Benign Prostatic Hyperplasia. Clinical Treatment Can Complicate Cataract Surgery

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ABSTRACT

Purpose: To investigate the effects of alpha-1 adrenergic receptor antagonists for the treatment of benign prostatic hyperplasia (BPH) regarding potential risks of complications in the setting of cataract surgery.

Aim: To address recommendations, optimal control therapy, voiding symptoms and safety within the setting of cataract surgery.

Materials 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 2009.

Results: The first report of intraoperative floppy iris syndrome (IFIS) was observed during cataract surgery in patients taking systemic alpha-1 AR antagonists in 2005. It has been most commonly seen related to use of tamsulosin. Changes of medication and washout periods of up to 2 weeks have been attempted to reduce the risk of complications in the setting of cataract surgery.

Conclusion: Patients under clinical treatment for BPH should be informed about potential risks of this drug class so that it can be discuss with their healthcare providers, in particular urologist and ophthalmologist, prior to cataract surgery.

Key words: benign prostatic hyperplasia; alpha-blocker; floppy iris syndrome; cataract complication; tamsulosin

INTRODUCTION

Benign prostatic hyperplasia (BPH) and cataract formation are common in older men. BPH affects nearly 3 out of 4 men by the age of 70 (1). Clinical management of BPH is often preferred to surgical treatment because surgery increases the risk of morbidities (2). Clinical treatments of symptomatic BPH include: 1) 5 alpha-reductase inhibitors, 2) alpha-1 adrenergic (alpha-1AAR) antagonists, and 3) a combination of a 5 alpha-reductase inhibitor and an alpha-1AAR antagonist. Currently, alpha-1AAR antagonists are an effective and commonly prescribed medication for BPH. These drugs improve urinary outflow by relaxing the smooth muscle in the prostate and bladder neck. There are four alpha-1AAR antagonists currently available in the United States: tamsulosin (selective alpha-1AAR antagonist subtype) and
three nonselective alpha-1AAR antagonist subtypes (alfuzosin, doxazosin, terazosin). The half-lives of the four available antagonists are similar, ranging from 10 to 22 hours (1,2). These drugs are used to treat lower urinary tract symptoms of BPH.

Cataracts are opacities within the natural crystalline lens of the eye that can result in impaired vision and even total blindness in advanced stages. Excision and replacement of the opacified lens with intraocular lens implants restores sight to 20/40 or greater in at least 90% of patients (3).

On the other hand, cataract surgery is the most commonly performed surgical procedure in the United States and in most developed countries. In 2001, over 1.6 million cataract surgeries were performed in the Medicare population alone. Reflecting the changing demographics of the U.S. population, the number of cataract extractions will increase substantially over the next quarter century (4).

Tamsulosin, an uroselective alpha-1AAR blocker, is believed to relieve the symptoms of BPH by relaxing the smooth muscle in the prostate and bladder neck through systemic blockade of alpha 1-adrenergic receptors. Because these receptors are present in the dilator smooth muscle of the iris, tamsulosin may also impede mydriasis during surgery and lead to intraoperative floppy iris syndrome (IFIS) (5). This complication was first described by Chang and Campbell in April 2005 (6), who identified IFIS in the intraoperative period in 63.0% (10/16) tamsulosin patients. In a prospective study of 900 consecutive cataract surgeries, the prevalence of IFIS was 2.2% (16/741 patients). Of these IFIS patients, ninety-four percent (15/16) were taking or had taken systemic tamsulosin (6).

MATERIALS AND METHODS

A comprehensive literature review was performed using MEDLINE with the 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 2009.

