HIPPOKRATIA 2015, 1, 20-24

ORIGINAL ARTICLE

Research on intraoperative iris behavior in rabbits treated with tamsulosin and finasteride

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Abstract

Aim: The purpose of this study was to investigate intraoperative iris behavior during some phacoemulsification maneuvers in rabbits treated with tamsulosin or finasteride.

Material and Method: An experimental study was conducted on 26 Metis male rabbits aged 1.5 - 2 years, body weight between 3.4 and 5.6 kg, divided into three groups: Group 1 - Control, 6 rabbits; Group 2 - tamsulosin, 10 rabbits; Group 3 - finasteride, 10 rabbits. Dose calculation was performed according to body surface area ratio man/rabbit, taking into account the median lethal dose LD50. Surgery study in rabbits was done over two days by the same specialist using an adapted protocol. He was not informed before or during surgeries which group the animal belonged to, the order being random with a quasi-uniform distribution. Valid results for a modified iris behavior were obtained from two steps of the procedure (cannula irrigation maneuver and irrigation-aspiration). The iris billowing was graded from 0 to 3, according to severity.

Results: The risk of intraoperative iris billowing was higher in rabbits included in tamsulosin group [OR=8.33 (CI 95% 0.63-110.09)], but insignificant statistically compare with control group (p= 0.13). In rabbits treated with finasteride the risk of intraoperative iris billowing is increased compared with those without treatment [OR=11.6 (CI 95% 0.92-147.6)], but insignificant statistically (p= 0.11).

Conclusion: In our research, we showed an increased risk of intraoperative iris billowing in rabbits treated with finasteride, almost similar with those obtained in rabbits treated with tamsulosin. Further experimental or clinical studies to confirm the role of finasteride in the etiology of intraoperative floppy iris syndrome in humans are needed. Hippokratia 2015, 19 (1): 20-24.

Keywords: alpha-blocker, cataract surgery, iris billowing, phacoemulsification

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Introduction

In 2005 Chang and Campbell described the intraoperative floppy iris syndrome (IFIS) during phacoemulsification procedure. This syndrome consists of the following triad: floppy iris (flaccid, atonic iris which flutters because of increased intracameral currents during surgery), iris prolapse through even very small corneal wound and a progressive miosis of the pupil[1].

Several studies showed the association between tamsulosin and the appearance of IFIS during cataract surgery[1,2]. This drug, widely used in the treatment of benign prostate hyperplasia, is a α1 blocker and has binding affinity to the α1A and D receptors of the iris dilator muscle. It is assumed, however, that other substances could trigger similar changes on iris. In a published clinical trial we reported the presence of a pseudo IFIS that could be correlated to the use of anxiolytics[2].

Recently, the appearance of intraoperative floppy iris syndrome during phacoemulsification procedure was noticed in three patients of our patients who were on oral finasteride therapy for benign prostate hyperplasia.

The aim of the current study was to investigate the intraoperative iris behavior during some phacoemulsification maneuvers (cannula irrigation and irrigation-aspiration) in rabbits treated with tamsulosin or finasteride.

Material and Method

We conducted an experimental study which was ap-

Table 1. Distribution of non treated animals (Group 1) by weight, intervention time, operated eye, billowing grade during cannula irrigation and irrigation aspiration.

Group 1 - Control

Animal No.	Weight (kg) Mean ± SD 4.48±0.913	Intervention (date, time)	Eye	Billowing grade cannula irrigation	Billowing grade irrigation aspiration	Total grade
1	5.6	30.05.12	Left	1	0	1
		14:30	Right	2	1	3
2	4.8	30.05.12	Left	0	0	0
		15:55	Right	0	0	0
3	3.6	30.05.12	Left	2	0	2
		15:20	Right	2	0	2
4	5.4	30.05.12	Left	2	0	2
		15:30	Right	1	0	1
5	3.5	30.05.12	Left	1	0	1
		15:36	Right	0	0	0
6	4	30.05.12	Left	1	1	2
		13:13	Right	1	1	2

SD: standard deviation.

Table 2. Distribution of animals treated with Tamsulosin (Group 2) by weight, intervention time, operated eye, billowing grade during cannula irrigation and irrigation aspiration.

