The substance's half life in the eye is considerable. Pärssinen and colleagues were able to identify residual tamsulosin in the aqueous humor after an interval of 7 to 28 days. All patients showed pathological mobility of the iris, which complicates the surgical procedure, in some cases even substantially (9).

Structural and anatomical changes in the anterior eye segment

The antagonistic effect on the alpha-1 receptors of the iris muscles is not the only factor contributing to changed iris function. IFIS is caused by effects on the receptor as well as by ultrastructural changes after long-term use.

Histopathology and transmission electron microscopy have shown significant attenuation of the iris dilator muscle in the tamsulosin group compared with controls; the iridial stroma was equally strong in both groups. The duration of intake did not make any difference. Furthermore, a reduced number of myofibrils and increased vacuoles in the iris dilator muscle were seen in the tamsulosin group. These changes were interpreted as an indication of muscular atrophy. This assumption was supported by in vivo studies using optical coherence tomography (OCT) (9, 10, e13).

Although all groups of substances used act as alpha-1 blockers, tamsulosin is different because of the higher specificity of its binding capacity (11, e11). The clinical relevance of these attributes are explained by a study reported by Blouin and colleagues, who retrospectively found problems with cataract surgery in 86% of patients taking tamsulosin, but in only 15% of those taking alfuzosin (e14). Another, histopathological, study, found alpha-1a receptors in the iris arteriolar muscularis. This gave rise to the assumption of a vascular component in IFIS (12). Even though the results lead to a conclusion of muscular atrophy, this phenomenon may simply represent the pharmacological effect of the alpha-1 blocker (e15). The induced miosis leads to measurable attenuation of the dilator muscle while the pupil contracts. A definite explanation of the pathomechanism is thus still lacking.

Intraoperative Floppy Iris Syndrome

The definition of intraoperative floppy iris syndrome (IFIS) comprises the triad of:

- A "billowing iris," which starts fluttering as a result of very small intraocular fluid currents during the operation, in spite of medication-induced mydriasis
- Progressive intraoperative miosis in spite of sufficient administration of mydriatic drugs
- A tendency to spontaneous iris prolapse through one of the incisions made to access the anterior chamber during the operation.

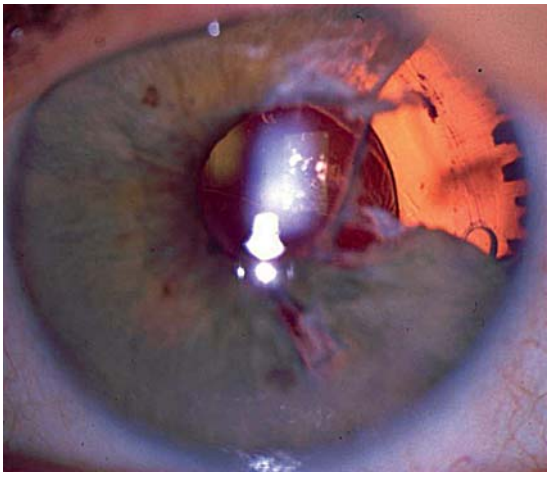

Figure 2: Iris damage in a patient with pseudophakia.
The stroma is damaged by the prolapse into the main incision and by an injury caused by the phaco probe (With permission from D F Chang, MD, Los Altos, CA, USA)

The association of a higher prevalence of these symptoms in patients taking an alpha-1 antagonist, namely tamsulosin, was first described by Chang and Campbell in 2005. The authors reported an incidence of 2% in all 706 retrospectively studied cataract operations, and of 63% in all patients taking tamsulosin. None of the patients who had taken a different alpha blocker (n = 11) had any symptoms of IFIS. A further, prospective study of 741 patients showed a prevalence of 2.2% (13). These results were confirmed in numerous other studies (14–16, e4, e7, e16–e18).

