

Intraoperative floppy iris syndrome caused by alpha1-blocker treatment in benign prostatic hyperplasia

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Abstract. Objective: is to evaluate the incidence and typical intraoperative signs of floppy iris syndrome revealed in patients diagnosed with cataracts and benign prostatic hyperplasia under alpha 1 blocker treatment. Methods: We studied two groups: the first one had a total of 144 eyes, which also was the control group, with the diagnosis of cataracts; the second one, the therapy group, had a total of 144 eyes with cataracts and continuous treatment for benign prostatic hyperplasia with Tamsulosin Hydrochloride 0,4 mg between 1 and 5 years. Results: We found significant differences between the patients under therapy and those without therapy. These parameters were compared in the two groups: iris prolapse in the incisions, iris prolapse during viscoat injection, the presence of floppy iris, postoperative visual acuity, preoperative pupillary dimension, the moment of mydriasis appearance of mydriasis and intra operator miosis, prolapse of the iris during phacoemulsification, the use of iris hooks, posterior capsular tear, corneal haze, the presence of high intraocular pressure and the extended surgery time. Conclusions: Floppy iris syndrome occurs in patients treated with Tamsulosin hydrochloride for benign prostatic hyperplasia, generating a series of difficulties during cataract surgery.

Key Words: cataract, alpha-blockers, phacoemulsification, floppy iris

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Introduction

Alpha-blockers bind with high specificity to alpha receptors type 1, receptors that are situated at the level of the bladder neck, prostate, but also at the level of the iris (Nicula et al 2013). Tamsulosin Hydrochloride is the only alpha 1 antagonist (systemic) which is selective for alpha subtype 1A receptor (Nicula et al 2013). Tamsulosin competitively inhibits the sympathetic nervous pathway, inducing smooth muscle relaxation in the peripheral blood vessels, and prostatic urethra as it was shown by Lowe (2004) and Thiyagarajan (2002). It is used to treat benign prostatic hyperplasia (BPH).

Clinical manifestations of the intraoperative floppy iris syndrome (IFIS) complicating cataract surgery are the following: iris prolapse into the main incision and in the side-ports incisions, intraoperative floppy iris and billowing during irrigation and aspiration in normal parameters and progressive intraoperative miosis (Nicula et al 2013). It is not mandatory that all the IFIS signs appear during cataract surgery, sometimes only one or two signs of the three listed above are present (Nicula et al 2013).. The literature (Goyal 2014) mentions that the prevalence of Tamsulosin use for BPH among men undergoing cataract surgery is 7.0% with incidence of IFIS of 4.78%.

Tamsulosin was found to be the drug which was most likely to be associated with IFIS, but IFIS was also observed in patients chronically using other alpha blockers and losartan, chlorpromazine,

aspirin, metformin (Altiaylik et al 2013). Among patients using Alfuzosin and Tamsulosin, the iris seems to be thinner on the dilator muscle region, but preserves the sphincter muscle region without any changes (Aktas 2015).

Sthein (2014) stated that although there were differences in pupillary measurements and intraoperative iris behavior between patients who had been on tamsulosin and control patients, there were no significant differences in iris vasculature on iris fluorescein angiography or in iris morphology on AS-OCT.

The reason behind the current study was to determine if knowing the medical history of the patient who will perform cataract surgery will help us diminish the intraoperative and postoperative complications. This can be achieved by using all the pharmaceutical and technical measures during surgery: high quantity of preoperatively dilation substance, iris hooks, capsular colorant substance, high molecular viscoelastic substance and high quantity of viscoelastic substance, all being done by an experienced surgeon.

Purpose

Our purpose is to evaluate the incidence and typical intraoperative signs of floppy iris syndrome revealed in patients diagnosed with cataracts and benign prostatic hyperplasia under alpha 1 blocker treatment.

Materials and methods

This study is a prospective one, its length being 48 months (January 2014-December 2017) on patients from Oculens Clinic, Cluj-Napoca, Romania. We included in the study two groups.

The first group, the control group, had a total of 144 eyes with the following inclusion criteria: males over 65 years old, diagnosed with cataracts in different developmental stages, but excluding the ones with benign prostatic hyperplasia (BPH).

The second group had a total of 144 eyes with the following inclusion criteria: males, over 65 years old, diagnosed with cataracts in different developmental stages, but also with benign prostatic hyperplasia (BPH) under alpha 1 blocker treatment for 1 up to 5 years, without cessation of preoperative treatment. We excluded patients diagnosed with BPH under different treatment or other types of cataract, for example posttraumatic, postuveitic cataract and posttrabeculectomy.