Group 2 - tamsulosin 0.4 mg/kg

Animal No.	Weight (kg) Mean ± SD 4.48±0.913	Intervention (date, time)	Eye	Billowing grade cannula irrigation	Billowing grade irrigation aspiration	Total grade	Remarks
T1	4.5	29.05.12	Left	0	0	0	
		14:50	Right	0	0	0	
T2	4.4	29.05.12	Left	3	2	5	
		17:40	Right	2	1	3	
T3	4.8	30.05.12	Left	2	1	3	
		14:02	Right	3	1	4	
T4	4.8	29.05.12	Left	2	1	3	
		16:11	Right	2	1	3	
T5	4.2	29.05.12	Left	-	-	-	incomplete protocol
		15:55	Right	-	-	-	
T6	4	29.05.12	Left	1	0	1	
		18:10	Right	0	0	0	
T7	4	29.05.12	Left	-	-	-	bilateral incomplete
		15:45	Right		-	-	protocol
T8	3.5	30.05.12	Left	1	0	1	
		14:02	Right	1	0	1	
T9	3.6	30.05.12	Left	-	-	-	Left eye
		14:02	Right	3	1	4	- incorect wound
T10	3.6	30.05.12	Left	-	-	-	Left eye
		14:02	Right	2	2	4	- incorect wound

SD: standard deviation.

proved by the Ethical Committee of the University of Medicine and Pharmacy of Tirgu-Mures. All possible steps were taken to avoid animal suffering. According to the "Severity classification of procedures" EU Directive 63/2010, maneuvers performed on anterior chamber of the eye belonged to moderate impact surgery (pain, suffering, distress).

Our study included 26 Metis male rabbits aged 1.5 - 2 years, with body weight 3.4 - 5.6 kg which were divided into three groups: Group 1 consisted of 6 rabbits which did not receive any treatment; Group 2 was formed of 10 rabbits, which received tamsulosin (TAMSOL® 0.4 mg, Gedeon Richter, Romania) 0.4 mg/kg for 43 days; Group 3 was composed of 10 rabbits, which received finasteride (PROSCAR® 5 mg, Merck Sharp & Dohme BV – Holland) 2.5 mg/kg for 43 days. Dose calculation was performed according to body surface area ratio man/rabbit, taking into account the median lethal dose LD_{50}. Drugs were administered through gavage feeding once daily. Tablets were crushed into powder, mixed with distilled water 0.8 - 1.2 mL and emulsifying agent Tween 80 (Croda International PLC Sigmaaldrich, Saint Louis, MO, USA). The operations were performed under general anesthesia, by the same surgeon, masked to animal's medication. He was not informed before or during surgeries which group the animal belonged to, the order being ran-

Table 3. Distribution of animals treated with finasteride (Group 3) by weight, intervention time, operated eye, billowing grade during cannula irrigation and irrigation aspiration.

Group 3 – Finasteride 2.5 mg/kg

Animal No.	Weight (kg) Mean ± SD 4.48±0.913	Intervention (date, time)	Eye	Billowing grade cannula irrigation	Billowing grade irrigation aspiration	Total grade	Remarks
F1	3.5	29.05.12	Left	1	0	1	
		17:55	Right	2	1	3	
F2	3.8	29.05.12	Left	1	0	1	
		17:00	Right	2	1	3	
F3	4.4	29.05.12	Left	0	0	0	
		16:25	Right	2	1	3	
F4	5	29.05.12	Left	2	0	2	
		16:45	Right	1	0	1	
F5	4.2	29.05.12	Left	3	2	5	
		18:10	Right	3	2	5	
F6	4.8	30.05.12	Left	3	2	5	
		14:10	Right	3	2	5	
F7	4.4	29.05.12	Left	2	1	3	
		18:30	Right	1	1	2	
F8	3.5	29.05.12	Left	1	1	2	
		17:48	Right	1	1	2	
F9	4.4	29.05.12	Left	2	1	3	
		18:19	Right	3	1	4	
F10	4.4	30.05.12	Left	0	0	0	Increased dosage
		15:00	Right	0	0	0	of anesthetic drug

SD: standard deviation.

Table 4. Risk of intraoperative iris billowing in non-treated animals (control), in animals treated with tamsulosin and in those treated with finasteride.

Medication risk factor (>=3)	Potential to induce complications			OR (CI:95%)	p value
	Present	Absent	Total		
Tamsulosin	5	3	8	8.33 (0.63-110.09)	0.13*
Finasteride	7	3	10	11.6 (0.92-147.6)	0.11**
Control	1	5	6	-	-

*Fisher's exact test: Comparison between Group 1 - Control and Group 2 – tamsulosin.
**Fisher's exact test: Comparison between Group 1 - Control and Group 3 – finasteride.
OR: odds ratio, CI: confidence interval.

dom with a quasi-uniform distribution. Anesthesia consisted of intramuscular administration of 10 mg/kg xylazine (solution 20 mg/mL) 10 minutes before 40 mg/kg ketamine (solution 100 mg/mL) with gradual induction over 5-10 minutes. Full sedation was obtained after 20 minutes. Few animals needed an increased dose of 20 mg ketamine (0.2 mL).

