REVIEW PAPER

FUNCTIONAL UROLOGY

Ten years of intraoperative floppy iris syndrome in the era of α-blockers

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Introduction The use of alpha-1 receptor antagonists in the treatment of benign prostatic hyperplasia (BPH) has created a 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.

Material and methods A comprehensive literature review was performed using MEDLINE with MeSH terms and keywords 'benign prostatic hyperplasia', 'intraoperative floppy iris syndrome', 'adrenergic alpha-antagonist' and 'cataract surgery'. In addition, reference lists from identified publications were reviewed to identify reports and studies of interest from 2001 to 2017.

Results The A total of 95% of experienced ophthalmologic surgeons reported that systematic treatment with tamsulosin represents a challenging surgical condition increasing the risk of complications. Alpha-blockers are commonly prescribed, with 1,079,505 packages of tamsulosin prescribed each month in 2014 in Austria. Dose modification may be one way to reduce the risk of IFIS. A lower incidence of IFIS was reported in patients on tamsulosin in Japan, but the recommended dosage was lower than that used in Europe and the US (0.2 mg vs. 0.4 mg).

Conclusions We showed that not all patients taking tamsulosin experience IFIS. Moreover, larger investigations with a prospective design are needed, including studies to monitor the pre- and post-therapeutic ophthalmologic changes under tamsulosin, as well as urodynamic improvements resulting from this therapy.

Key Words: benign prostatic hyperplasia ‹› cataract ‹› intraoperative floppy iris syndrome ‹› tamsulosin ‹› alphablocker ‹› cataract complication

INTRODUCTION

Benign prostate hyperplasia

Benign prostate hyperplasia (BPH) and lower urinary tract symptoms (LUTS) frequently affect the quality of life of men over 60. BPH affects 3 out of 4 men by the age of 70 [1], and the prevalence of LUTS is high, ranging from 22% (50–59-year-old patients) to 45% (60–69-year-old patients). In total, 19% of men suffering from LUTS require medical treatment, and only 10.2% are pharmacologically treated. The aim of treatment is to improve quality of life. According to the guidelines of the European

Association of Urology (EAU), these patients can be treated with α1-adrenergic antagonists (α1-ARA), 5-α-reductase inhibitors (5-ARIs), phosphodiesterase inhibitors, antimuscarinics/β-3 agonists, and phytotherapeutics [2].

The choice of treatment depends on the efficacy, time of onset, durability and tolerability. In addition, short-term and lifetime management outcomes should be considered since the average patient with BPH has a life expectancy between 15 and 20 years. α1-ARAs and 5-ARIs are commonly used treatments. There are four different types of α1-ARAs available, including the α1-1 subtype-selective ARA inhibitor, tamsulosin, and three non-selective α1-ARA inhibitors, alfuzosin, doxazosin, and terazosin [3, 4, 5].

The available alpha-blockers are equivalent in efficacy, but they differ in their tolerability. α-Blockers produce consistent improvements in symptom scores and urinary flow rates in approximately 60–70% of patients [6]. With a rapid onset of action, α-blockers are often used as the first-line therapy for patients with moderate to severe LUTSin the short-term and also in the long-term management of BPH [3]. Additionally, the results of the CombAT study support the use of combination therapy with dutasteride and tamsulosin to achieve a significantly improved benefit than monotherapy with regard to various patient-reported outcomes in men with moderate to severe LUTS [7]. In addition, α-blockers are used as smooth muscle relaxants for expulsive therapy for ureteric stones [8].

Three subtypes of α1-adrenoreceptors have been identified, designated as α1-A, α1-B, and α1-D. Various α1-adrenoreceptor antagonists that are selective for each α receptor subtype are available for the treatment of BPH. The α1-adrenoreceptor antagonists have variable efficacy and side-effect profiles. Tamsulosin (selective α1-ARA) and alfuzosin (non-selective α1-ARA) are the two most commonly used α-blockers [9].

Cataracts

Cataracts receive less attention as comorbidities of BPH than other conditions. Cataract is defined as a clouding of the lens or its capsule and is one of the leading causes of blindness. Surgery to remove the lens followed by the artificial lens replacement allows recovery of vision. Cataract surgery is the second most cost effective health intervention [10]. As many as 30% of adults over 65 suffer from cataracts, and more than 8 million of these patients undergo surgical cataract treatment every year according to WHO data [11, 12].

Intraoperative floppy iris syndrome

Cataract surgery is one of the most frequently performed surgeries worldwide. The key to success is an adequate pupillary dilation and the stability of the iris.

