

## A Possible Associated Risk Factor - Angiotensin-Converting Enzyme Inhibitors along with Systemic Administration of Alpha-1 Antagonists for IFIS Syndrome in Patients with Benign Prostatic Hyperplasia Undergoing Cataract Surgery

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### Abstract

**Purpose:** To evaluate the incidence of intraoperative floppy iris syndrome in relation to the usage of systemic administration of Alpha-1 antagonists for benign prostatic hyperplasia and conversion enzyme inhibitors for systemic hypertension and the influence on the course of cataract surgery.

**Materials and Methods:** Sixty nine eyes of 69 patients with benign prostate hyperplasia (BHP) were included in the study. They were divided into 2 groups: 40 patients in group 1 who were treated only with tamsulosin, and 29 patients in group 2 who were treated with tamsulosin and angiotensin-conversion enzyme inhibitors. Both groups presented age related cataract and underwent phacoemulsification with posterior chamber intraocular lens implantation.

**Results and Conclusion:** The mean age was  $76.19 \pm 5.28$  (range 67 - 90) and all the patients were males. The mean axial length (mm) of the globe was  $23.65 \pm 1.17$  (range 20.31 - 26.86). From the total of 69 patients, 20 (28.99%) were known with high blood pressure, 10 (14.49%) had diabetes mellitus, 2 (2.90%) were known with glaucoma and 4 (5.80%) had age related macular degeneration.

All patients had benign prostate hyperplasia and were under treatment with tamsulosin and 29 (42.03%) with tamsulosin and angiotensin-conversion enzyme inhibitors. In addition, 13 (18.84%) were under treatment with anticoagulants and 6 (8.70%) with betablockers. Preoperative pupil size was  $2.65 \pm 0.70$  in group 1 and  $2.86 \pm 0.69$  in group 2. Preoperative pupil size after dilatation was < 5 mm in 20 eyes (50%), between 5 - 7 mm in 11 eyes (27.5%) and > 7 mm in 9 eyes (22,5%) in group 1 and < 5 mm in 19 eyes (65.52%), between 5 - 7 mm in 9 eyes (31.03%) and > 7 mm in 1 eye (3.45%) in group 2. Intraoperative progressive miosis appeared in 8 eyes (20%) after hydrodissection, in 22 eyes (55%) during phacofragmentation and in 20 eyes (50%) during emulsification in group 1 and in 13 eyes (44.83%) after hydrodissection, in 10 eyes (34.48%) during phacofragmentation and in 6 eyes (20.69%) during emulsification in group 2. Iris prolapse through incisions after hydrodissection or first steps of phacoemulsification was present in 21 eyes (52.5%) in group 1 and in 12 eyes (41.38%) in group 2. Iris prolapse through main corneal incision appeared in 25 eyes (62.5%) in group 1 and in 17 (58.62%) eyes in group 2. Floppy iris was present in all the patients in both groups. Iris flexible retractors were used in 12 cases (30%) in group 1 and in 11 (37.93) eyes in group 2. The mean surgical time was significantly shorter in patients who did not require iris flexible retractors compared with those who did ( $p < 0.0001$ ).

**Keywords:** Benign Prostatic Hyperplasia; Alpha-1 Antagonists; Angiotensin-Converting Enzyme Inhibitors; Cataract Surgery; Floppy Iris Syndrome

