Complications of cataract surgery in patients with BPH treated with alpha 1A-blockers

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KEY WORDS

BPH ◗ cataract ◗ IFIS ◗ tamsulosin

ABSTRACT

The prevalence of benign prostate hyperplasia (BPH) and cataract increases with age. Both diseases may develop concomitantly and may affect almost 50% of elderly men as comorbidities. Cataract is treated surgically and it has been reported that there may be an association between use of alpha-blockers for BPH, particularly alpha1A-adrenergic receptor selective drugs, and complications of cataract surgery known as Intraoperative Floppy Iris Syndrome (IFIS). The article reviews literature published on this topic and provides recommendations on how to reduce incidence of iatrogenic IFIS or its severity and outcomes in patients with BPH.

Benign prostate hyperplasia (BPH) is a common disease, affecting most men over 60 with the prevalence increasing with age [1]. It has been shown that BPH is frequently accompanied by other diseases or disorders, including hypertension, diabetes and metabolic syndrome , ischemic heart disease, and hyperinsulinemia [2-5]. Comorbidities are related to advanced age and are known to affect the course of a disease and choice of treatment [3]. While some BPH comorbidities, like hypertension are obvious and physicians are well aware of them, some others may not be so well known [6]. Cataract may be one of less considered comorbidities of BPH. However, it is unquestionable that this ophthalmological disorder affects also BPH patients and urologists should be aware of the consequences of their coexistence. In this article we will focus on complications of cataract surgery that may be caused by common medicines used in pharmacotherapy of BPH.

Cataract is defined as a clouding of the lens or its capsule. In most cases it develops with age but can also occur at any age secondary to different factors, including eye injury, toxic agents or radiation, systemic conditions, medicines e.g. steroids etc.; cataract may also present as a congenital disease [7]. Generally, cataract is treated surgically with removal of patient's lens followed by replacement with an artificial lens [7, 8]. Cataract has been the major cause of blindness in the world [7]. It is estimated, that over 40-million people in the world suffer from cataract. As many as 30% of adults over 65 have cataract and more than 8-million of these patients undergo surgical cataract treatment every year around the world according to WHO data [9]. In the United States it is estimated that by age of 80 more than half of the population has cataract with more frequent appearance in women and in white population [7]. In Poland it is estimated that 770,000 people have cataract and cataract has been the most common cause of hospitalization in ophthalmological departments and a rapidly increasing number of cataract surgeries approaching 100,000 surgeries per year [7, 9, 11]. Similarly to BPH, age-adjusted incidence of all cataract types increased with increasing age [12] and many patients that undergo cataract surgery have systemic comorbidities including: angina (20.2%), previous myocardial infarct (15.0%), diabetes (27.5%), and hypertension (56.3%) [13]. No direct data can be found with query to PubMed database on coexistence of BPH and cataract, but as both occur in majority of old men it can be anticipated that such a coexistence exists and is significant.

Complications of cataract surgery that have been considered as related to alpha-1-antagonists (or at least some of them) are known as Intraoperative Floppy Iris Syndrome (IFIS). In the original study by Chang & Campbell IFIS was found to occur in about 3% of cataract extractions [14]. In a large Polish study by Adamski et al. the examined group included 2,705 consecutive patients (1,091 males) who had cataract phacoemulsification surgery in the Ophthalmology Department of the State Hospital in Elbląg; IFIS features were manifested in 2.37% of patients undergoing cataract phacoemulsification surgery including 4.12% of men and 1.18% of women [15]. The IFIS is characterized by loss of muscle tone in the iris resulting in flaccid and billowing iris, poor dilation of the pupil – pre-operatively and during surgery, iris prolapse through the surgical incisions, and progressive pupil constriction [16, 14]. A widely dilated pupil is essential for cataract surgery to minimize or avoid complications and it has been recognized that exposure to an alpha1-antagonist tamsulosin makes cataract surgery more technically difficult [17, 18].