Surgical protocol included the following steps: Betadine was instilled in the conjunctival bag; The surgeon used a phacoemulsification platform, and intracameral maneuvers were done through one main incision of 2.2 mm and two side ports of 1.2 mm; Only irrigation-aspiration and cannula irrigation maneuvers were carried out as these induced in the anterior chamber identical turbulence with those observed in humans' phacoemulsification procedures. Irrigation-aspiration parameters were: vacuum 300 mmHg continuous, and aspiration 30 mL/min linear. Cannula irrigation was performed without causing injuries to the lens. In some cases, iris sampling biopsies were taken for histopathological anlysis. At the end of intervention, antibiotic (1 drop of 5 mg/ml moxifloxacin) was instilled into the conjunctival bag.

The investigated criteria in our study were: pupil miosis, iris billowing and iris prolapse.

We considered the following grades according to the billowing appearance: Grade 0 - without billowing; Grade 1 - mild billowing; Grade 2 - moderate billowing; Grade 3 - severe billowing.

Statistical analyses were performed using MedCalc Software (Version 12.3.0 bvba, Marikerke, Belgium). Data were considered as nominal or quantitative variables. Nominal variables were characterized using frequencies. Quantitative variables were tested for normality of distribution using the Kolmogorov-Smirnov test and were characterized by mean and standard deviation (SD). Student's t-tests were used to assess differences between continuous variables (expressed as mean/SD), and Fisher's exact test for quantitative variables. A significance level of 0.05 was used for all analyses, and all reported p values are two-tailed.

Results

Pupil miosis and iris prolapse were not noticed during surgical maneuvers.

In the Control group rabbits' mean ± SD weight was 4.48 ± 0.913 (minimum 3.5, maximum 5.6 kg). We recorded only few cases in which the iris behavior changed during intervention (Table1). From 12 operated eyes, we noticed the following total grade of iris billowing: 0 in 25.0%, 1 in 25.0%, 2 was recorded in 41.7%, and 3 in 8.3%.

In rabbits treated with tamsulosin (Group 2) mean ± SD weight was 4.14 ± 0.483 (minimum 3.5, maximum 4.8 kg). We observed that cannula maneuver induced grade 3 of iris billowing in 3 eyes and grade 2 in 5 eyes. During irrigation-aspiration maneuver, grade 2 was recorded in 2 eyes (Table 2). Total grade of iris billowing was 0 in 21.4%, 1 in 21.4%, 3 in 28.6%, 4 in 21.4%, and 5 in 7.1% of the operated eyes.

In Group 3, mean ± SD weight was 4.24 ± 0.503 (minimum 3.5, maximum 5.0 kg). Grade 3 of iris billowing appeared in 5 eyes during cannula irrigation, and grade 2 in 4 eyes after irrigation-aspiration procedure (Table 3). Iris billowing total grade 0 was recorded in 15.0%, 1 in 15.0%, 2 in 20.0%, 3 in 25%, 4 in 5.0% and 5 in 20.0% of rabbits treated with finasteride.

The comparison between groups is recorded in Table 4. In our study, there were no statistically significant differences between groups in terms of animal means mass ($p>0.05$). The risk of intraoperative iris billowing was higher in rabbits included in tamsulosin group compared with those without treatment [OR=8.33 (CI 95% 0.63-110.09)], but without clear difference, statistically significant ($p=0.13$).

By comparing Group 1 (Control) and Group 3 (finasteride) there were no statistically significant differences ($p=0.11$). In rabbits treated with finasteride the risk of intraoperative iris billowing was increased compared to those without treatment [OR=11.6 (CI 95% 0.92-147.6)]. The results are almost similar compared to those obtained in rabbits treated with tamsulosin.

Discussion

In the current experimental study we noticed that the number of eyes which developed changes of the iris behavior in rabbits treated with tamsulosin and finasteride as well as the grade of iris billowing increased compared to the Control group. Furthermore, the comparison between treated rabbits and those without therapy showed an approximately similar risk in developing complications in animals treated with tamsulosin or finasteride.