This study was approved by the Ethics Committee and by "Iuliu Hațieganu" University of Medicine and Pharmacy. All the procedures performed on patients comply with the European Directive for scientific purposes. The project was approved by the Comity for Bioethics of UMF (accord no.148/20.04.2016). All data are reported as the mean \pm SEM. The Gaussian distribution was checked by D'Agustino & Person normality test. Two tailed unpaired Student's t test with Welch's correction was performed for comparisons between the patients receiving therapy and those who did not. Logistic regression model for the potential association between tamsulosin hydrochloride administration and various associated ocular pathology was analysed by Fishers exact test followed by odds ratio. Statistical significance was at $p < 0.05$ (95% confidence interval). Statistical values were obtained using GraphPad Prism version 5.0 for Windows, GraphPad Software, SanDiego California USA.

Results

The eye exam included: preoperative and postoperative visual acuity without correction - uncorrected visual acuity (UCVA) and with correction - best corrected visual acuity (BCVA), refractometry, keratometry, biomicroscopy, fundus examination, intraocular pressure determination, ocular biometry, preoperative and postoperative pupillary diameter using the pupillometer in day light, endothelial cells counting.

The preoperative course included mydriasis with topical Mydrum (Tropicamide 0.5%) two drops, Fenefrin 10% (Phenylephrinum) two drops, topical nonsteroidal anti-inflammatory drugs (Indocollyre 0.1%) one drop, and local Povidone Iodine for local disinfection. All patients underwent phacoemulsification surgery for cataracts with implantation of artificial lens, using suction and vacuum parameters smaller than normal.

Post operative, topical treatment was performed with topical corticosteroids and antibiotics for six weeks, systemic anti-inflammatory drugs for five days.

We've noticed cases of floppy iris, situations where the iris was shaking and billowing. The prolapse in the main incision or in the side-port refers to the fact that the iris slides into the incisions during or even in the absence of surgical maneuvers. Prolapse of the iris during the injection of serum indicates slippage during injection through side ports. The iris rupture is due to the iris atrophy under tamsulosin treatment and represents

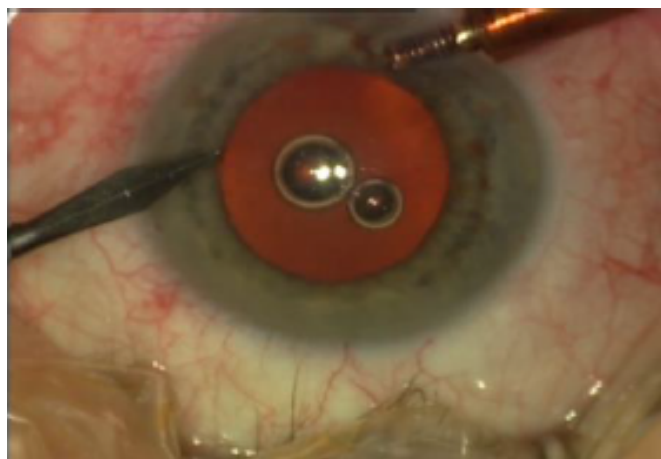


Fig.1 Preoperative mydriasis

its friability. The posterior capsule can break more easily in the low visibility situation, stronger ultrasound intra operator parameters, and intense surgical maneuvers when tamsulosin is used as a treatment. The posterior capsule of the lens can be easily broken in low visibility, and high surgery parameters, intensive maneuvers, aggravating the operator steps. Lens fragments may also appear in the vitreous by breaking the posterior capsule, complicating the surgery process. Corneal haze means a cloudy cornea, also being a result of high intra operator parameters and a long total intervention time.

The age distribution recorded the following values: the no therapy group had a mean value of 76.23 years of age and a standard deviation of 5.47, while the therapy group had a mean value of 76.45 years of age and a standard deviation of 5.21, with $p > 0.05$, with no statistically significant difference between the two groups compared.