Often, development of IFIS during surgery is not an early event. In fact, the ophthalmologist may have a false sense of safety due to easy capsulorrhexis early during the cataract surgery and the syndrome develops during phacoemulsification [19]. Commonly used methods as pupil stretching and small sphincterotomies are ineffective in this case and use of iris hooks or pupil expanders following completion of the capsulorrhexis can easily tear the anterior capsulorrhexis edge, destroying the integrity of the curvilinear capsulorrhexis [14, 20-24]. Special pharmacological treatment, surgical techniques, including additional suturing, and surgical devices such us Y-hooks and iris retractors have to be used in patients with IFIS [15, 24-27) and this can be perceived as additional complication, and potential risk for a patient. There are a number of problems listed as associated with IFIS in the literature. In 2008, Chang et al. published results of a large global online survey for members of the American Society of Cataract and Refractive Surgery (ASCRS) [28]. Responses were received from 957/6,000 ASCRS members. According to this survey the most commonly reported complications of IFIS vs. non-IFIS patients were (in brackets – according to % of respondents) significant iris trauma (52%) and posterior capsule rupture in IFIS eyes (23%). As mentioned by Friedman IFIS was associated with increased intraoperative risk and complications, such as iris prolapse, pupillary miosis, iris trauma, iris aspiration, iridodialysis, hyphema, posterior lens capsular rupture, and vitreous loss. In the first paper presenting data on IFIS among alpha1-blocker (tamsulosin) – treated patients, investigators noted posterior capsular tear, vitreous body loss, increased intraocular pressure on the first postoperative day, and a significant permanent decrease in visual acuity [14, 17]. In the retrospective study comparing the risk

of IFIS between patients taking tamsulosin versus alfuzosin based on medical charts, major complications were observed in 15% of the patients with IFIS and included iris laceration, focal iris stromal atrophy, iris dialysis, iris hemorrhage, posterior capsular tear with vitreous loss, zonular dehiscence, transient postoperative hypertension, major iris trauma, and postoperative cystoid macular edema [21]. A prospective study detected higher tendency towards postoperative miosis in patients under treatment with tamsulosin than in the patients in the control group [29].

Interestingly, very recently a case report was published on IFIS secondary to tamsulosin following another ophthalmological surgery – Descemet's stripping automated endothelial keratoplasty (DSAEK). This procedure was applied in a 62-year-old male with Fuch's endothelial dystrophy. The developed IFIS leads to pupillary block glaucoma, which presents with classic symptoms of an acute attack of glaucoma with intraocular pressure of 50 mmHg [30].

Reasons for IFIS development remain unclear. In a group of 660 patients IFIS was shown to be related to use of tamsulosin, history of use (but not current use) of other alpha1-antagonists, and hypertension; however, no correlation was found with individual use of angiotensin antagonists, anticholinergics, cholinergic agonists, muscle relaxants, nitric oxide donors, saw palmetto (but a positive trend was observed with P = 0.06 for current use), diabetes, or congestive heart failure [31]. It must be noted that in this study only cases with all three components of the triad (flaccid and billowing iris, iris prolapse through the surgical incisions, and progressive pupil constriction) present during the case were classified as IFIS. However, other investigators did also report a correlation between IFIS and diabetes and case reports that linked this syndrome to some other drugs e.g. beta-blockers (labetalol) and the antipsychotic agent risperidone [14, 32, 33]. Tamsulosin seems to be responsible for significantly higher incidence of IFIS than non-selective alpha1-antagonists. Blouin and co-workers reported that the risk of IFIS was significantly greater for men taking tamsulosin compared with alfuzosin [21]. Patients exposed to tamsulosin <14 days before their cataract surgery were shown to perform inferiorly with an odds ratio of 2.33 (95% CI 1.22-4.43) (adverse events were significantly more common among patients with recent tamsulosin exposure: 7.5% *vs.* 2.7% *vs.* matched control) [34]. According to the authors, this study demonstrated a link between tamsulosin exposure and clinically important postoperative complications rather than IFIS alone [34]. In a prospective study of patients on alpha-blockers who underwent phacoemulsification, IFIS signs occurred in 13 out of 31 subjects with 92% of them demonstrating only one or two features of the syndrome. In this study, 9/13 (69%) eyes of patients on tamsulosin 0.4 mg/day developed IFIS in contrast to another alpha1-antagonist (doxazosin), which was associated with IFIS in only 6% of patients (one eye out of 18 studied) [35]. In a review of prospective and retrospective studies prepared by Leibovici et al., 57-100% of patients exposed to tamsulosin had IFIS during cataract surgery [36]. In a large survey of UK consultant ophthalmologists, partly funded by a company marketing tamsulosin in Europe (Astellas), 53% of them encountered IFIS (altogether 606 cases reported), with the majority of IFIS in patients that used tamsulosin (363/606 *vs.* 12/606 on other alpha1-antagonists or prazosin) [20]. Another report came from Egypt where 70/122 ophthalmologists attending an annual meeting of the Egyptian Society of Cataract and Corneal Diseases responded to a questionnaire and declared that 32.9% of them had previously encountered IFIS during phacoemulsification. Among them, 26.1% declared it was associated with tamsulosin, 8.7% with prazosin, and 4.3% with doxazosin. The other 60.8% did not specify any alpha1A receptor antagonist. Lastly, in a prospective parallel groups study, 19 males being treated with tamsulosin and 19 non-treated controls were enrolled. All patients underwent cataract surgery and were observed for IFIS features. IFIS did not occur in the control group; however, in the tamsulosin group, 67% of patients had one or more signs of IFIS [29].