## Introduction

Systemic alpha 1 antagonist are used to treat benign prostatic hyperplasia (BPH) [1]. Their effect is linked to the relaxation of smooth muscles in the prostate and urinary bladder neck [2]. Of the three subtypes of alpha-1 receptors (a, b and d), the alpha-1 a receptor dominates the iris dilator muscle as well as the smooth muscles of the prostate tissue. Of the currently used alpha 1 antagonist that are given to treat BPH, only Tamsulosin is subtype specific and has the greatest affinity to the alpha 1 a receptor [2,3]. Tamsulosin has a long half-life (between 10 - 24 days), and a constant receptor blockade may result in atrophy of the iris dilator smooth muscle. All alpha 1 antagonists give a poor dilation of the pupil. Intraoperative floppy iris syndrome (IFIS) was first described by Chang and Campbell, in 2005 as a condition during cataract surgery associated with the use of Tamsulosin- alpha 1 antagonist (Flomax: Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT) [4]. The first sign of IFIS is often a poorly dilating pupil prior to cataract surgery. During the surgery there is the excessive floppiness of the iris, lax tone, tendency for the iris to prolapse through one of the incisions despite proper wound architecture and continuous intraoperative miosis even though of sufficient administration of mydriatics drops. Previous studies showed an incidence of IFIS syndrome between 2 to 2.2% [4-7]. Chatzaralli and Sergentanis' meta-analysis showed that the risk ratio for IFIS in patients treated with Tamsulosin was 40 times higher than for patients taking alfuzosin, another alfa-blocker, but rather decreased in patients treated with doxazosin [8]. Previous studies have reported an association between IFIS and the systemic administration of alpha-blockers [4,9,10]. Mostly IFIS was independently associated with Tamsulosin [4,8-12]. The risk of IFIS was as high as 53.3% - 93.8% with intake of Tamsulosin [4]. Furthermore, several reports have been published, suggesting an association between IFIS and other drugs such as doxazosin [8,13,14], terazosin [15], alfuzosin [11] or labetalol [16], finasteride [17], mianserin [18], antipsychotic agents [19], chlorpromazine [20], donepezil [21], imipramine [22], warfarin [23], aspirin [24], losartan [24] and metformin [24].

Angiotensin-converting enzyme inhibitors (ACEIs) are used since 1980s, being an efficient antihypertensive medication [25]. They have been extensively indicated in patients with cardiovascular diseases, especially high blood pressure, myocardial infarction, heart failure and stroke. ACEIs may give rise to adverse effects in some patients, especially chronic cough and angioedema and in rare cases hyperkalemia, hypotension, liver dysfunction and bone marrow depression [26].

## Purpose of the Study

The purpose of the study was to evaluate the incidence of intraoperative floppy iris syndrome in relation with the usage of systemic administration of Alpha-1 antagonists for benign prostatic hyperplasia in association with ACEIs for hypertension and the influence of the cataract surgery course.

## Materials and Methods

Sixty-nine consecutive eyes of 69 patients undergoing cataract surgery in Oculens Clinic, Cluj-Napoca Romania, under treatment with alpha 1 antagonists for benign prostate hyperplasia (BPH) and Angiotensin-converting-enzyme inhibitors (ACEs) for systemically hypertension potentially inducing IFIS syndrome were recorded. Group 1 included 40 eyes (66.7%) from patients who received only treatment with Tamsulosin and Group 2 included 29 eyes (48.3%) from patients who received both Tamsulosin and ACEIs. This retrospective analysis was conducted from September 2015 to December 2019 and included cataract surgery patients identified to be at risk for intraoperative miosis before surgery and, therefore anticipated to require the usage of iris fixation ring to maintain adequate surgical visualization and pupil management. The study was in concordance with the tenets of Helsinki Declaration and was approved by the Ethical Committee of the Oculens Clinic.

The inclusion criteria were: patients who received Tamsulosin (for BPH for several months), patients who received ACEIs drugs, patients who were required to have a pupil dilation of < 5.0 mm with topical mydriatics at presurgical examination, or history of IFIS during

cataract surgery in the fellow eye. The exclusion criteria were patients with other types of cataract (posttraumatic, post uveitis) or others type of surgeries (trabeculectomy, pars plana posterior vitrectomy).

Patients undergoing routine cataract surgery were dilated with topical tropicamide 1% (S.C. Rompharm Company S.R.L., Otopeni, Romania), phenylephrine 10% (Unimed Pharma Ltd., Orišekova 11, 82105 Bratislava, Slovakia) and cyclopentolate 1% (S.C. Rompharm Company S.R.L., Otopeni, Romania), and topical nonsteroidal anti-inflammatory drugs such as Indocollyre (Laboratoire Chauvin/Bausch and Lomb, 416 rue Samuel Morse CS 99535 34961 Montpellier Cedex 2, France) were used for mydriasis support.

