Intraoperative floppy-iris syndrome

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ABSTRACT

Objective: Intraoperative-floppy iris syndrome (IFIS) has been recently described. It has been demonstrated that this new syndrome complicates cataract surgery. In this paper we have reviewed the syndrome, and offer practical information specially related to the origin and management of this syndrome and we offer practical information.

Material and methods: A review of the related medical literature using PubMed and Cochrane databases. Combining the search terms tamsulosin, cataract, IFIS and intraoperative floppy iris syndrome, more than 200 articles were found. Eighty-two of them were obtained and analyzed. In the remaining only the abstract could be studied.

Results: The aetiological association between IFIS and tamsulosin (and to a lesser degree between IFIS and other alpha-antagonists) is well established. Other aetiological associations are doubtful. Most of the literature is centered on cataract surgery. However, a similar syndrome has been described during trabeculectomy. A possible association between these drugs and choroidal detachments has also been described. Undoubtedly tamsulosin treatment makes cataract surgery more difficult and increases the probability of intraoperative complications. Protocols to manage the syndrome have not yet been developed. Intracameral injection of alpha-adrenergic agonists seems to be useful. However, there is no evidence of the usefulness of discontinuing the drug or using preoperative mydriatics.

Conclusion: The aetiological and clinic features of the syndrome are well established. More studies are needed to provide scientific evidence on the most appropriate way to cope with this syndrome.

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Síndrome del iris flácido intraoperatorio

Resumen

Objetivos: Recientemente se ha descrito el síndrome del iris flácido intraoperatorio (IFIS). Este síndrome complica la cirugía de catarata. Con este trabajo pretendemos revisar el síndrome, y ofrecer información práctica, especialmente en relación con los aspectos etiológicos y terapéuticos del mismo.

Palabras clave:
IFIS
Síndrome del iris flácido intraoperatorio

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Tamsulosina
Catarata
Receptor adrenérgico alfa1A

Material y métodos: Revisión de la literatura biomédica relacionada, utilizando las bases de datos PubMed y Cochrane. Combiniando los términos tamsulosin, cataract, IFIS e intraoperative floppy iris syndrome se identifican más de 200 articulos. Ochenta y 2 pudieron ser localizados y estudiados. En los restantes se estudió el resumen.

Resultados: La asociación etiológica con la tamsulosina, y en menor medida con los restantes antagonistas de los receptores alfa, está bien establecida. Otras posibles asociaciones etiológicas son más dudosas. Aunque la mayor parte de los articulos se centran en la cirugía de catarata, también se ha documentado la aparición de un síndrome similar durante trabeculectomía, y se ha descrito la asociación de los antagonistas alfa con desprendimientos coroídeos. El consumo de tamsulosina hace más difícil la cirugía de catarata y aumenta la probabilidad de que se produzcan complicaciones. La forma más adecuada de manejar el síndrome no está protocolizada. La inyección intracameral de un agonista alfa adrenérgico mejora el comportamiento del iris. No existe evidencia científica de que suspender el fármaco o el uso de mióditicos preoperatorios resulte útil.

Conclusiones: Los aspectos etiológicos y clínicos del síndrome están bien establecidos. Se precisan estudios que aporten evidencia científica sobre la forma más adecuada de manejar este síndrome.

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Introduction

In 2005, Chang and Campbell published an article describing a new syndrome which they named intraoperative floppy iris syndrome [IFIS] which they related to the consumption of tamsulosin. Since then, interest in this syndrome has grown and to date over two hundred articles have been published on this topic.

The significance of this new syndrome is derived from three facts. Firstly, tamsulosin is a very frequently prescribed drug (there is a clear tendency toward medical treatment for benign prostate hypertrophy). Secondly, cataract surgery is the most common surgical procedure. Thirdly, the appearance of this syndrome is an unquestionable factor which increases the difficulty of the surgery and the probability of complications. A number of articles have been published not only in the ophthalmological but also in general biomedical literature which leave no doubt at all that an important number of complications which arise during cataract surgery in recent years are attributable to the consumption of tamsulosin.

While the syndrome is very well defined from the aetiological, physiopathological and clinical viewpoints, the fact remains that the most adequate management is far from being protocolized. There is no scientific evidence to support the usefulness of the withdrawal of tamsulosin or the application of presurgery mydriatics.