Based on quite consistent reports it is believed that a typical, but not unique, underlying factor for IFIS is tamsulosin use with a spectrum of other factors for IFIS induction potential [36, 37]. What separates tamsulosin from other alpha-blockers reported in the IFIS context is the selectivity for alpha1 receptor subtypes. Tamsulosin is supraselective for the alpha1A and alpha1D subtypes, while such medicines as doxazosin, prazosin, alfuzosin, or terazosin are not considered as subtype selective [38]. The balance between pupil constriction and dilation is classically maintained by an interplay between alpha and beta-adrenergic receptors and the cholinergic system, with the alpha-1A adrenergic receptor found as the most abundant receptor in the iris that mediates pupil dilation and major subtype detectable in binding and RT-PCR studies in the rabbit iris [39, 40]. In addition, the A subtype of alpha-1 receptor is the most widespread adrenergic receptor in small iris arterioles while alpha1B subtype mediates iris arteriolar contraction; though this has not been confirmed, changes in local blood flow may contribute to iris pathology [36, 41]. The iris arterioles are end arterioles and the iris probably does not depend on its vascular supply for its nutrition. Bill showed that the iris obtains nutrients from the surrounding aqueous humor [17, 42]. Instead, the iris vasculature was proposed to provide a "skeletal" framework that supports the iris tissue. Takayanagi et al. reported that, in iris dilator muscles, the potency of norepinephrine, which altered with aging, was proportional to the receptor reserve [43]. This could suggest age-dependent changes in susceptibility of iris to adrenergic control but further studies are needed on this phenomenon. Also, it was demonstrated, that topically administered sympathomimetic drugs have been associated with an increase in floating cells within the anterior chamber of the human eye [44]. It needs to be remembered that alpha2-adrenergic receptor agonist brimonidine is used locally to decrease intraocular pressure via decrease of aqueous humor production and increase of uveoscleral outflow but anterior eyeball segment vasoconstriction by this agent was also noted [45]. It should not be neglected that alpha2A receptors are localized both post- and presynaptically and stimulation of presynaptic alpha2A receptor inhibits norepinephrine secretion into synaptic space thus decreasing sympathetic activity [37]. There is lack of evidence for postsynaptic alpha2 adrenergic receptors involvement in pupil size, but presynaptic receptors have been found to exist and function on sympathetic nerve terminals in the iris [46, 47]. Whether these facts matter with respect to IFIS development needs to be elucidated (though current opinion is that alpha2 agonists do not influence iris), however they also confirm the role of adrenergic receptors in the eye [37]. Initial suggestions that not only alpha1A but also alpha1B subtype may directly act on iris dilator muscle seem not to be supported in view of recent studies and the B subtype, detected by molecular analyses is probably localized in iris vessels only [37]. In animal studies, tamsulosin appeared to be a more potent antagonist of iris dilator muscle contraction in pigmented rabbits as compared to alfuzosin in at least one laboratory investigation [48]. It needs to be mentioned that according to experimental data, the contraction and relaxation of the iris dilator muscle results from complex signaling including sympathetic, parasympathetic, dopaminergic, serotonergic, tachykinergic, and peptidergic pathways, as well as prostaglandin and nitric oxide–regulated pathways [49, 50]. Also, endothelin A (ETA) seems to be important as it mediates iris dilator contraction [51] and changes in endothelin levels are observed e.g. in diabetes and hypertension suspected as associated with higher risk for IFIS [52]. However, association of IFIS with subtype A of alpha1 adrenergic receptor seems to have strongest confirmative clinical data behind.

