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Pupillary Dynamics of Patients on Tamsulosin Exhibiting Intraoperative Floppy Iris Syndrome During Cataract Surgery

Bella J Wolf*, **Chetra Yean, Poonam Misra, Jimmy K Lee, Jeffrey Schultz and Anurag Shrivastava**

Department of Ophthalmology and Visual Sciences, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA

***Corresponding author:** Bella J Wolf, Department of Ophthalmology and Visual Sciences, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA, Tel: +1 7189206665; Fax: +1 7188815439; E-mail: Bellajwolf@gmail.com

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Abstract

Purpose: To examine the pupillary dynamics of patients on tamsulosin who exhibited intraoperative floppy iris syndrome during cataract surgery using the Neuroptics NPi-200 (Irvine, CA), a handheld, digital pupillometer

Setting: Patients who underwent cataract surgery at a University-affiliated eye surgery center

Design: Prospective cohort study

Methods: Pupillary dynamics of patients on tamsulosin and control patients who underwent cataract surgery at an ambulatory surgery center at Montefiore Hospital in the Bronx NY were measured prior to and after dilation for surgery. Measured pupillary dynamics included: resting/maximum pupil diameter (mm), constricted/minimum pupil diameter (mm), constriction latency (ms), constriction velocity (m/s), and dilation velocity (m/s). The operating surgeon, masked to the groups, determined the presence of intraoperative floppy iris syndrome and rated severity based on a grading scale developed from criteria described in the literature. Exclusion criteria included age under 18, concurrent medications known to have autonomic effect, prior ophthalmic laser or incisional surgery, prior diagnosis of optic neuropathy, primary or secondary glaucoma. Two-tailed t-tests were used to compare differences between the two groups. A p-value of <0.05 was considered to be statistically significant.

Results: 15 eyes of 15 tamsulosin patients and 22 eyes of 22 control patients were included. Mean pre-dilation minimum aperture (mm) for tamsulosin patients was significantly smaller than that of control patients (2.24 ± 0.40 *vs.* 2.64 ± 0.73; p=0.05). Similarly, results were approaching significance for the mean pre-dilation maximum diameter in which the tamsulosin group had smaller pupils than controls (3.09 ± 0.70 *vs.* 3.63 ± 0.93; p=0.07), as well as for mean post-dilation maximum diameter in which the tamsulosin group measured had smaller pupils than controls (6.59 ± 1.11 *vs.* 7.20 ± 0.56; p=0.07). All other pupillary dynamics were not significantly different between the two groups. 7 out of 15 (47%) tamsulosin patients experienced IFIS to varying degrees, and of the 7 tamsulosin patients that experienced IFIS, 29% were Grade 1 IFIS, 43% were Grade 2 IFIS, and 29% were Grade 3. Finally, a difference in mean post-dilation maximum diameter (mm) was significant, with IFIS patients being significantly smaller than non-IFIS (5.97 ± 1.12 *vs.* 7.14 ± 0.82; p=0.04).

Conclusion: The pupillometer measured significant differences in pupillary dynamics between patients on tamsulosin and controls. It also identified a statistically significant difference in post dilated maximum pupil size between IFIS patients and non-IFIS patients. Therefore, pupillary dynamics of patients on tamsulosin may be measured prior to surgery to determine if IFIS is likely to occur informing surgeons to use special precautions.

Keywords: Tamsulosin; Intraoperative floppy iris syndrome; Cataract surgery; Pupillometer

Introduction

Intraoperative Floppy Iris Syndrome (IFIS) secondary to Flomax (tamsulosin) exposure was first described by Chang et al. in 2005, and is commonly seen in patients undergoing cataract extraction. The syndrome is characterized by a triad of signs including pupillary miosis, iris billowing, and subsequent iris prolapse. These factors can lead to inadequate pupillary dilation for surgery, and a resultant increased risk of intraoperative posterior capsule rupture [1].

Tamsulosin is an alpha-1A and alpha-1D adrenergic receptor antagonist and is most often prescribed for the treatment of benign prostatic hyperplasia (BPH) [2]. The medication relieves symptoms of urinary retention by relaxing smooth muscle in the prostate and bladder neck. As these same adrenergic receptors additionally exist within various structures of the eye, the medication specifically may lead to alterations in iris dilator muscle anatomic structure and function [2,3]. Pharmacologically, as tamsulosin is known to be an irreversible adrenergic antagonist, even short durations of exposure may have lasting effect [4,5].

Measurement of iris function, while not typically performed prior to routine cataract extraction, can be obtained utilizing infrared pupillometry. Alterations in resting pupil diameter, changes in

constriction and dilation velocities, along with latency to bright light stimulus confrontation, have been described in tamsulosin patients [6]. It is estimated that while roughly 50% of those taking tamsulosin will display features consistent with IFIS, 13.5% will experience intraoperative complications [7]. Given this high rate of surgical complications, a preoperative test allowing surgeons to better predict and risk stratify a patient's relative susceptibility to IFIS would be of benefit. Our aim in this analysis is to evaluate pupillary dynamics in tamsulosin patients as compared to controls, and further determine if there are metrics that predict the likelihood and severity of IFIS in patients taking tamsulosin.