Historical review

Six years ago, Chang and Campbell published an article under the title Intraoperative floppy iris syndrome associated with tamsulosin which for the first time related this syndrome with the use of tamsulosin. Until then, the situation was not systematically defined as a syndrome although many ophthalmologists were aware that in some situations the patient experienced an incomprehensible loss of pupil dilatation during surgery. In said paper, Chang and Campbell published the first series and classified the findings to categorize the entity as a syndrome. The new syndrome was defined on the basis of three criteria: poor initial mirosis, sudden loss of pupil dilatation during surgery and a tendency toward iris prolapse through the incisions. The study criteria combined in varying degrees during surgery, increasing the probability of complications.

Epidemiology

This syndrome appears in 0.5–2% of the general population but has an incidence of about 60% in patients who consumed tamsulosin at the time or had consumed it in the past. A review published by the American and European Cataract Surgery Societies established an odds ratio (OR) of 206.5 with a confidence interval of 50.9–836.5, estimating a relative risk (RR) of 99.3 with a confidence interval of 30–327.8. On very few occasions OR and RR of this magnitude have been published in biomedical literature.

Some studies considered that benign prostate hypertrophy affects half of the male population over 50 and 90% of males over 85. As regards cataracts, a prevalence of 20% is estimated for the age group between 65 and 74 years, and this prevalence is of 50% in the age group over 75. The prevalence of cataracts doubles every decade after 40 years of age and there is no doubt that cataract surgery is the most frequent surgery (it is estimated that in the United States about 2,000,000 cataract surgeries are performed each year). It is easy to understand that both entities go together in a very high percentage of the adult male population.

In recent years, improvements in alpha receptor antagonist drugs have brought about changes in the therapeutic approach to benign prostate hypertrophy, to the point that pharmacological treatment is more frequent nowadays than a few years back. In addition, the increased safety of alpha 1A receptor antagonist drugs has made them the most prescribed drugs. Precisely this group of drugs has been clearly related to the appearance of IFIS. Of all the adrenergic alpha receptor blocker drugs available at present to treat obstructive prostate disease,
Tamsulosin and alfuzosin are more prescribed than terazosin and doxazosin because they are better tolerated. As prostate problems and cataracts affect the same age group, both situations combine in a significant percentage giving rise to IFIS which clearly is a factor in the prognosis of cataract surgery.

Considering the aging of the population in Western countries and the tendency toward medically treating benign prostate hypertrophy, this problem will be increasingly frequent in our environment. At any rate, we must not believe that this syndrome exclusively affects males because alpha receptor antagonists are also applied for treating arterial hypertension, as adjuvant in the treatment of nephrolithiasis and are applied compassionately for treating urine retention in females.

**Etiology**

It is believed that the syndrome is due to alpha 1A receptor inhibition by tamsulosin and is characterized by poor midriasis, flaccid iris and a tendency toward iris prolapse through corneal incisions. It is estimated that this complication appears in at least half of the patients taking tamsulosin and even though some studies suggest a possible association of this syndrome with other drugs, the fact is that the majority of referred cases are related to the use of alpha-1 antagonists (Table 1).

**Tamsulosin**

Tamsulosin (tamsulosin hydrochloride) is a molecule belonging to the group of sulfonamides. It was introduced in 1994 to treat symptoms produced by benign prostate hypertrophy. As in many cases patients do not know the active principle of the drugs they consume, it is important to know the trademarks under which this drug is marketed. In Spain there are at least commercial presentations (Omic, angeneric Tamsulosina, Tamsulosina bexal, Tamsulosina edigen, Tamsulosina Gp-pharm, Tamsulosina Merk, Tamsulosina Ratiopharm, Tamsulosina Sandoz, Tamsulosina stada, Tamsulosina teva, Urolosin). It is administered in a daily dosage of 0.4 mg after breakfast. In addition, there is a slow release formula named OCAS (oral controlled absorption system) that has a mean life of approximately 24 h.

In Japan a considerably lower incidence of this syndrome has been reported in patients who use tamsulosin (38 vs 63% in the original series). This discrepancy is probably due to the fact that the recommended dosage in Japan for treating benign prostate hypertrophy is lower than the recommended dosage in the United States and Europe (0.2 mg against 0.4 mg).