Efforts have been made by different groups to investigate potential morphological changes leading to the observed pathophysiological changes of iris function. In one of the first reports of human data, Prata and co-workers studied the eyes of 27 patients treated with tamsulosin and untreated controls (n = 22) using ocular coherence tomography (OCT) and noted a significantly dose-dependent decrease in dilator muscle thickness in irises of tamsulosin-treated patients (P = 0.001) compared to controls [53, 54]. In a recently published study, light microscopy was performed on 14 eyes removed *post mortem* from patients treated with tamsulosin prior to death and compared to specimens taken from untreated controls. Mean iris dilator muscle thickness was significantly decreased in tamsulosin-treated patients (with P = 0.004) compared to controls, without differences noted within iridial stroma [55]. No correlation with dose of the alpha-blocker, or influence by presence of diabetes or lens changes was found in this study. In transmission electron microscopy decreased myofibrils and increased vacuoles in the tamsulosin-treated eyes were spotted and those findings were assumed as evidence for dilator muscle atrophy related to treatment with this α-blocker [55]. In a small study on 11 patients DeStefano and Kim observed no histopathological change of thickness of the iris dilator muscle in specimen from patients using tamsulosin however they noted altered muscle architecture on electron microscopic specimens [56]. Goseki et al. also attributed IFIS to dilator muscle atrophy on the basis of histological findings in their case report of IFIS [57]. This data, though limited, may at least partly explain mechanism through which alpha1A adrenergic receptor antagonists lead to IFIS, however some authors suggest, that thinning of the dilator muscle is simply a result of miosis invoked by alpha-blockers and that decreased myofibrils and increased vacuoles do not necessarily indicate muscular atrophy (Flach 2009). Such an interpretation is challenged by the fact that IFIS has been associated to not only current but also past tamsulosin use [14]. Reassuming, there is clinical and non-clinical data supporting the hypothesis stated in the original Chang and Campbell study that IFIS is associated with use of alpha1A selective drug – tamsulosin [14].

Surprisingly, it was found that even minimal exposure to tamsulosin may be enough to promote IFIS development and patients who have discontinued the drug for over 12 months remain at increased risk [58]. According to a case report published by Shah it is possible that tamsulosin use may lead to increased risk of IFIS in as short time as two days from the beginning of the treatment [59]. This suggests, that despite data demonstrating that IFIS is caused by the disuse atrophy of dilator iris muscle due to constant receptor blockade, there is also a possibility that IFIS can result from the receptor blockade alone [59]. Of course, this will not be the case in patients that developed IFIS a long time after cessation of tamsulosin treatment. However, possible pharmacologic action of tamsulosin on iris is very long. In a Finnish prospective study tamsulosin was suspended for 7 to 28 days before surgery. Despite this, irises continued to be sluggish. Investigators measured tamsulosin concentrations in serum and in the aqueous humor – in serum fell below the limits of quantification in all patients but in the aqueous humor, tamsulosin remained quantifiable after a pause of up to 28 days, suggesting a very prolonged drug receptor binding time [58, 60].

Apart from understanding the pathophysiology it is important to learn how to prevent IFIS, and how to deal with it and its consequences. Unfortunately, based on prospective study it has been concluded that patients who are at risk for intraoperative floppy iris syndrome cannot be identified simply by assessing preoperative dilation which seemed an easy and natural approach based on pharmacological action of alpha-blockers on iris dilator muscle [61]. Another straightforward solution based on deprivation of triggering agent has failed as well. Though according to results of a very small study tamsulosin suspension fifteen days prior to surgery might help in preventing iris prolapse other studies have shown the opposite. In a prospective study Chang and co-workers demonstrated that tamsulosin cessation for 1 to 8 weeks before cataract surgery did not result in change of IFIS severity, however it did result in a larger pupil size at the beginning of surgery [23, 62]. In the original report, published in 2005, cessation of tamsulosin use for as long as 1-year was shown not to prevent IFIS [14]. In other publications IFIS occurred even a few years after stopping tamsulosin [63, 64]. Another considered approach to prevent IFIS was to replace tamsulosin with another alpha-blocker before cataract surgery. However, according to recently published results from a small, prospective trial switching tamsulosin to alfuzosin four weeks prior to cataract surgery resulted in continuously poor pupil dilation and iris prolapse during the surgery despite the switch; authors concluded, that tamsulosin-associated iris changes may be permanent and cannot be reversed by switching to a different α1-AR antagonist [65]. Thus, it does not seem IFIS can be avoided once tamsulosin has been used and the aim should be to identify patients at risk, minimize the risk, prepare for the surgery predicting the possibility of IFIS onset, and apply special procedures and interventions during ocular surgery when signs of IFIS appear.