BPH-IFIS AND ADRENERGIC RECEPTORS

BPH is the most common benign tumor in men with an incidence that is age-related. The etiology of BPH is not completely understood, but it seems to be multifactorial and endocrine controlled. BPH consists of two components: static (related to absolute size of the prostate gland) and dynamic (related to prostate smooth muscle contractions), that result clinically in lower urinary tract symptoms of BPH (urinary frequency, urgency, sensation of incomplete emptying, weak stream, straining to initiate urination). BPH is a common urological disorder in older men, and increases the risk of complications such as urinary retention, recurrent urinary tract infections, hematuria and bladder stones. The treatment goal for men with BPH links two different therapeutic classes: 1) 5-alpha reductase inhibitors (finasteride and dutasteride) and 2) alpha-1AAR antagonists. Tamsulosin is the most uroselective alpha-1AAR antagonist approved for use in the treatment of symptomatic BPH, which, although it improves urinary outflow, is also thought to inhibit the iris dilator smooth muscles causing varying degrees of IFIS (7-9). The effectiveness of tamsulosin is similar to other alpha-1AAR blocker drugs. Low dose preparations of tamsulosin provide similar benefits and have fewer side effects than higher dose preparations (9). Side effects of tamsulosin are generally mild but increase substantially at higher doses with common side effects including dizziness, rhinitis (runny nose and other cold-like symptoms) and abnormal ejaculation (9). The nonselective alpha-1AAR antagonists can cause orthostatic hypotension. Future studies should focus on complications in patients taking systemic alpha-1AAR antagonists before cataract surgery.

Adequate pupillary dilation and subsequent stability of the iris during surgery are important for successful and safe phacoemulsification (10). Chang and Campbell (6) described IFIS that occurred during cataract extraction surgery (phacoemulsification). They found that patients using systemic alpha-1AAR antagonists (tamsulosin) had an increase risk of iris complications during surgery. The initial description defined the following triad: floppy iris stroma that surges and billows in response to normal intraopera-
tive fluidics; prolapse of iris stroma due to surgical incisions despite well-constructed wounds; and progressive intraoperative miosis despite standard preoperative dilation. Recently, Chang et al. divided IFIS into a) mild IFIS: slight iris billowing, b) moderate IFIS: iris billowing and progressive miosis without prolapse and c) severe IFIS: presenting the triad of billowing, progressive miosis, and iris prolapse (11). With the aging of the population, an increasing number of elderly patients requiring cataract surgery chronically take alpha-1AAR antagonists. As currently available alpha-1AAR antagonist drugs are diffused to all tissues in the body, they would be expected to have effects such as relaxing the iris dilator smooth muscle. It is now clear that alpha-1AAR predominates and mediates contractions in the human prostate, urethra, and bladder neck.

**IRIS, ALPHA ADRENORECEPTORS AND IFIS**

The iris is, by far, a more complex tissue than originally recognized, with multiple layers and sources of innervation, as well as signaling systems that work together to regulate iris muscle tone (7). Functioning of the iris smooth muscle involves a complicated network of competing pathways (sympathetic, parasympathetic, serotoninergic, dopaminergic and peptidergic), which also includes the prostaglandin and nitric oxide regulated pathways (7,12). Pupil size, both dilatation and constriction, is controlled by two muscles, the iris dilator and sphincter smooth muscles, each one with its own separate innervation and blood supply. Classically pupil dilation was thought to be mediated by a simple balance between sympathetic and parasympathetic nerve activity, via adrenergic receptors (AR) and muscarinic receptors, respectively. AR stimulation in the iris dilator smooth muscle causes contractions and consequently mydriasis.

In respect to the subtypes, iris contraction is 100-fold more sensitive to alpha-1AAR antagonists than to alpha-2 adrenergic antagonists, suggesting that alpha-1AAR antagonists predominate in sympathetically mediated iris dilator contraction; it has been observed that this subtype mediates iris dilator smooth muscle contractions in all species studied to date. Another structure where alpha-1AAR antagonists have potentially important effects is iris arterioles.

Friedman et al. (12) proposed that the blockade of receptors in blood vessel walls in patients taking tamsulosin is associated with vascular dysfunction of the vessels that supply the iris. These authors concluded that the iris vasculature provides the “skeletal” framework which supports the iris and that impairment of the smooth muscle of the iris arteriole wall damages this skeletal framework and leads to severe dysfunction. Both iris dilator contraction and vascular dysfunction actions can contribute to the IFIS observed in patients submitted to phacoemulsification who were taking this drug. Thus, patients taking tamsulosin may be at risk for IFIS during cataract surgery.