Tamsulosin is a competitive antagonist and for this reason the intracameral administration of phenylephrine or noradrenaline can displace it and improve miosis. The mean life of the drug in serum is of 14–15 h and its distribution volume is of 161, which is consistent with a mainly extracellular distribution. It is excreted through the liver (via cytochrome P450) and kidney. However, the mean life of the drug in the body as well as its metabolites is unknown. In the case of the ocular globe, it is particularly complicated to determine this because the retina and iris pigment epithelium can act as a reservoir for some drugs.

Even though the expression of the syndrome has been documented months or even years after terminating tamsulosin treatment, most authors agree in that there is a certain reversibility. Some suggest suspending the drug one week prior to surgery. For these reasons it would be advisable to refer these patients to the ophthalmology practice before prescribing treatment with tamsulosin.

**Other possible risk factors for developing the syndrome**

This syndrome has also been described in relation to other alpha receptor antagonists such as terazosin, doxazosin, alfuzosin, prazosin and indoramine, and beta receptors such as labetalol or even with other groups of drugs, including antipsychotics such as chlorpromazine, zuclopenthixole or risperidone, antidepressants such as mianserin, s alpha reductase inhibitors such as finasteride or with dietary supplements or health food products such as a palm extract known as saw palmetto (serenoa repens). The latter association, which is surprising in a first approach, is justifiable because the extracts of this plant have demonstrated high affinity for muscarinic and alpha-adrenergic receptors in the urinary tract of rats (Table 1).

Be that as it may, the fact remains that the greater part of the literature evidences a particularly close relationship with tamsulosin. One of the papers mentioned above studied 92 eyes and found an OR of 32.15 between tamsulosin and alfuzosin toward the former. In a recently published article, a drug called doxazosin, which is broadly prescribed for treating
arterial hypertension, did not exhibit a significant association with the probability of exhibiting the syndrome.\textsuperscript{10}

The publications that related the syndrome with zuclopentixol, finasteride and mianserin reported only individual cases.\textsuperscript{12,25,26} Taking into account that the majority of elderly patients take multiple medications and that in many cases they are not fully knowledgeable about them, it is likely that these associations described in individual cases are not real.

The possible association with arterial hypertension and antihypertensive drugs (above all angiotensin inhibitors) could explain some of the IFIS cases in patients who have not consumed tamsulosin and the expression of this syndrome in women.\textsuperscript{29} In fact, a recently published meta-analysis demonstrated the existence of this association as independent of the drugs being administered.\textsuperscript{30}

The association with other alpha receptor antagonist drugs is more consistent than with the previous drugs. Even so, recent prospective design studies were not able to demonstrate an association with doxazosin after analyzing 1842 cataract surgeries (Table 1).\textsuperscript{10} As doxazosin is broadly prescribed for treating arterial hypertension, probably its use does not produce the syndrome or, if it does, its effects are of a small degree to the point that a prospective study of this sample size is unable to detect. Even so, it is true that in the case of doxazosin there is no standard dosage as in the case of tamsulosin because the dosage is adapted to patient response.

Table 1 – Etiological agents involved in the flaccid iris syndrome.