The dilator muscle is a smooth muscle that runs radially in the iris and therefore acts as a dilator. The pupillary dilator increases the size of the pupil. It is innervated by the sympathetic system through the release of noradrenalin which acts on contraction of the iris muscle resulting in mydriasis, which is necessary during cataract surgery. The triad of characteristics defining IFIS includes a floppy iris stroma that surges and billows under normal intraoperative fluidics, the prolapse of the iris stroma upon surgical incision despite well-constructed wounds, and the occurrence of progressive intraoperative miosis. This phenomenon was first described in 2005 [13].

IFIS has been associated with the intake of the selective α1-1ARA inhibitor Tamsulosin and, at a lower rate, with the intake of Alfuzosin. However, IFIS was also noticed in patients with no history of α antagonist intake.

The association with IFIS has been confirmed in many studies reporting widely varying rates [14]. Keklikci et al. published a prospective trial that determined the risk ratios and incidence of intraoperative floppy iris syndrome during cataract surgery in patients using tamsulosin. The odds ratios (ORs) and relative risk (RR) ratios showed strong positive correlations between tamsulosin use and IFIS [15].

The clinical presentation varies from mild cases, with only a fluttering iris, to more severe cases featuring the whole spectrum of symptoms. IFIS is associated with high rates of intraoperative complications, such as iris trauma, zonula dehiscence, posterior capsule rupture, and vitreous loss, as well as postoperative complications, including intraocular pressure elevation and cystoid macular edema.

The α1 receptors in the iris smooth dilatator muscle are targeted by tamsulosin in IFIS. Alfuzosin, doxazosin, and terazosin (nonselective α1-ARA) also inhibit the contraction of vascular smooth muscle cells, which is associated with an increased incidence of orthostatic hypotension. The affinity of tamsulosin for the α1 receptor subtype is up to 20 times higher, and it improves urinary outflow with minimal effect on vascular smooth muscles.

A total of 95% of experienced ophthalmologic surgeons reported that systematic treatment with tamsulosin represents a challenging surgical condition increasing the risk of complications [16].

Tamsulosin

Tamsulosin is a α-blocker relaxing the bladder neck muscles and muscle fibers in the prostate to improve voiding It is a selective α1 receptor antagonist with preferential selectivity for the α1-A receptor in the prostate compared to the α1-B receptor in the blood vessels. Tamsulosin has a long half-life (between 10–14 days), and a constant receptor blockade may result in atrophy of the iris dilatator smooth muscle. Tamsulosin is an irreversible antagonist of α1-ARA; discontinuation of tamsulosin 4–7 days prior to surgery may be beneficial, but does not prevent IFIS completely. This might explain the poor pupil dilatation in patients receiving tamsulosin as well as the flaccid and floppy iris stroma observed even after medication is stopped [17–20].

Doxazosin

Doxazosin is indicated for the treatment of both the subvesical obstruction and irritation symptoms associated with BPH. Doxazosin may be used in all BPH patients whether they are hypertensive or normotensive. In patients with hypertension and BPH, both conditions are treated with α1-blockers. Doxazosin provides a rapid progress in the symptoms and urinary flow rate. Sustained improvements with doxazosin were seen in patients treated for up to 14 weeks in double-blind studies and up to 2 years in open-label studies. Previous studies reported an increased incidence of IFIS in the doxazosin arm, but IFIS occurred less frequently with doxazosin compared to tamsulosin [21].

Silodosin

Silodosin is a selective α- blocker that inhibits postsynaptic α1-adrenoreceptors located in the prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra. The half-life is approximately 13.3 h, and the half-life of its major metabolites (a glucuronide conjugate KMD 3213G and KMD 3293) is about 24 h. Silodosin has a high affinity for melanin, which is important in the mechanism of IFIS, at least in animal models [20].

Alfuzosin

Alfuzosin significantly increases the risk of IFIS, and severe IFIS was statistically more likely with tamsulosin than with alfuzosin. In men with symptomatic BPH and cataracts requiring an uroselective α1-antagonist, alfuzosin is recommended as a first-line medication [22].

Terazosin

Terazosin hydrochloride is a α-1-selective adrenoceptor blocking agent. Smooth muscle tone is mediated by sympathetic nervous stimulation of α-1 adrenoceptors, which are abundant in the prostate, prostatic capsule, and bladder neck. The reduction of symptoms and improvement in urine flow rates following administration of terazosin is related to the relaxation of smooth muscles due to blockade of α-1 adrenoceptors in the bladder neck and prostate. Terazosin also influences the dilatator pupillae muscle, but the effect is significantly lower than that of tamsulosin [23].