We compared the two groups in terms of preoperative uncorrected visual acuity (UCVA) and had the following result: there were no statistically significant difference between the control group and the other group. The no therapy group had a mean value of 0.73 logMAR and the therapy group had a mean value of 0.75 logMAR. (Table 1)

Regarding the postoperative UCVA there was a significant difference between no therapy group compared with the one with continuous therapy ($p < 0.001$). The no therapy group had a mean



Fig. 2 Intraoperative miosis

Table 1 The influence of Tamsulosin therapy upon the ocular parameters (Mean and SEM) (***)= $p < 0.001$ as compared to no therapy group; two tailed unpaired Student's t test with Welch's correction)

Type of treatment	No therapy group	Therapy group
Age (years)	76.23 ± 0.45	76.45 ± 0.43
Preoperative UCVA(logMAR)	0.73 ± 0.02	0.75 ± 0.02
Preoperative BCVA(logMAR)	0.72 ± 0.02	0.74 ± 0.02
Postoperative UCVA(logMAR)	0.13 ± 0.02	0.36 ± 0.02 ***
Postoperative BCVA(logMAR)	0.03 ± 0.01	0.14 ± 0.02 ***
Preoperative pupillary dimension(mm)	3.33 ± 0.06	2.66 ± 0.05 ***
Mydriasis(min)	39.5 ± 0.78	53.95 ± 1.31 ***
Miosis(min)	22.83 ± 0.53	14.5 ± 0.39 ***
Surgery time(min)	29.16 ± 0.47	40.83 ± 0.93 ***

UCVA: uncorrected visual acuity (using logMAR scale);
BCVA: best corrected visual acuity (using logMAR scale).

value of 0.13 logMAR and the therapy group had a mean value of 0.36 logMAR (Table 1).

We also compared the two groups in terms of preoperative best corrected visual acuity (BCVA) and had the following results: there were no statistically significant difference between the control group and the other group. The no therapy group had a mean value of 0.72 and the therapy group had a mean value of 0.74 logMAR. (Table 1)

Regarding the postoperative BCVA there was a significant difference between no therapy group compared with the one with continuous therapy ($p < 0.001$). The no therapy group had a mean value of 0.03 logMAR and the therapy group had a mean value of 0.14 logMAR. (Table 1)

There was a significant difference between no therapy group compared with the one with continuous therapy ($p < 0.001$). The

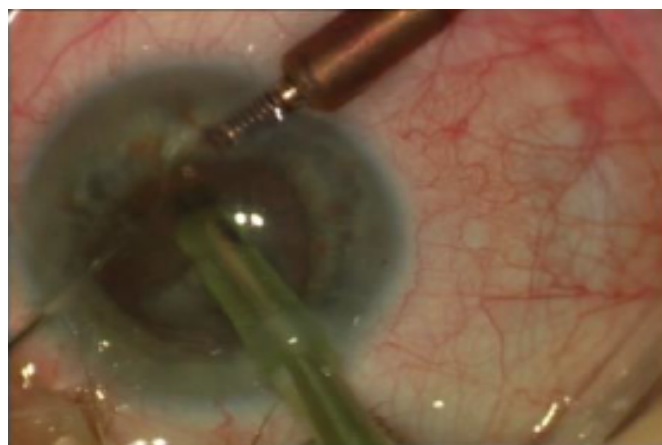


Fig. 4. Iris prolapse during phacoemulsification

pupillary dimension was recorded before application of tropicamide drops (mydriatic and cycloplegic drops). The no therapy group had a mean value of 3.33 mm and the therapy group had a mean value of 2.66 mm. (Table 1)

We noted the moment when mydriasis occurred during surgery (we considered mydriasis a value of 5 mm or above in bright light). There was a significant difference between no therapy group compared with the one with continuous therapy ($p < 0.001$) regarding the moment of occurrence of the mydriasis. The no therapy group had a mean value of 39.5 minutes and the therapy group had a mean value of 53.95 minutes. (Table 1, Fig. 1)

The normal pupillary diameter is considered between 2 and 4 mm in bright light, so a value under 2 is considered miosis. There was a significant difference between no therapy group compared with the one with continuous therapy ($p < 0.001$) regarding the moment in which miosis occurred during surgery.

The no therapy group had a mean value of 22.83 minutes and the therapy group had a mean value of 14.5 minutes. (Table 1, Fig. 2) The total surgery time recorded a significant difference between no therapy group compared with the one with continuous therapy ($p < 0.001$). The no therapy group had a mean value of 29.16 minutes and the therapy group had a mean value of 40.83 minutes. (Table 1)

Floppy iris occurred at a peak frequency for the group with continuous treatment ($p < 0.001$) (Fig.3), the control group being the reference group (Table 2).