<table>
<thead>
<tr>
<th>Etiological agent</th>
<th>Pharmacological group</th>
<th>Author (year)</th>
<th>Number of cases</th>
<th>Study design and conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamsulosin</td>
<td>Alpha blocker (specific to RA1A)</td>
<td>Chang (2005)</td>
<td>16 cases/706 surgeries</td>
<td>Retrospective and prospective, double design. Initial article defining the syndrome and identifying the etiological agents</td>
</tr>
<tr>
<td>Zuclopentixol</td>
<td>Antipsychotic agent. Dopaminergic but also alpha-1 serotoninergic and adrenergic receptor blocker</td>
<td>Pringle (2005)</td>
<td>1 case</td>
<td>Case report</td>
</tr>
<tr>
<td>Risperidon</td>
<td>Antipsychotic agent. It blocks adrenergic and serotoninergic receptors</td>
<td>Ford (2009)</td>
<td>3 cases (2 pacientes)</td>
<td>Case report</td>
</tr>
<tr>
<td>Mianserin</td>
<td>Antidepressants that blocks serotoninergic, histaminergic, alpha-1 and alpha-2 receptors</td>
<td>Ugarte (2007)</td>
<td>1 case</td>
<td>Case report</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Beta blocker (and weak alpha blocker)</td>
<td>Calotti (2007)</td>
<td>1 case</td>
<td>Observational</td>
</tr>
<tr>
<td>Saw palmetto extract</td>
<td>Health food shop product obtained from a palm tree (serenoa repens). It has exhibited muscarinic and alpha-adrenergic receptor blocking properties in the urinary tract of rats</td>
<td>Yeu (2007)</td>
<td>2 cases</td>
<td>Case report</td>
</tr>
<tr>
<td>Vitamin complexes</td>
<td>Antioxidant vitamin complex obtainable without prescription</td>
<td>Seth (2010)</td>
<td>2 cases</td>
<td>Case report</td>
</tr>
<tr>
<td>Alfuzosin</td>
<td>Alpha blocker (nonspecific to receptor 1A)</td>
<td>Blouin (2007)</td>
<td>22 patients in treatment with tamsulosin and 13 patients in treatment with alfuzosine</td>
<td>Prospective OR appearance of the syndrome of 32.15 toward tamsulosin</td>
</tr>
<tr>
<td>Finasteride</td>
<td>5-alpha-reductase inhibitor (it inhibits the formation of dihydrotestosterone)</td>
<td>Issa (2007)</td>
<td>2 cases</td>
<td>Case report</td>
</tr>
<tr>
<td>Alpha-blockers</td>
<td>Alpha blockers</td>
<td>Chadha (2008)</td>
<td>74 cases</td>
<td>Tamsulosin clearly involved; doxazosine not associated; diabetes mellitus not associated</td>
</tr>
<tr>
<td>Prazosin</td>
<td>Alpha blocker</td>
<td>Issa (2008)</td>
<td>2 cases</td>
<td>Prospective study</td>
</tr>
<tr>
<td>Indoramin</td>
<td>Alpha blocker</td>
<td>Issa (2008)</td>
<td>1 case</td>
<td>Prospective study</td>
</tr>
<tr>
<td>Angiotensin inhibitors</td>
<td>Inhibiting the angiotensin conversion enzyme</td>
<td>Neff (2009)</td>
<td>Multivariate analysis of 899 cases</td>
<td>IFIS more frequent in patients with arterial hypertension. However, multivariate analysis does not demonstrate association with antihypertensive drugs</td>
</tr>
</tbody>
</table>
and this could explain greater variability in the severity of the syndrome. In what concerns alfuzosin, as commented above, the appearance of IFIS has been described but with an OR significantly lower to that of tamsulosin of “only” 32.15. The administration of bunazosin, another alpha receptor antagonist utilized in treating ocular hypertension and glaucoma, does not produce the syndrome despite the high concentration that can be reached in the anterior chamber after topical administration. Once again, the explanation is found at the molecular level. Bunazosin is a nonspecific alpha antagonist for receptors 1A, 17

Recently the FDA has approved a new alpha antagonist: silodosin, launched in the United States in October 2008 and more recently in Europe. Silodosin has a very high affinity for alpha 1A receptors and even though to date there are no published studies it can be assumed that it will also exhibit high floppy iris syndrome incidence.4

In what concerns the possible relationship with diabetes mellitus, a disease related for a number of years to poor pupil midriasis probably due to the associated diabetic neuropathy, after analyzing 1842 surgical procedures said article did not find any association with the syndrome.10

Accordingly, it can be concluded that even though other drugs and conditions could be involved in the expression of the syndrome, without a doubt the use of tamsulosin constitutes the most important risk factor for its appearance as it has exhibited a very strong association in the majority of studies.

Does the association of IFIS with tamsulosin fulfill the cause criteria?

(1) Strength of the association: this criterion is undeniably fulfilled because, as commented above, the OR in the majority of studies is very high. The possible influence of confusion factors seems highly improbable, at least at this point. A Surgeon General report in the mid-seventies demonstrated for the first time the existence of an aetiological relationship between tobacco and mortality due to lung cancer, establishing an OR of 10.33 Since then this association has become a paradigm of aetiological studies. In the case of the association between tamsulosin and IFIS, the OR is a three-digit number, i.e., an association at least 20 times more intense. A recently published meta-analysis confirmed the intensity of this association.30

(2) Consistency: this criterion is also fulfilled because the association has been broadly proved in literature by a large range of research groups.