5α-reductase inhibitors (5-ARIs)

Finasteride is a 5α-reductase inhibitor that specifically inhibits type II and III isoenzymes. By inhibiting 5α-reductase, finasteride prevents conversion of testosterone to dihydrotestosterone (DHT) by blocking type II and III isoenzymes, resulting in a decrease of the serum DHT levels by approximately 65–70% and a decrease of the prostate DHT levels by up to 85–90%. Unlike triple inhibitors of all three 5α-reductase isoenzymes, Dutasteride reduces DHT levels in the entire body by more than 99%. Finasteride does not completely suppress DHT production because it does not have a significant inhibitory effect on the type I 5α-reductase isoenzyme, with a 100-fold lower affinity for type I 5α-reductase than for type II. In addition to blocking the type II and III isoenzymes, finasteride competitively inhibits 5β-reductase type II isoenzyme, though this is not believed to affect androgen metabolism [24, 25, 26].
Finasteride is commonly used to treat BPH. An association between finasteride and cataracts has been reported in only a small number of cases. In these cases, finasteride was suspected to be the cause of the anterior subcapsular cataracts and IFIS. Therefore, finasteride can be associated with cataracts and IFIS, and it should be stopped before cataract surgery [27, 28, 29].

Saw palmetto

Saw palmetto is an extract from the fruit of the American dwarf palm tree, Serenoa repens. In men with BPH, saw palmetto was associated with an improvement in the urinary peak flow rate and a reduction in nocturia compared to placebo [30]. Saw palmetto was reported to have a non-significant association with IFIS [13].

MATERIAL AND METHODS

A comprehensive literature review was performed using MEDLINE with MeSH terms and keywords 'benign prostatic hyperplasia', 'intraoperative floppy iris syndrome', 'adrenergic alpha-antagonist' and 'cataract surgery'. In addition, reference lists from identified publications were reviewed to identify reports and studies of interest from 2001 to 2017.
We performed a critical review of the published articles and abstracts on the association of IFIS with alpha-blockers and other medications as well as other medical conditions.
The article reviews literature published on this topic and provides recommendations on how to reduce the incidence of iatrogenic IFIS or its severity and outcomes in patients with BPH.
Data were collected on the frequency of tamsulosin among patients undergoing cataract surgery, the reported occurrence rate of IFIS among patients who were 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
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

RESULTS

Many reports including seven patient series with more than 5000 patients and 6995 operated eyes were published (please see Table 1). In their initial report, Chang and Campbell 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 between tamsulosin and IFIS prospectively in another series of 741 patients (900 eyes). 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 patients, 72 were taking various alpha-blockers including 21 who had taken tamsulosin. 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). In another large patient series of 2390 operated patients, IFIS occurred in 11 of 15 patients (65%) who had taken tamsulosin prior to the operation.
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. Blouin et al. prospectively compared the occurrence rate

Table 1. *Occurrence or IFIS among patients exposed to tamsulosin alld 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

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.