Fig. 3 Intraoperative floppy iris



Fig. 5. Iris prolapse during viscoelastic insertion

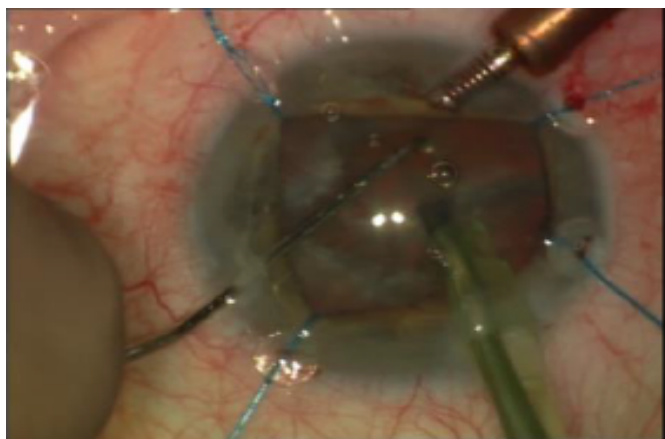


Fig. 6 Iris hooks in place

Iris prolapse during phacoemulsification appeared with maximum frequency for the group with continuous treatment (odds ratio 16.43, confidence interval 95% “6.800 to 39.69” and p value <0.001)(Fig.4, Table 2).

Iris prolapse in the incisions appeared with maximum frequency for the group with continuous treatment (odds ratio 15.84, confidence interval 95%”7.697 to 32.58”and p value <0.001 (Table 2). Iris prolapse during viscoat and serum injection occurred with the highest frequency for the group with continuous treatment(p<0.001) and low frequency in the control group (Fig.5, Table 2).

The rupture of the posterior capsule (posterior capsule tear) had a significant presence in the therapy group (odds ratio 7.58, confidence interval 95% “2.199 to 26.13” and a p <0.001 (Table 2). Lens fragments in the vitreous had no statistical relevance in the two groups (Table 2).

The corneal haze complicated the cataract surgery as follows: the group with continuous therapy had an odds ratio of 3.40, confidence interval 95% “1.472 to 7.853” and a p<0.01 (Table 2). The iris rupture appeared with decreasing frequency: the therapy group with odds ratio 21, confidence interval 95% “7.350 to 60.00” and a p <0.001 with statistical relevance, followed by the control group (Table 2). Iris hooks were used in the therapy group with odds ratio of 17.51 and a p<0.001 (Fig. 6, Table 2). High intraocular pressure was present In the therapy group with odds ratio of 6.45 confidence interval 95% “1.417 to 29.39” and a p<0.05 (Table 2).

Discussions

David Chang et al (2005) were the ones who first described Intraoperative Floppy Iris Syndrome (IFIS), characterized by a flaccid iris. They noticed flutter iris moves during phacoemulsification at normal current levels of circulating fluid, iris prolapse through the side-ports and progressive intraoperative miosis (Chang et al 2005). The syndrome was revealed in patients with Benign Prostatic Hyperplasia (BPH) treated with Tamsulosin . In our study, the frequency of IFIS was 2% of the total number of cataract surgeries. The results are quite similar with those reported in literature (2%), supported by the fact that a Tamsulosin medication is used quite commonly in older men with BPH (Chang et al 2005). By its long action, Tamsulosin Hydrochloride performs a quite constant receptor blockade, generating a diffuse atrophy on dilator muscle of the iris (Chang et

Table 2. Logistic regression model for the potential association between Tamsulosin Hydrochloride administration and various associated ocular pathology.

Variable	Odds ratio	95% Confidence Interval	P value
Iris prolapse during phacoemulsification			
No therapy	1	Reference category	
Therapy	16.43	“6.800 to 39.69”	p<0.001
Floppy iris			
No therapy	1	Reference category	
Therapy	55.86	“22.87 to 136.4”	p<0.001
Iris in the incisions			
No therapy	1	Reference category	
Therapy	15.84	“7.697 to 32.58”	p<0.001
Iris hooks			
No therapy	1	Reference category	
Therapy	17.51	“7.657 to 40.05”	p<0.001
Posterior capsular tear			
No therapy	1	Reference category	
Therapy	7.58	“2.199 to 26.13”	p<0.001
Iris rupture			
No therapy	1	Reference category	
Therapy	21	“7.350 to 60.00”	p<0.001
Iris prolapse during viscoat or serum injection			
No therapy	1	Reference category	
Therapy	22.93	“8.034 to 65.45”	p<0.001
Postoperative corneal haze			
No therapy	1	Reference category	
Therapy	3.4	“1.472 to 7.853”	p<0.01
High Intraocular pressure			
No therapy	1	Reference category	
Therapy	6.45	“1.417 to 29.39”	p<0.05
Lens fragments in the vitreous			
No therapy	1	Reference category	
Therapy	4.73	“1.004 to 22.31”	p>0.05

al 2005). This explains the presence of the floppy iris phenomenon and poor preoperative dilation.