(3) Temporal precedence of the cause: undoubtedly fulfilled

(4) Biological gradient: this criterion is also fulfilled because the dosage administered in Japan is lower and the incidence of the syndrome is also lower in that country.

(5) Biological plausibility: the selectiveness of tamsulosin for alpha 1A receptors clearly explains the pathogeny of the syndrome; therefore, it can be concluded that this criterion is also fulfilled.

(6) Experimental evidence: this criterion also seems to be fulfilled due to the probable and relative reversibility when the drug is withdrawn a period of time prior to surgery.

Finally, the specificity criteria, which are not considered to be essential by most authors because rarely that can be demonstrated, are also present in this association. The majority of articles agree in that it is a side effect which, if not pathognomic, is at least a highly selective side effect of this drug.

### Physiopathology

From the physiopathological viewpoint it is believed that the syndrome is due to the fact that the continued inhibition of the pupil dilating muscle leads to its atrophy. The consequence is poor or intermediate initial midriasis which is largely lost during surgery. After hydrodissection the loss of pupil midriasis is characteristic. The lack of tone in the iris makes it behave as the sail of a ship which is continuously wobbling until it finally prolapses through the incisions. For all these reasons, the duration of the surgery is significantly extended and the probability of complications is increased (Table 2). As the syndrome is not due to the lack of elasticity of the pupil sphincter, the pupil stretching maneuvers and the execution of sphincterotomies are not effective. Therefore, the surgeon is frequently obliged to carry out a number of mechanical maneuvers to maintain midriasis during surgery, such as the application of iris retractors.3

In addition, many aspects of the syndrome are yet to be resolved. It is surprising that hypersensitivity due to deinervation does not arise or that the syndrome may appear even years after terminating its use. For these reasons, some authors proposed alternative approaches to prevent the locking of iridial vessel adrenergic receptors.6,34

### Table 2 – Syndrome-related complications.

<table>
<thead>
<tr>
<th>Syndrome-related complications</th>
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<tr>
<td>Iris atrophy</td>
</tr>
<tr>
<td>Posterior capsule rupture</td>
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<tr>
<td>Zonular deinsertion</td>
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<tr>
<td>Vitreorrugia</td>
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<tr>
<td>Iridodialysis</td>
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<tr>
<td>Post-surger hypertensive peak</td>
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<tr>
<td>Hyphema</td>
</tr>
<tr>
<td>Diplopia and photophobia due</td>
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<tr>
<td>to iris lesion</td>
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### Alpha receptors

Even though adrenergic receptors were subdivided into large groups on the basis of their cellular effects, the current classification is based on their affinity for certain synthetic ligands. Subsequently, adrenergic receptors were divided into various subclasses after studies made with endogenous and cloned receptors.35,36

Alpha 1A adrenergic receptors can be pharmacologically differentiated according to their high affinity for phenylephrine agonist and prazosin antagonist. These are extended throughout the body and reach important concentrations in the liver, heart, vessel walls, intestine and genital-urinary system as well as in the central and peripheral nervous system.

The alpha 1A receptor has the molecular structure of a membrane receptor and is linked to a G protein. When the receptor is stimulated by the appropriate hormone, in the case
of adrenaline or noradrenaline, it activates the production of cyclic AMP and activates a protein-kinase.

To date, 3 subtypes of-alpha-1 receptors have been identified (alpha 1A, alpha 1B, alpha 1D). The alpha 1C receptor is not included because it has become known that the initially cloned gene encodes for a subtype of alpha 1A receptor. Since the mid-nineties it is known that receptor alpha 1A predominates in the prostate and in the iris dilating muscle, both in rabbits as in humans. About 70% of receptors in the prostate are of the alpha 1A type (Fig. 2). Receptor alpha 1B has a vasoconstrictor action and alpha 1D is present in the detrusor muscle. Tamsulosin is the only selective antagonist for alpha 1A receptors. In vitro and animal studies have determined that tamsulosin has an affinity 20 times greater for receptor alpha 1A than for receptor alpha 1B. This selectivity explains its high cardiovascular safety (with tamsulosin postural hypotension is much more infrequent than with other alpha antagonists), and could explain to a large extent the specificity of the syndrome not with a pharmacological group but with a specific molecule.