IFIS during treatment with alpha-1 blockers

Chatziralli and Sergentanis provide an overview of the evidence in a meta-analysis. After a thorough literature search, they reviewed 17 studies including a total of 17 588 eyes. In the meta-analysis, the odds ratio for IFIS in patients treated with tamsulosin was some 40 times higher than for patients taking alfuzosin (or 16.5 times in an alternative analysis) (17).

Intraoperative complications in IFIS

Often, a sufficient degree of mydriasis can be achieved in patients taking alpha-1 blockers, which can be sustained during the early phases of the operation up to the point of capsulorhexis of the anterior lens capsule, as only low intraocular fluid currents prevail in the anterior chamber up to this point of the surgery. This seemingly normal start to cataract surgery can create a false sense of security in the operating surgeon and impair his or her attention. Only when the actual phacoemulsification starts and currents develop in the anterior chamber as a result of irrigation and aspiration,

TABLE 2

Therapeutic strategies and their effectiveness

Therapeutic strategy	Effectiveness
Preoperative topical administration of atropine eye drops	Although atropine is hardly ever used nowadays because of its long-term effects, individual case reports testify to its positive effect in IFIS (7, 14, 19, e21).
Intraoperative intracameral administration of phenylephrine/epinephrine	In addition to the preoperative topical administration of mydriatic eye drops, a sympathomimetic drug can be administered into the anterior chamber during the procedure. According to several studies, the intracameral administration of epinephrine or phenylephrine did not yield unequivocally positive effects (19, 20, e4, e17).
Use of ophthalmic viscoelastic device (OVD)	By administering an ophthalmic viscoelastic device into the anterior chamber at the pupillary level, the pupil can be dilated. However, this effect wears off during the operation, since the viscoelastic solution continually drains from the anterior chamber, or it is aspirated during phacoemulsification (7).
Mechanical dilation of the pupil	In case of insufficient mydriasis, pupil stretching—occasionally even sphincterotomy of the iris muscles—can help improve mydriasis. This strategy is ineffective in case of an atonic iris in IFIS. The use of mechanical devices, such as iris retractors or pupil expanders, yielded greater success rates (6, 18).
Surgical techniques	Some authors have reported that when using microincisional techniques (MICS), greater stability in the anterior chamber and reduced throughflow can contribute to improved stability of the iris. Similarly, constructing the accesses in a particularly careful manner can prevent iris prolapse or at least make it less likely (e22, e23).
Stopping treatment?	Clinical practice has shown that stopping tamsulosin treatment does not lead to any improvement, which can be explained with the long half life and resulting anatomical changes, which, in contrast to the effect on the receptor, are irreversible (11, 21). This should prompt critical weighing-up of the benefits and risks (urinary retention?) of stopping the treatment (7, 13, e26). It has been shown that in patients receiving combination treatment with tamsulosin and the 5-alpha reductase inhibitor dutasteride, stopping treatment with tamsulosin is perfectly feasible in a scenario of mild to moderate LUTS after an initial phase of combination treatment, without the symptoms deteriorating. The combination therapy should, however, be given for about six months (e24).

the extent of the changes becomes fully obvious. The iris often starts moving even when the intracameral current is small, which is difficult to calculate. In the worst case scenario, the iris is aspirated and injured by the tip of the phaco probe. A further common complication is prolapse of the iris through the incision. This commonly results in lasting damage to the iris. These iridial pathologies make the operation markedly more difficult because they impair the visibility of the operative field (*Figure 2*) (18, e19). These uncertainties also result in a notably higher rate of complications in other structures of the eye during the operation; Chang et al, for example, reported a 10 times higher rate of ruptures to the posterior capsule and loss of vitreous body, with an average rate of 1% to 2% in the entire patient cohort (13). In 2012, between 650 000 and 750 000 cataract operations will be conducted in Germany, and such a marked increase in the risk is therefore of great importance.

Avoidance strategies and management of intraoperative complications

The described effect on the iris dilator muscle via the effect on the receptor and ultrastructural reconstruction [okay?] processes prevents the pupil from dilating to a sufficient degree, which presents a problem for the operating surgeon. A maximum degree of mydriasis is the prerequisite for good intraoperative visibility, however, not least because the pupil constitutes the access to the lens.