Before cataract surgery all patients underwent a full ocular assessment, including the pre-operative uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA) measured as Logarithm of Minimum Angle of resolution (logMAR scale), refractometry, keratometry (Kmax, Kmin) using the autorefracto-kerato-meter (Topcon, KR 8900, Japan) and the Oculus Pentacam topographer (Pentacam® HR Premium; Oculus Optikgerate GmbH, Wetzlar, Germany), anterior segment slit lamp examination and pupillary diameter (Slit-Lamp BX 900, Haag-Streit AG), fundus examination, intra-ocular pressure (applanotonometer), endothelial cell count (Konan SP-9000, Hyogo, Japan), optical coherence tomography of the macula and optic nerve (Triton Topcon, Japan) when it was possible. Ultrasonic (Ocuscan, Alcon, USA) and optical biometry with interferometry was performed (IOL Master, Meditec Carl Zeiss, Germany) to establish the dioptric power of the IOL. The formulas used were concordant to the eyeball axial length: between 22 - 24 mm Hoffer Q, under 22 mm Hoffer Q and beyond 24mm SRK T. The company provided "A" constant was used. Targeted postoperative refraction was emmetropia  $\pm$  0.5 D Sph. After these examinations and a discussion with the patient regarding the steps of surgery, possible intraoperative and postoperative complications, all the patients signed a written informed consent to agree with the surgery. None of the patients stopped the Tamsulosin medication. The pupil size was measured before the surgery and after dilatation at slit lamp and during the surgery using Geuder Castroviejo caliper (Geuder AG, Heidelberg, Germany).

Cataract surgery was performed in each case with topical anaesthesia (Ophtacaine, S.C. Rompharm Company S.R.L., Otopeni, Ilfov, Romania) or parabolbar injection (Xyline 2 - 4%) and consisted in phacoemulsification using Alcon Centurion machine (Alcon, Fortworth, TX, USA). Manually created clear corneal incision of 2.2 mm was followed by a 4.5 mm capsulorhexis using a cystotome needle," stop and chop" technique for phacofragmentation and intrabag implantation of posterior chamber intraocular lens (PCIOL). In order to control the IFIS syndrome we used some strategies. After making the 2.2 mm clear corneal incision at 11 o'clock, slightly more anterior than usual and square-shaped, 1.5 mm tunnel, Viscoat (Alcon Laboratories, Inc., Fort Worth, Tx, USA) and Provisc (Alcon Laboratories, Inc. Fort Worth, Tx, USA) was injected (soft shell technique), followed by continuous curvilinear capsulorhexis (after dyeing the anterior capsule with blue tripan, in some cases) and hydrodissection with hydrodelimitation. In cases with small pupils we used the iris flexible retractors (in a diamond pattern) (Ophtha Surgical Incorporated, Memnagar, Ahmedabad, Gujarat, India) before performing the capsulorhexis Healon 5 (sodium hyaluronate 5,000 2.3%) was injected in order to deepen the anterior chamber. In order to keep the Healon 5 (Advanced Medical Optics) in the anterior chamber during the procedure, slow-motion phacoemulsification was performed with lowered parameters within the capsular bag-flow rate at 20 ml per minute and vacuum level below 350 mmHg and low bottle height. Torsional ultrasounds started at 20% and went up to 60% for routine cataracts but for dense cataracts went up to 100%. Torsional ultrasounds improved the flow and the reduction of intraocular turbulence. In some cases Viscoat (Alcon Laboratories Inc., Fort Worth, Tx, USA) was injected into the angle of the anterior chamber before beginning bimanual irrigation-aspiration of the cortex in order to tamponade the peripheral iris and minimise the iris tendency to prolapse toward the incisions (Osher technique) [27]. Before implanting the foldable PCIOL additionally Provisc (Alcon Laboratories Inc., Fort Worth, Tx, USA) was injected inside the lens bag. Afterwards, the viscoelastic substance was removed in front and behind the IOL and tightened very well the incisions by hydration. During the last year we used in cases of improper pupil dilatation, intracameral injection of 0.2 ml Mydrane (Laboratories THEA 12, Rue Louis Blériot - 63017 Clermont- Ferrand Cedex 2, France).