The mechanisms through which medications induce changes of iris behavior during surgical procedures are not entirely known. In 1967, Walls revealed a unique morphologic relationship between pigment epithelium and iris smooth muscle cells that influences drug action[3].

Pupil diameter is influenced by a complex balance of multiple neural pathways (serotonine, dopamine, peptide, kinine systems) and mediators (prostaglandins, nitric oxide, endothelin) are involved[4].

Nitric oxide relaxes the iris sphincter and dilator. In congestive heart failure, malfunction in its homeostasis occurs. Iris's endothelin receptor blockers, drugs used for diabetes mellitus and arterial hypertension, may contribute to relaxation of smooth muscle[5].

Saw Palmetto extract is a natural remedy which can be found in multivitamin preparations. There are reported cases of IFIS appearance in patients who used this extract to treat benign prostate hyperplasia[6].

Sympathetic and parasympathetic complementary action through adrenergic receptors (α1, α2, β1, β2), respective cholinergic muscarinic agents (M1-5), is responsible for pupil motility[4]. Nine types of adrenergic receptors are described in human as well as in rabbit iris (these bind the endogenous catecholamines, epinephrine and norepinephrine): α1A, α1B, α1D, α2A, α2B, α2C, β1, β2, β3. Alpha receptors contribute to dilator smooth muscle contraction through α1 type: α1A subtype beeing involved in the dilator contraction which produces mydriasis; α1B is present in the arterioles of the iris contributing only on their constrictions. β receptors are involved in the relaxation of iris smooth muscle dilator[4].

A recent study by Goseki *et al* concluded that high affinity of alpha-blockers for α1 adrenergic receptors is an important factor for the appearance of IFIS. Furthermore, drug/melanin interaction causing dilator muscle atrophy is probably the other important mechanism for IFIS[7].

Several studies revealed the association between IFIS and selective α1 blockers treatment, such as tamsulosin used in urinary retention from benign prostate hyperplasia.

Although the improvement of lower urinary tract symptoms occurs after a longer period of treatment compaired to alpha-blocker medication, finasteride is reccomended by some authors as a first-line treatment for benign prostate hyperplasia, whether or not cataract is present[8]. A degree of uncertainty of this claim is brought by few case reports[9-11], as well as by our clinical observation, in which a possible correlation between finasteride and IFIS is described.

Finasteride is a 5α-reductase inhibitor which lowers the level of dihydrotestosterone, thus reducing the hypertrophy of the prostate. It seems to have binding affinity to androgen receptors. Androgen receptors are found in skin, liver and prostate. finasteride could be used in benign prostate hyperplasia, prevention of urological symptoms such as acute urological retention, treatment of androgenic alopecia, and to reduce the risk of prostate cancer (a reduction of 25-30% in men over 55 years)[12]. Chatterjee S *et al* showed that finasteride can be an effective inhibitor for vascular endothelial growth factor receptor[13].

Currently we know that the iris dilator muscle is composed of myoepithelial cells which have different types of receptors, like α1 adrenergic receptor[14]. We do not know if the iris has androgen receptors or not.

The limitations of our study are the small number of

animals and the short period of finasteride administration (drug was available only for 43 days). Despite these limitations, p-values in Table 4 still achieve a level of certainty of 87% and 89% for tamsulosin and finasteride respectively. Furthermore, because iris changes in patients treated with finasteride are reported in a very small number of studies, the widespread use of this pharmaceutical preparation requires paying attention to any effects that might occur during ophthalmic surgery, until better quality evidence becomes available. Ophthalmic surgeons are advised of the possibility of an iris billowing in patients receiving 5α-reductase inhibitors and it may be justified to take measures accordingly, to minimize the occurrence of complications that would jeopardize the success of surgery. Although in our experimental study we did not find statistically significant differences between the behavior of rabbits treated with finasteride and rabbits included in the control group, we believe that the changes observed may raise questions concerning the action of 5α-reductase inhibitor on iris behavior.

Conclusion

We were not able to show an increased risk of intraoperative iris changes, almost similar in the two groups of rabbits treated with tamsulosin and finasteride due to our study limitations. It is unclear whether finasteride can cause IFIS. Furher studies are needed to confirm or to deny a possible interaction between finasteride, the androgenic receptors and the myoepithelial cells of the iris dilator.

Conflict of Interest

The authors report no conflict of interest.

Acknowledgement

The study has been reported in abstract form and oral presentation at ASCRS (American Society of Cataract and Refractive Surgery) Meeting, San Francisco, April 2013.

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