It has been suggested that long-term tamsulosin administration leads to a disuse atrophy of the muscular plate leading to poor pupil dilation and which could explain the flaccid nature of this tissue found during cataract surgery (13,14). This evidence needs further corroboration and additional scientific support.

Parssinën et al. (15) were the first authors to report finding tamsulosin in the aqueous humor after a pause in its use of up to 28 days, suggesting prolonged binding of tamsulosin to the iris and perhaps to the ciliary body. In our understanding, tamsulosin can cause long-term or possibly even permanent changes in iris function, the interval between the cessation of tamsulosin treatment and full recovery of the eye is uncertain and requires further investigation.

**RECENT FINDINGS**

BPH is one of the most common health problems in elderly men. Half of men older than 50 years and 90% of men older than 85 years have BPH (16). Cataracts also have a common occurrence in the elderly, with the incidence increasing with age and affecting 20% of individuals aged 65 to 74 years and 50% of those older than 75 years. BPH and cataracts go hand-in-hand in the elderly male population (17-19).

IFIS may occur within a few weeks of starting treatment using tamsulosin (11). This condition
is also seen, in smaller numbers, in patients treated with nonselective alpha-1AAR blockers (20). While the incidence of IFIS in the general population is reported to be between 0.6% and 2.2%, male patients prescribed tamsulosin develop the syndrome at a rate of 57% to 100% (6). Bell and colleagues (21) reported the results of a case-control analysis of a population-based retrospective cohort study using linked healthcare databases in Ontario, Canada. Among men aged 66 years or older who had cataract surgery between 2002 and 2007, 3,550 patients (3.7%) had had recent exposure to tamsulosin and 7,426 (7.7%) had had recent exposure to other alpha-1AAR blockers. Major ophthalmologic adverse events occurred in 284 patients (0.3%); these events were significantly more common among patients who had recently been taking tamsulosin (adjusted odds ratio: 2.33; 95% confidence interval: 1.22-4.43). These findings, regarding the serious consequences of tamsulosin-related IFIS in the 14-day period following cataract surgery, are most certainly the consequence of posterior capsular rupture, loss of lens fragments into the vitreous body, and vitreous loss. Retinal detachment is a potential consequence of these events and one of the most serious complications of IFIS. Thus, the result of the discontinuation of tamsulosin appears to be unpredictable and may not reliably reduce the severity of IFIS. Chang and Campbell (6) noted the occurrence of IFIS in patients who had stopped tamsulosin more than a year previously. The observations of Bell et al. (21) of a 14-day window in which complications occurred are directly related to the intraoperative difficulties produced by IFIS. To mitigate the potential intraoperative problems, several pharmacological and mechanical strategies have been proposed including preoperative dilation with strong cycloplegic agents such as atropine and homatropine or the intraoperative use of highly viscous agents, low flow of fluids into and out of the eye, iris retractors, and mechanical pupillary expansion rings (22). Following the report suggesting a strong link between tamsulosin and IFIS compared to other alpha-1AAR antagonists, case reports have been published of IFIS in men taking alfuzosin, doxazosin, and terazosin (23). Furthermore, saw palmetto (Serona repens), a widely used alternative therapy for BPH, is also reportedly associated with IFIS in 2 patients (24). Both patients had not taken prescription medications for BPH and developed moderate IFIS during cataract surgery. In contrast, a recent study has reported that nonselective alpha-1AAR antagonists are unlikely to be associated with IFIS (25).

However, many studies have advocated selectively discontinuing medications that increase risk for IFIS prior to cataract surgery. An alpha-1AAR antagonist washout period of up to 2 weeks prior to surgery has also been recommended (6). Again, the benefit of discontinuing these drugs prior to surgery has not been determined as IFIS has been reported several months after discontinuing therapy.