At the time of the surgery, all eyes were defined by the surgeons as IFIS or non-IFIS. In some cases, the classical triad was not present in all aspects and the syndrome was called as partial IFIS.

Post-operative all the patients received local treatment with antibiotics and steroids (Tobradex, Alcon, Fortworth, TX, USA) 5 times/day, for 6 weeks. Follow up was performed in the first day after the surgery, at 3 days, at 6 weeks.

The following data were recorded: sociodemographic features (age, gender), clinical data (diabetes, hypertension) ophthalmological conditions (pseudoexfoliation, glaucoma and age related macular degeneration), axial length of the eye, smoking, medications being taken at the time of surgery, pupil size before dilatation, after dilatation (before surgery) and during the phacoemulsification, use of iris flexible retractors during the surgery, presence of IFIS during the surgery in complete or partial form, iris prolapse through the incisions, floppy iris during the surgery, the amount of using ultrasound- cumulative dissipated energy (CDE), intraoperative complications (iris damage, posterior capsule rupture, vitreous loss, nuclear or cortical fragments into the vitreous), time of surgery (from the initial incision to the tightening of the incisions). In order to establish the severity of IFIS we used the criteria defined by Chang, *et al.*: 0- no IFIS; 1-mild IFIS (noticeable iris billowing without significant miosis or iris prolapse); 2-moderate IFIS (iris billowing associated with iris prolapse or < 2 mm pupil diameter reduction); 3-severe IFIS (iris billowing associated with iris prolapse or > 2 mm pupil diameter reduction) [28].

**Statistics**

Data were reported as mean ± standard deviation or number (frequency). Outcomes were analysed with the two sample unpaired t-test and the Fisher’s exact test. P values < 0.0001 were estimated as high statistically significant, p > 0.05 not statistically significant, p = 1 equal series.

**Results**

A total of 69 cataract surgery patients at risk for intraoperative IFIS were included in the study, from 2334 eyes operated for age related cataract during the studied period. All the patients were treated for BPH with Tamsulosin. The patients from both groups underwent standard phacoemulsification with implantation of foldable posterior chamber intraocular lens (PCIOL).

The demographic data and associated ocular diseases are presented in table 1.

	<b>Group 1</b>	<b>Group 2</b>	<b>P value between groups</b>
Number of eyes	40	29	
Age	76.53 ± 4.89	75.72 ± 5.84	0.5383
Axial length (mm)	23.45 ± 1.25	23.92 ± 1.09	0.0746
Pseudoexfoliation	1	1	1
Open angle glaucoma	1	1	1
Age related macular degeneration	3	1	0.6337

**Table 1**

In addition, 10 patients (14.49%) had diabetes mellitus, 2 (2.90%) were known with primary open angle glaucoma and 4 (5.80%) had age related macular degeneration. Furthermore, 13 patients (18.84%) were under treatment with anticoagulants and 6 (8.70%) with betablockers.

Preoperative and intraoperative parameters regarding the pupil size after dilatation, the mean cumulative diffusive energy (CDE), the presence of IFIS syndrome, use if iris retractors, presence of intraoperative complications between both groups are presented in table 2.

	<b>Group 1</b>	<b>Group 2</b>	<b>p value</b>
Preoperative pupil size 2 - 4 mm	2.65 ± 0.70	2.86 ± 0.69	0.2272
After dilatation < 5 mm	20	19	0.3399
After dilatation 5 - 7 mm	11	9	0.7926
After dilatation > 7 mm	9	1	0.0369
Intraoperative progressive miosis	10.88 ± 5.18	6.86 ± 2.64	0.0011
After hydro dissection	8	13	0.0356
During phacofragmentation	22	10	0.1419
During emulsification	20	6	0.0226
CDE	9.64 ± 7.57	7.29 ± 5.54	0.1677
Iris prolaps through side-ports	21	12	0.4652
Iris prolaps through main corneal incision	25	17	0.8056
Incomplete IFIS	18	11	0.0288
Complete IFIS	22	18	0.6261
Iris flexible retractors	12	11	0.6064
Time of surgery	33.95 ± 9.08	39.62 ± 7.59	0.0079