DISCUSSION

According to the 2012 Austrian health report of (Yearbook of Health Statistics 2014 Statistik Austria) and the demographic data by the numbers of individual medical performance 2013 (Statistik Austria 2014), the most commonly performed surgery was cataract surgery with 92.771 cases in 2012 and 96.647 in 2013. The distribution by gender was 40.92% male versus 59.08% female.
α-Blockers are commonly prescribed, with 1,079,505 packages of Tamsulosin prescribed each month in 2014 (Central federation of Social insurance Carrier) in Austria. The numbers of the prescriptions refers to extramural prescriptions (except hospitals).
Intraoperative floppy iris syndrome was first described by Chang and Campbell in 2005 as a condition characterized by the triad of a flaccid iris stroma that undulates and pillows in response to ordinary intraocular fluid currents, a propensity for the floppy stroma to prolapse towards the phaco- and sideport incisions despite proper wound construction, and the presence of progressive intraoperative pupil constriction despite standard preoperative pharmacologic preventive measures. The authors found a strong association between IFIS and the systemic use of tamsulosin [31]. Ninety percent of ophthalmologists report that IFIS is more common in patients treated with tamsulosin than in patient treated with non-specific α-blockers. A retrospective study reported that 86% of patients on tamsulosin had IFIS compared with the 15% on alfuzosin. An animal model using α1-ARA from iris dilatator muscle strips isolated from rabbits demonstrated that tamsulosin is a stronger antagonist of the iris dilatator muscle than alfuzosin [32, 33].
The incidence of IFIS in the population ranges between 0.6% and 2%, and men on tamsulosin develop IFIS at a rate of 57% to 100% [18, 31, 34].
Poor preoperative pupil dilatation was reported to be more frequent in tamsulosin-treated patients than those receiving alfuzosin. The overall rate of complications in IFIS patients was 49.2% compared to 9.7% in patients without IFIS [35]. This may result in intraoperative complications such as an insufficient degree of sustained mydriasis on capsulorhexis of the anterior lens capsule, as low intraocular fluid currents predominate in the anterior chamber up to this point in the surgical procedure. Furthermore, the iris begins to move even when the intracameral current is small, or in the worst case, if the iris is aspirated and injured by the tip of the phaco probe. Another complication is the prolapse of the iris through the incision, resulting in damage to the iris. These uncertainties result in a higher rate of complications in other structures of the eye [36]. The α-blockers cause a decrease in the pupil diameter; tamsulosin results in a decrease in mesopic and scotopic light, while alfuzosin results in a decrease in the scotopic pupil diameter [32]. However, adequate pupil dilatation and normal iris function are important factors for the safety of cataract surgery.
Cataract is a common disease with a prevalence that increases with age, affecting 20% of those between 65 and 74 years and 50% of those over 75 years in age. In addition, LUTS occur in 50–70% of men aged over 60 years and in 80–90% of men over 80 years [35, 37].
LUTS associated with benign prostatic hyperplasia (BPH) are related to bladder outlet obstruction, which is composed of static and dynamic components. The static component is related to an increase in the size of the prostate. The dynamic component is a function of an increase in smooth muscle tone in the prostate and bladder neck leading to the constriction of the bladder outlet.
Over the last decade, the primary therapeutic algorithm of BPH changed from surgical intervention to pharmacological treatment with the α1-ARA tamsulosin as the most commonly prescribed drug for LUTS, with a mean treatment duration of 26 months treatment in patients with IFIS and 19.7 months in those with no signs of IFIS. The differences in α1-ARA prescription vary geographically according to the incidence of BPH and preferences for treatment strategies. Only a few studies have reported that there was no significant difference in the occurrence of IFIS in patients treated with non-selective α-blockers [38].
Although the potential risk of IFIS has been repeatedly demonstrated, α1-adrenergic antagonists are still widely prescribed for daily use, not only in aging men, but also as a spasmolytic therapy in stone diseases, according to current guidelines [39].
The timing of taking blocker and/or the duration of long-term treatment may influence the risk of IFIS. Previous studies investigating the time frame of α-blocker therapy reported that stopping tamsulosin more than two months prior to surgery had no effect on the incidence of IFIS and some patients reported a negative long-term effect of tamsulosin on the iris muscle, even after a medication-free interval of 3 years. These data suggest that Tamsulosin has an irreversible effect on the iris [35].

Dose modification may be one way to reduce the risk of IFIS. A lower incidence of IFIS was reported in patients on tamsulosin in Japan, but the recommended dosage was lower than that used in Europe and the US (0.2 mg vs. 0.4 mg) [37].

α1-ARA should be stopped before undergoing cataract surgery. We recommend that patients stop using the drug as early as possible, to minimize potential risks; changing the α1-ARA is of no value. Starting therapy with a non-selective α1-ARA or phytotherapeutic may be potentially beneficial. Furthermore, patients must be asked if cataract surgery is planned or has already been carried out. In the latter case, any type of α1-ARA is applicable. However, if cataract surgery is planned, the urologist must consider other treatment options, including surgery, or whether a delay of any type of therapy is justifiable. Treatment with a 5-ARI is a potential alternative, or in the case of α1-ARA therapy, starting with alfuzosin may be the first choice. In both cases, an ophthalmologist should be involved in the treatment decisions [38]. In contrast to the clinical guidelines of the EAU, Pickard et al. note that although tamsulosin has been used as a smooth muscle relaxant in expulsive therapy to increase stone passage in patients with ureteric colic, α-adrenoceptor antagonists (tamsulosin) are ineffective. In cases of ureteric stones, the use of tamsulosin should be avoided [8].

Urologists and general physicians should recommend a pre-treatment eye evaluation in patients with cataracts or decreased vision before starting a pharmacological prostate treatment with α1-ARA because two thirds of these patients could avoid this type of therapy or undergo cataract surgery first [33]. Before initiating therapy with α1-ARA, patients should be informed that these drugs might increase the difficulty of cataract surgery, and their ophthalmologist should be notified [39].

CONCLUSIONS

The conclusion of this review is, that not all patients taking tamsulosin evolve intraoperative floppy iris syndrome (IFIS). In order to ascertain the aspects concerning IFIS relating the time of intake and the time of therapy intermission, larger investigations with a prospective design are needed, including studies to monitor the pre- and post-therapeutic ophthalmologic changes under tamsulosin, as well as urodynamic improvements resulting from this therapy.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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