Materials and Methods

Institutional Review Board approval was obtained for a prospective cohort analysis of cataract surgery patients at an ambulatory surgery center at Montefiore Hospital in the Bronx NY, and informed consent was obtained in the preoperative area in compliance with the Declaration of Helsinki. Exclusion criteria included age under 18, concurrent medications known to have autonomic effect, prior ophthalmic laser or incisional surgery, prior diagnosis of optic neuropathy, and primary or secondary glaucoma. All patients were enrolled in the preoperative area prior to their routinely scheduled cataract extraction.

Pupillary measurements were taken with a NeurOptics NPi-200 infrared pupillometer in standardized scotopic ambient lighting, prior to instillation of any preoperative medications. The measurements recorded by the pupillometer included resting/maximum pupil diameter (mm), constricted/minimum pupil diameter (mm), constriction latency (ms), constriction velocity (m/s), and dilation velocity (m/s). The pupillometer was positioned in the visual axis to allow centration and registration of the pupil margin using standard techniques. Measurements were taken prior to the instillation of any preoperative medications.

Patients were then dilated using a standard protocol of 2.5% phenylephrine, 1% tropicamide, and 1% cyclopentolate drops. These medications were administered at three time points (1st set: 0 min, 2nd set: 10 min, 3rd set: 20 min). Ten minutes after the last set of medications was administered, post-dilation pupillary measurements were taken in the same manner and lighting conditions as the preoperative assessment. The recordings for each patient were then electronically transferred to a de-identified database, and the patients were transported to the operating room for cataract extraction by a single attending surgeon.

Immediately following the procedure, the degree of IFIS was assessed utilizing the following grading system devised based upon prior studies [8] and taking into account the three features associated with IFIS first noted by Chang et al. [1]:

Grade 1 (mild): Iris billowing without intraoperative miosis or prolapse.

Grade 2 (moderate): Iris billowing and miosis without iris prolapse.

Grade 3 (severe): Iris billowing and miosis with iris prolapse through any incision.

Use of intraoperative pharmacological agents, pupil expansion devices (such as Malyugin rings or iris hooks), and/or necessity for additional ophthalmic viscoelastic devices (OVD) were furthermore recorded.

Statistical analysis was performed utilizing two-tailed t-tests to compare differences between tamsulosin patients and controls. A p-value of <0.05 was considered to be statistically significant. Pre- and post-dilation pupillary dynamics were compared between the two groups, and then correlated to the incidence and degree of severity of IFIS. Furthermore, a sub-analysis was conducted comparing the pupillary dynamics of tamsulosin patients who developed IFIS with tamsulosin patients who did not.

Results

15 eyes of 15 tamsulosin patients and 22 eyes of 22 control patients were included in the study. Prior to dilation, there were no significant differences in pupil dynamics, such as dilation or constriction velocity, when comparing tamsulosin and control groups. There was a statistically significant difference in the mean pre-dilation minimum aperture (mm) however, for the tamsulosin group compared to controls (2.24 ± 0.40 *vs.* 2.64 ± 0.73; p=0.05), with tamsulosin patients having smaller diameter pupils prior to pharmacological dilation.

		Predilation			Postdilation		
Parameter		**Mean (SD)**	**Mean Difference**	**P Value**	**Mean (SD)**	**Mean Difference**	**P Value**
Maximum aperture (mm)	Control	3.63 (0.93)	-	0.07	7.20 (0.56)	-	0.07
	Tamsulosin	3.09 (0.70)	-0.54		6.59 (1.11)	-0.61	
Minimum aperture (mm)	Control	2.64 (0.73)	-	0.05			
	Tamsulosin	2.24 (0.40)	-0.4				
Percentage change	Control	27.23 (6.49)	-	0.82			
	Tamsulosin	26.62 (7.74)	-0.61				
Constriction velocity (m/s)	Control	1.91 (0.73)	-	0.35			
	Tamsulosin	1.68 (0.69)	-0.23				
Dilation velocity (m/s)	Control	0.85 (0.23)	-	0.49			
	Tamsulosin	0.70 (0.26)	-0.15				

Latency (m/s)	Control	0.27 (0.04)	-	0.79		
	Tamsulosin	0.27 (0.02)	0			

Table 1: Control *vs.* Flomax

A similar relationship was found in maximum aperture (mm) prior to dilation, with tamsulosin patients having smaller pupils than controls (3.09 ± 0.70 *vs.* 3.63 ± 0.93; p=0.07). After dilation, the maximum aperture (mm) in the tamsulosin group compared to controls was 6.59 ± 1.11 *vs.* 7.20 ± 0.56; p=0.07.