Changes in surgical education of ophthalmologists on the IFIS proved to effectively, and significantly diminish frequency of major complications of phacoemulsifications in tamsulosin-treated patients [66]. Ophthalmologists have been continuously educated since 2005 to collect thorough medication history of a patient planned for cataract surgery and when surgeons are aware of previous or ongoing exposure to alpha1 adrenergic receptor antagonists, specific surgical techniques can be used to reduce complication rates and improve outcome [27, 62]. Presentation of these measures is not within the scope of this review. On the other hand, the education of majority of ophthalmologists may take years, and another problem may be underreporting of concomitant medicines use by patients admitted for cataract surgery. It is possible that patients who experience IFIS are more likely to remember and report past and present medications use than those who have not experienced IFIS so it may be easier to retrospectively identify the reason for IFIS than to identify such patients preoperatively [31]. Thus, the focus should be put on increasing patients' awareness and educating primary care doctors and/or urologists on the problem, particularly with respect to use of the alpha1A subtype selective blocker, tamsulosin, and alpha-blockers in general, as these are modifiable risk factors for IFIS [28]. In-line with these considerations, the American Academy of Ophthalmology (AAO) and the American Society of Cataract and Refractive Surgery (ASCRS) issued a recommendation that patients taking alpha-blockers to treat prostate enlargement or other conditions informed their ophthalmologist about these medications before undergoing eye surgery [67]. Simultaneously, prior to being started on this class of drugs, patients should be asked by their family doctor or urologist about possible eye problems and suggested an ophthalmologic consultation prior to prescribing tamsulosin and possibly other alpha-blockers [36]. Advanced age should be considered as a risk factor even if patient does not declare any problems according to cataract epidemiology [7]. Those diagnosed with cataract should be informed that alpha-blockers, in general, and tamsulosin, in particular, may increase the difficulty of cataract surgery [67]. American Society of Cataract and Refractive Surgery (ASCRS) and American Academy of Ophthalmology (AAO) jointly stated in their recommendation, that the ophthalmologist performing the cataract surgery can advise a patient how much risk the alpha-blocker medication poses for his or her surgery, and whether stopping, delaying, or avoiding the drug is ad-

visable [67]. In another statement AAO and ASCRS indicate that in a patient with a known diagnosis of cataract, prescribing physicians may wish to consider involving the patient's cataract surgeon prior to initiating non-emergent, chronic tamsulosin or alpha blocker treatment [68]. Hence referring patient with BPH and diagnosed or suspected cataract, or other ophthalmological problem to an ophthalmologist before starting treatment with alpha-blocker and tamsulosin in particular may be recommended as practical and appropriate approach. Similar prophylactic measures were also proposed by other authors. Cantrell et al. has suggested that if cataract surgery is planned in the near future, patients and providers may elect to delay medical treatment for BPH until after surgery [22]. According to Chadha, physicians should refrain from prescribing tamsulosin to any patient being evaluated for, or waiting for cataract surgery, and if treatment is necessary, doxazosin, if appropriate, may be a safer drug to consider [69]. Concluding, in a patient at risk for cataract surgery, based on observed predominant and permanent-like effect of tamsulosin, one may consider initiation of treatment of lower urinary tract symptoms due to BPH with a non-subtype selective alpha1-adrenergic receptor antagonists, such as doxazosin, terazosin, or alfuzosin. Striking data, supporting such an approach came from a survey conducted by Chang et al. The surveyed members of the American Society of Cataract and Refractive Surgery were asked „Would you take tamsulosin if you had BPH and mildly symptomatic cataracts?"; only 36.1% answered "Yes, Would Do So If Recommended" with others choosing more cautious answers, namely not to take the tamsulosin or alpha-blockers at all, or having the cataract surgery first [28].

CONCLUSION

The concept of routine screening of men for cataracts before starting alpha blockers may be impractical, but a diligent approach is recommended. The likelihood of upcoming intraocular surgery should be considered before prescribing alpha-blockers, particularly tamsulosin, for lower urinary tract symptoms in men [28, 70]. In Poland, on the basis of estimated number of performed phacoemulsifications and reported incidence of IFIS by Adamski et al. and Krajka-Lauer et al. we may expect around 3-4 thousands of IFIS cases per year. This is significant number and presented considerations should be taken into account by both ophthalmological, urological and general medicine societies. Probably as much as half of these cases may be iatrogenic and could be prevented if we used alternative pharmacotherapy, e.g non-selective alpha1-adrenergic receptor antagonist, instead of the A subtype selective one.

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