Furthermore, if cataract surgery is planned in the near future, patients and providers may elect to delay medical treatment for BPH until after surgery. The severity of symptoms and risk of BPH-related complications such as acute urinary retention should be considered against the potential complications related to cataract surgery. It is important that patients and providers make an educated decision on this matter. While there is still much to elucidate about the relationship between alpha-1AAR antagonists and IFIS, urologists should be knowledgeable when counseling patients about these emerging risks and their clinical significance and explain the importance of patients sharing their drug histories with their ophthalmologist prior to cataract surgery.

**COMMENTS**

Currently there is insufficient information to determine the exact underlying mechanism of IFIS. There are few reported studies large enough to assess the connection between tamsulosin exposure and postoperative complications. In addition, it is unclear whether proximity of therapy to the surgery is important or whether complications are equally likely with alpha-1AAR blockers other than tamsulosin (6). Studies have demonstrated more complications with tamsulosin than with other alpha-1AAR blocking drugs (6,21). This may relate to differences in receptor affinity with tamsulosin and with other related medications. It is believed that tamsulosin is more highly selective for alpha-1AAR antagonists than other alpha-1AAR blocker drugs (8). These particular
receptors are present in bladder-neck smooth muscle and in the iris dilator muscle. Blockage of the iris dilator smooth muscle allows unopposed action of the parasympathetically innervated iris constrictor muscle and loss of iris tone, resulting in clinical IFIS (8). Chang and Campbell (6) found that preoperatively discontinuing the medication for 4 to 7 days was helpful but not completely effective in preventing this syndrome. One patient manifested intra-operatively mild iris floppiness in both eyes but without the iris prolapse or pupil constriction necessary for the diagnosis of IFIS. On postoperative questioning, the patient described a history of tamsulosin use that was discontinued 3 years before the surgery. Some authors also report patients with true IFIS who had been off tamsulosin for 1 year, including patients reported in a prospective series. These observations may be consistent with the hypothesis of disuse atrophy of the dilator smooth muscle. Nevertheless, because it may increase the surgical pupil diameter, it is recommended that ophthalmologists, in consultation with urologists, consider temporarily discontinuing tamsulosin in patients for 1 to 2 weeks before surgery and using a maximum dilating regimen in the eyes of these patients (6).

In future studies it is important not only to enroll more patients, but also include clinical covariates in the analysis, age; coexisting diseases (e.g., diabetes, hypertension, congestive heart failure); concurrent drugs; intraoperative drugs administered (e.g., opioids or serotonergic drugs used for nausea/vomiting prophylaxis), and the doses of the alpha-1AAR antagonists taken by patients.

CONCLUSION

In the reviewed literature, we found a strong association between IFIS and the systemic use of the selective alpha-1AAR antagonist, tamsulosin, for BPH. However, new, randomized, placebo controlled, prospective studies are needed to determine the most effective management in patients with longstanding medical conditions requiring alpha-1AAR blockers and cataract surgery. Efforts will advance understanding, knowledge, and recognition of this syndrome which may lead to a lower incidence of surgical complications in patients with BPH undergoing cataract surgery.

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

This detailed review/up-to-date paper is a great opportunity to call the attention of physicians and patients about the intraoperative floppy iris syndrome (IFIS), since several ophthalmologists, as well as urologists and general physicians, still are not familiarized with it.

IFIS is a recently described (2005) drug related condition, associated to higher morbidity in cataract surgery in patients on systemic sympathetic alpha-1 antagonist medications for benign prostatic hypertrophy (BPH). This syndrome is characterized by a triad of intraoperative features during phacoemulsification: 1) a flaccid iris that undulates and billows in response to ordinary intraocular surgical fluid currents; 2) a propensity for the floppy iris to prolapse towards surgical incisions and aspiration port of the phacoemulsification machine handpiece; and 3) progressive intraoperative pupil constriction.

Good pupil dilation throughout the surgery is important to facilitate the extraction of the opacified lens. Miosis (pupillary constriction) and iris laxity not only make the surgery longer and more stressful, but are associated to complications that can compromise permanently the vision of the operated eye, like iris damage, more inflammation, vitreous loss and retinal detachment.