A preoperative assessment is also an option: If the pupil is difficult to dilate the likelihood of IFIS is higher (e8). However, this approach is not particularly reliable as poor preoperative dilation can also be caused by other constellations, for example, pseudoexfoliation syndrome.

In order to avoid the described complications, different strategies have been tested (e20). An at least moderate improvement to the intraoperative situation has been achieved by means of the measures shown in *Table 2*.

The measures presented here enable experienced surgeons to manage cataract patients receiving treatment for BPH with very few complications (22). A strategy that is reliable in any setting and totally safe in avoiding complications has thus far not been formulated. Although, as we explained, a series of measures for the management of complications is available and the problem is often even played down, a survey among the members of the American Society of Cataract and Refractive Surgery (ASCRS) provided a different perspective. The survey showed that 64% of surgeons would refuse to be treated with alpha-1 antagonists if they themselves had incipient lens opacity; if required the surgeons would even plan early cataract surgery and start treatment for BPH immediately afterwards.

59% of surgeons recommend an examination by an ophthalmologist before starting treatment for BPH (7).

Communication in the collaboration between doctors and in the relationship between doctors and patients

Many of the cited publications mentioned a deficit in information as a key problem. This is true for the patients as well as the treating doctors.

In a written survey of referring primary care physicians, Sallam, Gunasekera, et al. studied the extent to which referring general practitioners were aware of a correlation between alpha-1 blockers and possible problems, such as IFIS, during cataract surgery. 96.8% of primary care doctors stated that they were not aware of this association. This is all the more important as some 80% of those surveyed regularly prescribed tamsulosin (more often than 5× per month) (10).

The necessity of communication between all involved doctors was repeatedly emphasized (18). The ASCRS survey mentioned earlier showed that 91% of participants wished for better information for doctors who prescribe alpha-1 antagonists (4).

When they are being prescribed an alpha-1 blocker, patients have to be instructed in great detail. They should be told that the medication can affect a potential cataract operation and that a good surgical result can be achieved if the approach is coordinated accordingly (22).

Patients are mostly able to name their medications. The question of whether they are taking prostate medication, although it seems inappropriate at first glance, should become standard for the consultation preceding cataract surgery.

In order to raise awareness of the problem, several articles on the topic have been published in specialty journals for urology, general practice, and primary care (23, 24, 25, e25–e28).

Conclusions for clinical practice

In recent years intraoperative floppy iris syndrome (IFIS) has become an increasingly reported complication in cataract surgery. A safe strategy that applies to all cases has so far not been formulated; in most cases IFIS complicates the operation. Preoperative awareness on the part of the surgeon about a patient's treatment with tamsulosin and the higher degree of difficulty that is to be expected for the operation as a result of this was identified as a safety factor. Depending on the surgeon's experience and technique, measures can then be taken to avoid complications. The information flow between treating urologists, ophthalmic surgeons, and primary care physicians as the interface has to be optimized, in order to make the necessary information available for all cases. Information about medication with alpha blockers should be as routinely included in the referral as, for example, information on anticoagulation. Optimized collaboration between all treating doctors is the best documented factor for a safe operation.

KEY MESSAGES

- Treatment with alpha blockers for disorders of the urinary tract may cause intraoperative floppy iris syndrome as one of its side effects. The associated changes to the iris make cataract surgery more difficult.
- So far no gold standard exists for the effective and safe treatment of this syndrome.
- Communication among the treating physicians with regard to treatment with alpha-1 blockers is essential.
- In the preoperative consultation, every cataract surgeon should ask their patient by default whether they are taking medication for prostate problems.
- If a patient is known to take alpha-1 blockers an experienced surgeon can adapt the operative technique and thus minimize the risk for complications.

Conflict of interest statement
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Dr Rausch acts as an adviser to the advisory board of Janssen Cilag.

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