Out of the 139 men with treatment for BPH in the study of Chiselita (2012), 23,02% showed IFIS, but only the patients treated with tamsulosin. After introducing a surgical protocol including large amounts of viscoelastic material (Viscoat), intracameral phenylephrine, the use of iris retractors and low phacoemulsification parameters the incidence and severity of IFIS was significantly reduced (Chiselita 2012).

Nakamura et al (1999) revealed the existence of alpha1 receptor at the level of dilator smooth muscle of the iris in rabbits. Yu et al (2003) concluded in their studies on rabbits that alpha1 receptor mediates mydriasis.

Prevention of intraoperative floppy iris syndrome by withdrawing tamsulosin preoperatively has not shown consistent result (Osher 2007 and Gupta 2011).

The literature (Haridas 2013) said that the incidence of IFIS(1,9%) was significantly higher in doxazosin and tamsulosin patients and his advice was that all patients receiving alpha-antagonists (not only those receiving tamsulosin) should be identified preoperatively, receive appropriate modifications in preparation, and also have alternative techniques made by a senior surgeon available at the time of surgery .

We had statistical significant p in continuous therapy group following these parameters: iris prolapse in incisions, iris prolapse during viscoat injection, the presence of floppy iris, postoperative visual acuity, preoperative pupillary dimension, the moment of occurrence of the mydriasis, intraoperative miosis occurrence, prolapse of the iris during phacoemulsification, the use of iris hooks, posterior capsular tear, corneal haze, the presence of high intraocular pressure and the total surgery time.

Preoperative mydriasis failure associated with progressive constriction of the pupil determined the need for iris retractors. In other cases bimanual phacoemulsification was sufficient, without the need to use iris hooks (Nicula et al 2013). Chang (2005) suggests using a chopper with a maintainer keeping this way circulatory irrigation anterior to the iris and consequently reduce this behavior. Storr-Paulsen (2014) finds the same manifestations: significant miosis during surgery, less preoperative dilatation plus significantly greater postoperative endothelial cell loss compared with no treated patients despite recommended precautions.

Other studies suggest that sub-Tenon lidocaine reduces significantly the incidence of IFIS in patients taking oral α -adrenergic inhibitors as compared with intracameral lidocaine (Klysik 2014). Intracameral phenylephrine is a highly efficient measure for prophylaxis against IFIS (Lorente 2012). Moreover, the drug can reverse IFIS, causing the pupil to return to its preoperative size and restoring iris rigidity (Lorente 2012).

We found iris prolapse through the incisions and during viscoelastic introduction in the therapy group with high statistical relevance. To reduce this effect Chang (2005) and, after a while, Nicula et al (2013) recommended correctly performed incision and using viscoelastic substance with big molecular weight (ex. Healon 5). Predisposing factors for the iris prolapse are anterior chamber depth, iris configuration, and the position and the architecture of the corneal tunnel (Tint 2012). Strategies for management and prevention include the use of ophthalmic viscosurgical devices, pharmacological agents and iris retractors .

We had in the therapy group posterior capsular rupture with statistical relevance. This was accompanied by vitreous loss, which required anterior vitrectomy, but with favorable intraoperative and postoperative evolution. Other authors like Chang (2005) have had a 12% frequency of this complication in cases with IFIS. The difference between the mean age of the two groups was not statistically significant ($p>0.05$).

The preoperative visual acuity without and with correction had no statistical relevance in the two groups. Regarding the postoperative visual acuity with and without correction, there was a significant difference between the two groups ($p<0.001$).

Conclusion

Highlighting the chronic use of tamsulosin through a detailed patient questionnaire and anticipation of IFIS can reduce intraoperative complications and also obtain a good postoperative visual acuity.

Progressive pupil constriction increases the risk of intraoperative complications, but using iris retractors, viscoelastic substances and other mydriatic agents can maintain a normal surgical course.

It is recommended that these procedures to be performed by an experienced surgeon that must take all measures to prevent the occurrence of intraoperative complications.

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Citation Popescu RM, Ober C, Sevastre B, Nicula C, Coman I. Intraoperative floppy iris syndrome caused by alpha1-blocker treatment in benign prostatic hyperplasia. *HVM Bioflux* 2018;10(3):169-174.

Editor Stefan Vesa

Received 25 June 2018

Accepted 13 September 2018

Published Online 15 October 2018

Funding None reported

**Conflicts/
Competing
Interests** None reported