Iris atrophy

Since the beginning, the chronological behavior of the syndrome attracted a lot of attention. The syndrome is described as appearing 3 days after beginning the use of tamsulosin up to several years after terminating it. It is believed that the persistence of this effect is due to the fact that the continued locking of the alpha receptor causes the pupil dilator muscle to atrophy. These morphological changes have been confirmed in 2 recent studies. The first was an in vivo demonstration by means of optic coherence tomography (OCT) exhibiting a significant reduction of the overall iris thickness in the group of drug consuming patients. The second study was a histological analysis of 51 corpse eyes and was not able to demonstrate overall iris thinning although it did exhibit a significant reduction in the thickness of the pupil dilator muscle.

Even though said atrophy was attributed to the chronic locking of the pupil dilator muscle adrenergic receptors, the fact remains that the mechanism is not clear. The expression of the alpha 1A receptor has been documented in the smooth muscle of the arterioles that irrigate iridian tissue. For this reason, some authors believe that the atrophy could be regulated by tissue ischemia. It has also been proposed that the sympathetic locking induced by the use of said drug could also induce pigment changes in the iris.

Clinical aspects

Usual clinic

In their initial article, Chang and Campbell defined the syndrome as a triad (intraoperative loss of initial midriasis, tendency to iris prolapse through iris incisions and iris flaccidity) (Fig. 3). This definition has not changed in recent years and many studies assess the presence of one, 2 or 3 of these elements to quantify the severity of the syndrome (Table 3).

Other possible expressions of the syndrome

Tamsulosin has been related to iris prolapse during trabeculectomy, which is easy to understand. For this reason, some authors consider that nonperforating techniques would be indicated in these patients. If a perforating technique is executed, the insertion of 2 iris hooks at III and VI h will tense the iris and prevent prolapse during trabeculectomy.

| Table 3 – Syndrome severity classification (taken from Manvikar). |
|------------------|------------------|
| Grade 0          | Good dilatation, midriasis maintained |
| Grade 1          | Good initial dilatation, subsequent constriction |
| Grade 2          | Intermediate initial midriasis, subsequent constriction |
| Grade 3          | Poor dilatation from the beginning |

Fig. 2 – Scheme showing the distribution of adrenergic receptors in the urinary system. Receptor alpha 1A makes up the majority of receptors in the prostate and urethra. It also makes up the majority of receptors in the pupil dilator muscle. The specificity of tamsulosin for this receptor explains the specific relationship of the syndrome with this drug.

Fig. 3 – Probably the most effective technique is the utilization of mechanical devices such as iris hooks.
Additional associations have been reported which are more difficult to justify with choroidal detachments.\textsuperscript{35,46} There are 2 studies published on this topic and both reported only individual cases and also both reported the disappearance of the detachment when the use of the drug was discontinued. One of the studies reported 3 choroidal detachment episodes in a single patient, related to the use of terazosin, tamsulosin and saw palmetto extract. This could lead us to think that the association is casual were it not for the withdrawal of the antagonist whereupon the choroidal detachment disappeared and its reintroduction caused the repetition of the detachment on 2 occasions. It is likely that alpha receptors, in addition to being present in the anterior uvea, could also be present in the posterior uvea. In fact, it has been demonstrated that alpha 1A receptor is the most abundant receptor in rabbit choroids. However, the high frequency of tamsulosin use and the fact that these are the only 2 published cases casts doubts on said association.

In addition, it has been suggested that the use of tamsulosin could interfere with some diagnostic tests such as the apraclonidine test utilized for diagnosing Horner syndrome as an explanation for some of the false negatives published in the literature.\textsuperscript{47}

**Prognostic implications**

Even though the use of tamsulosin will depend on the prevalence of benign prostate hypertrophy and the prescription habits of urologists, it is estimated that between 5% and 10% of male patients who underwent surgery have received or are receiving said treatment. The fact that some studies find a 40% higher incidence of complications in patients exhibiting this syndrome (iris atrophy (Fig. 4), post-surgery hypertensive peak, iris dyslasia, hyphema, diplonia or photophobia due to iris lesion, capsule rupture, zonule deinsertion and vitreorrasia) portrays the true transcendence of the syndrome (Table 2).\textsuperscript{13}