**Table 2:** Preoperative and intraoperative parameters.

Iris flexible retractors were used in 12 cases (30%) in Group 1 and in 11 eyes in Group 2 (37.93%). The mean surgical time was significantly shorter in patients who did not require iris flexible retractors compared with those who needed ( $p < 0.0001$ ) (Table 3).

<b>Iris retractors</b>	<b>Present</b>	<b>Not present</b>	<b>P value</b>
Mean surgical time	44.13 ± 6.65	32.30 ± 7.18	< 0.0001

**Table 3:** Surgical characteristics by treatment group.

In our study, there was no statistically significant difference regarding intraoperative complications between the two groups ( $p = 0.7855$ ) (Table 4).

<b>Intraoperative complications</b>	<b>Group 1</b>	<b>Group 2</b>	<b>p value</b>
Posterior capsule rupture	1	2	0.5683
Dropped nuclear fragments into the vitreous	1	0	1
Iris rupture	10	5	0.5591
Total	12	7	0.7855

**Table 4:** Intraoperative complications in both groups.

Posterior capsule rupture was followed by anterior vitrectomy and implantation of the PCIOL in sulcus or using the Yamane technique implanting in the sclera. In cases of dropped nuclear fragments into the vitreous was performed pars plana posterior vitrectomy.

## Discussions

The main purpose of this study was to establish the incidence of IFIS syndrome due to the systemic administration of alpha blockers for BPH and ACIs which can influence the iris behavior and pupil size during cataract surgery. Our results confirm the findings of previous studies [8,9,16,12,29-34].

The overall incidence of IFIS among patients undergoing cataract surgery was 2.95% in our study population, which is higher than that reported by Chang and Campell [4], 2%. Oshika, *et al.* [3] showed an incidence of IFIS in patients treated with Tamsulosin of 1.1%, lower than the incidence demonstrated by Chang and Campell [4], probably due to the difference in the recommended dosage of Tamsulosin for the treatment of BPH in USA and Japan.

Previous studies have reported an association between IFIS and the intake of alpha blockers, used for the treatment of BPH [4,9,8,11,12] IFIS was mostly associated with Tamsulosin [4,8,9,11,12]. Our study showed that all the patients who used Tamsulosin for PBH developed intraoperative IFIS, in 22 eyes (55%) complete IFIS and in 18 eyes (45%) partial IFIS. Nakamura, *et al.* revealed the existence of alpha 1 receptor in iris dilator smooth muscle in rabbits [35]. Yu and Koss [36] showed in their studies that the receptors that mediate mydriasis in rabbits is the alpha 1. The results are similar with those showed by our previous experimental study on Wistar rats undergoing treatment with Tamsulosin which suggested there is a clear connection between the time of administration of the alpha-blocker medication and most cataract complications [37]. In time, tamsulosin performs a constant blockade on the iris receptors, inducing a diffuse atrophy of the iris dilator muscle. This explains the appearance of IFIS syndrome and poor dilatation of the pupil during the surgery [4] In our study, the patients did not discontinue the treatment with tamsulosin based on the literature conclusion that showed that stop of medication cannot prevent intraoperative IFIS [27].

In our study, there was a statistical significant difference in pupil size after mydriasis between both groups, regarding the 7 mm size ( $p = 0.0369$ ) that demonstrated that in Group 2 we could not achieve in the same percentage as in Group 1 the pupil size mentioned above. Our supposition was that the ACEIs could influence the dilatation of the patients. Moreover, Cassucio, *et al.* showed that in patients with Tamsulosin treatment, the pupil size was significantly smaller preoperatively and postoperatively compared with the control group [38]. Furthermore, Chen, *et al.* found that patients with preoperative dilated pupil diameter  $< 6.5$  mm had a higher incidence of IFIS. [39] Cassucio, *et al.* demonstrated that preoperative dilated pupil diameter  $< 7.0$  mm was at risk for IFIS [38].