		Pre-dilation			**Post-dilation**		
Parameter		**Mean (SD)**	**Mean difference**	**P value**	**Mean (SD)**	**Mean difference**	**P value**
Maximum aperture (mm)	IFIS	3.16 (0.77)	-	0.87	5.97 (1.12)	-	0.04
	Non-IFIS	3.10 (0.69)	-0.06		7.14 (0.82)	1.17	
Minimum aperture (mm)	IFIS	2.18 (0.35)	-	0.49			
	Non-IFIS	2.33 (0.44)	0.15				
Percentage change	IFIS	29.71 (6.92)	-	0.16			
	Non-IFIS	24.00 (7.84)	-5.71				
Constriction velocity (m/s)	IFIS	1.75 (0.55)	-	0.77			
	Non-IFIS	1.64 (0.83)	-0.11				
Dilation velocity (m/s)	IFIS	0.67 (0.19)		0.1			
	Non-IFIS	0.90 (0.28)	0.23				
Latency (ms)	IFIS	0.27 (0.02)		0.69			
	Non-IFIS	0.27 (0.03)	0				

Table 2: Flomax: IFIS *vs.* non-IFIS

Within the tamsulosin group, 7 out of 15 (47%) patients demonstrated clinical signs of IFIS as defined by the predetermined grading criteria. Within this IFIS group, 29% were Grade 1, 43% were Grade 2, and 29% were Grade 3. In terms of operative interventions required, Grade 1 required no additional interventions, whereas Grade 2 and 3 required varying degrees of additional viscoelastic device, intracameral epinephrine, and iris hooks. The mean post-dilation maximum diameter (mm) comparing tamsulosin patients who experienced IFIS with those who did not have signs of iris dysfunction was statistically significant, with the IFIS patients having smaller dilated pupils prior to surgery (5.97 ± 1.12 *vs.* 7.14 ± 0.82, p=0.04).

Discussion

The effects of adrenergic blockade on pupil dilator function, with subsequent increased propensity for IFIS, have been well described in patients exposed to tamsulosin [8-11]. Given an aging demographic, there is an increasing awareness and concern for the intraoperative ophthalmic complications that can occur in patients being treated for BPH [11].

Our results indicate that approximately half of tamsulosin patients experience IFIS, consistent with prevalence measurements in the literature [7]. There remains no reliable preoperative screening test to objectively determine relative risk of IFIS in tamsulosin patients, and our results with a handheld infrared pupillometer demonstrate that pupil size remains the most reliable metric to predict subsequent IFIS. To the best of our knowledge, this study is the first to objectively correlate preoperative pupillometry with subsequent risk of IFIS. We furthermore corroborate prior studies demonstrating that a handheld pupillometer can easily detect and quantify subtle differences in iris function [6].

Patients taking tamsulosin had significantly smaller pupils than controls prior to being pharmacologically dilated, (Table 1), as measured by the average mean minimum diameter (p=0.05), a difference that corroborates prior work by our group [12]. This difference is likely the result of alpha-adrenergic blockade of the iris dilator muscle causing a reduction in tone, and the subsequent relative over-action of the pupillary constrictor muscle. This difference in pupil size between the groups was noted post dilation as well, and approached statistical significance with a p-value of 0.07. Interestingly, the amplitude of pupillary athetosis (hippus), as measured by the percent change between the minimum and maximum pupil diameters, was not significantly different between the controls and the tamsulosin groups (Table 1). Similarly, there were no significant differences within the tamsulosin subgroup with regards to percentage change (Table 2), with p-values of 0.82 and 0.16 respectively.

Within the tamsulosin subgroup (Table 2), when comparing the IFIS to the non-IFIS group, there were no significant differences in baseline pupil size, as measured by both the minimum and maximum pre-dilation diameter (p=0.49 and p=0.87 respectively). However, once the patients were dilated, the patients that went on later to have IFIS had significantly smaller pupils than the non-IFIS patients, with the IFIS patients being on average 1.17 mm less dilated (p=0.04) after receiving the same regiment of dilating drops. This data is confirmatory of what is noted intraoperative, with patients at higher risk of IFIS having smaller pupils initially [6]. Although, even patients with subjectively adequate preoperative dilation may go on to exhibit signs of IFIS during the procedure [2].

The data furthermore confirms prevalence estimates from the literature [7] that approximately half of tamsulosin patients experience some degree of IFIS when compared to patients who have never been exposed to tamsulosin or other similar agents (47% *vs.* 0%, respectively). We furthermore confirm prior studies in which tamsulosin patients were noted to have smaller pupils than controls [6]. These results are intuitive given that tamsulosin selectively antagonizes receptors found in the iris dilator muscle. Conversely, significant reductions in 'constriction velocity' and 'percent change' were not seen in our tamsulosin group.

As our diagnostic tools continue to become more sensitive, subtle pathophysiological changes in function may be able to be more reliably detected, and objective risk assessment may become part of routine preoperative evaluation. At the current time, measurement of pupil size remains the most reliable predictive metric for the development of IFIS, although additional measures and care must be taken with all patients who have had exposure to tamsulosin and similar agents irrespective of preoperative dilation. Timely and appropriate response when IFIS is detected is of course critical in minimizing vision threatening surgical complications regardless of preoperative examination.

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