There are some ways to manage this miotic and floppy iris. The use of atropine, intraoperative phenylephrine and pupil expansion devices are some examples of strategies that decrease surgical complications. The biggest problem is when the cataract surgeon is not aware of the possibility of IFIS in their patient.

Systemic alpha-1 adrenergic antagonists are commonly used for BPH, since they improve bladder emptying and reduce urinary frequency by relaxing the smooth muscle in the prostate and bladder neck. These drugs are also prescribed for hypertension, urinary retention and as an adjunct for the treatment of renal calculi, which make women susceptible to IFIS too. Studies have shown that IFIS is more frequent and severe in patients using selective alpha-1 antagonists drugs (to alpha-1A subtype receptors, more common at the prostate and probably in the iris too), like tamsulosin (Flomax) and maybe silodosin. IFIS has also been associated with saw palmetto (Serenoa repens) and a variety of other medications, including antipsychotic drugs that may possess some alpha-antagonistic effects.

Although it would seem logical, the utility of stopping tamsulosin preoperatively remains controversial and of unproven benefit. Also, there is a risk for causing acute urinary retention, but it is believed to be small. The serum half-life of tamsulosin is approximately 48 to 72 hours, associated to a prolonged drug-receptor binding time. In addition, there are some evidences that IFIS can occur shortly after the drug is initiated.

As well described in this paper, the IFIS pathophysiology seems to involve iris vascular dysfunction secondary to the alpha-1 antagonists. This would damage the iris skeletal framework. In addition, the iris dilator muscle action decreases, showing some atrophy. Both factors would lead to severe and permanent iris malfunction.

The prevalence of BPH, as well as cataract, increases with age and tend to be more frequent as the population ages. Studies have shown the prevalence of men receiving tamsulosin for BPH among the patients operated for cataract around 1-3%. Moreover, 52-90% of the patients receiving tamsulosin presented at least one manifestation of IFIS.

Medical societies and public agencies have taken several measures in order to better divulgate IFIS. The American Society of Cataract and Refractive Surgery (ASCRS) first issued a global advisory alert regarding tamsulosin in January 2005. The US Food and Drug Administration instituted a labeling warning about alpha-1 antagonists and cataract surgery in the same year. The ASCRS, American Academy of Ophthalmology (AAO), and American Urological Association issued a joint press release in 2006 highlighting the need for patients taking systemic alpha-1 antagonists to inform their ophthalmologist before cataract surgery. Soon after, this message was incorporated into the direct-to-consumer advertisements for Flomax. ASCRS and the AAO also issued a joint educational update statement in July 2008 that was disseminated by the American College of Physicians and the American Academy of Family Physicians to
more than 200000 members. For patients with known cataracts, prescribing physicians were asked to consider involving the cataract surgeon before initiating chronic tamsulosin or alpha-1 antagonist treatment.

More research should be done to better clarify this drug related syndrome and prevent patients under treatment for BPH to have eyesight complications in cataract surgery.

EDITORIAL COMMENT

The authors showed in this interesting review the unexpected relationship between two entities: benign prostatic hyperplasia (BPH) and cataract. The use of tamsulosin, a selective alpha1- adrenergic antagonist used in the treatment of BPH, may lead to the development of intra-operative floppy iris syndrome (IFIS) and interfere with the dilation of the pupil. Interestingly, cases of IFIS during cataract surgery have been reported in patients under treatment for BPH with other drugs such as finasteride, also used for BPH treatment (1).

The technique of phacoemulsification for cataract extraction has gained popularity in the last decade. In this modern surgery, the lens is broken by ultrasound and extracted from the eye through a combination of irrigation and aspiration of fluids. The instability of the iris and inadequate pupillary dilation during surgery can make this dynamic surgery, technically, more difficult. Facio et al. have shown the importance of careful selection of patients and planning for both BPH treatment and cataract surgery, emphasizing the necessity of a multidisciplinary approach by urologists and ophthalmologists in such cases.

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