Our findings showed that the intraoperative progressive miosis appeared in 8 eyes (20%) after hydrodissection and in 22 eyes (55%) during phacofragmentation and in 20 eyes (50%) during emulsification in group 1 and in 13 eyes (44.83%) after hydrodissection and in 10 eyes (34.48%) during phacofragmentation and in 6 (20.69%) eyes during emulsification in group 2. An explanation for this is the release of prostaglandins generated by excessive mechanical maneuvers on iris. Different strategies were proposed in order to manage IFIS syndrome, including several pharmacologic measures, the use of bimanual microincision phacoemulsification with viscous ophthalmic substances with high molecular weight, in association with low-flow fluid parameter and positioning of different mechanical dilating devices [6,40-44]. The pharmacologic measures in IFIS cases included instillation of preoperative atropine 1% [45], intracameral of alpha 1- agonist drugs (phenylephrine, epinephrine) [42,46,47]. Since 2015, Mydrane (Laboratoires Th ea, Clermont-Ferrand, France) was introduced on the market and used as a standardized intracameral mydriatic solution, combining two mydriatics and an anesthetic. The drug was proposed to maximise the dilatation of the pupil during cataract surgery, optimizing the surgery course.

Hargitai, *et al.* showed in their retrospective study the efficacy of a mydriatic cocktail-soak sponge comparative with the conventional dilating pupil drops, in order to obtain a satisfactory pupil dilation in patients taking Tamsulosin [48]. Their conclusion was that patients under treatment with tamsulosin had significantly smaller pupil diameter after nucleus delivery and before IOL implantation compared with the preoperatively pupil size [48].

Iris prolapse through incisions after hydrodissection or first steps of phacoemulsification was present in 21 eyes (52.5%) in group 1 and in 12 eyes (41.38%) in group 2. Hargitai, *et al.* [47] revealed in their study a lower incidence of iris prolapse of 23 - 25% which was inferior to the incidence reported by Chang, *et al* [4].

In our study, systemic hypertension was present in 20 patients (28.99%), 10 (14.49%) had diabetes mellitus, 2 (2.90%) were known with glaucoma and 4 (5.80%) had age related macular degeneration. It was demonstrated by other studies [31,48] that systemic hypertension is a potential risk factor for IFIS. In our study, we observed the presence of complete or partial IFIS syndrome in the group with systemic treatment of ACEIs for hypertension (group 2). Future randomized studies are required to demonstrate our supposition.

## **Conclusion**

IFIS syndrome can influence the course of cataract surgery. Therefore, it is of major concern to identify properly the appearance of the syndrome during the surgery, to use mechanical devices in order to enlarge the pupil and viscoelastic substances in order to deepen the anterior chamber. Furthermore, is crucial to identify all the drugs administrated to the patient potentially inducing IFIS syndrome.

## **Disclosure**

This paper has several limitations that should be acknowledged. This was a retrospective study and there was no randomization. IFIS was subjectively diagnosed intraoperatively. The positive aspects of the study are that we had a large sample of cases and we analyzed the ACEI medication taken by the patients which may increase the risk for IFIS.

## **Data Availability Statement**

The data used to support the findings of this study have not been made available due to General Data Protection Regulation (GDPR)2016/679. The informed consent process did not include the share of individual raw data.

## **Financial Interest**

None.

## **Conflict of Interest**

The authors declare that there is no conflict of interest regarding the publication of this article.

## **Authors' Contributions**

Cristina Ariadna Nicula participated in surgeries, conceived of the study, and was the major contributor in writing the manuscript and in design. Dorin Nicula participated in surgeries, made the analysis and interpretation of data. Anca Maria Rednik helped to collect the data, made the statistical analysis and draft the manuscript. Adriana Bulboaca contributed in its design and coordination. All authors read and approved the final manuscript.

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