A study recently published in JAMA leaves no room for doubt. Overall, the study analyzed 96,128 surgical procedures carried out in males over 66 between 2002 and 2007 in the Canadian province of Ontario. Until then, the parameter applied by most of the papers was the evaluation of the surgery according to the surgeon. In this retrospective study totally free from the bias of the non-blind interpretation of the surgery by the surgeon, the probability that the patient required a second procedure in the 2 weeks after cataract surgery was 2.3 times higher in the group that had used tamsulosin.\textsuperscript{2} Considering that most of the complications are resolved intraoperatively, that only a small percentage of complicated patients required a second surgery and that only 4 procedures were included (vitrectomy, vitreous aspiration or injection, extraction of a dislocated lens fragment or air–liquid exchange) gives us an idea about the true dimensions of this syndrome. At any rate, the syndrome was described in 2005 and this retrospective paper includes surgical procedures carried out between 2002 and 2007. It is safe to say that nowadays the improved knowledge of the syndrome and the surgeon’s ability to predict and manage it adequately will significantly reduce the impact of the use of these drugs on the prognosis of cataract surgery.

**Treatment**

Without a doubt the best strategy to treat the syndrome would be to avoid it. Perhaps the phakic condition of the subject should be considered as a relative contraindication to initiate treatment with tamsulosin. Some authors believe that these patients should undergo an ophthalmological assessment to identify cataracts before beginning treatment with Alpha receptor antagonist drugs and, if present, surgically remove them first. If the patient exhibits very severe urinary symptoms making the ophthalmological evaluation unfeasible, the initial treatment could be limited to some alpha receptor antagonists that block the alpha 1A receptor in a non-specific manner (alfuzosin, terazosin o doxazosin). It is true that terazosin and doxazosin can produce orthostatic hypotension, but with alfuzosin this hypotension is also infrequent and the syndrome incidence with alfuzosin is 30 times lower than with tamsulosin. This apparently simple approach is not possible today because in the past 5 years “urological literature” has published very few articles on this topic\textsuperscript{39,48-51} and urologists are not aware of the ophthalmological significance of prescribing this treatment.\textsuperscript{8}

The best treatment begins in the practice with a good clinical record which systematically inquires about the present or past use of these drugs. Having this information will facilitate the preparation of surgery and avoid unexpected and subsequent surprises.

From the surgical viewpoint, multiple strategies have been proposed to manage the syndrome, including suspending tamsulosin, pre-medicating with atropine, injecting intracameral phenylephrine and using high density viscoelastics.\textsuperscript{39,52,53} Of all these, the best is probably the injection of an alpha agonist (phenylephrine or adrenaline) in the anterior chamber during surgery. Even so, occasionally the surgeon is obliged to...
apply mechanical devices such as iris hooks or the Malyugin ring to maintain adequate mi- diasis.\textsuperscript{54}

**Is it useful to suspend the use of the drug?**

Initially, as the inhibition is reversible, suspending the use of the drug should be efficient. An increased response to adrenergic eyedrops should be expected even as a consequence of hypersensitivity due to de-innervation. However, changes induced by tamsulosin are not only functional. Atrophy of the iris and the pupil dilator muscle recently demonstrated in vivo by means of anterior segment OCT as well as in vitro in corpse eyes demonstrate that the syndrome can appear even years after interrupting the use of the drug.\textsuperscript{40,41}

The first of the above-mentioned studies, published in May 2009 by Prata et al., compared 29 patients who were receiving or had received treatment with Alpha receptor blockers with 22 control patients. The control group exhibited a mean thickness of the iris in the region of the pupil dilator muscle of 447 μm against 355 μm in the group who had received treatment with Alpha receptor antagonist drugs.\textsuperscript{40} This reduction of nearly 100 μm demonstrates at least partially the irreversible nature of the syndrome.

The second study made a histological review of 51 corpse eyes from 27 patients (14 had been exposed to the drug and 13 were controls). A statistically significant reduction was observed in the thickness of the pupil dilator muscle (8.5 μm in the control group against 6.53 μm in the group exposed to tamsulosin).\textsuperscript{41} Accordingly, suspending treatment with said drug is partially inefficient and in any case we must not forget that the patient could be exposed to urinary retention.

**Presurgery atropine**

One of the first strategies to be proposed was the use of atropine a few days prior to surgery.\textsuperscript{55} Arguments for this approach indicates that it is as effective as intracameral phenylephrine but without the risk of anterior segment toxic syndrome. However, there is no scientific evidence supporting the usefulness of this approach and, taking into account that the syndrome is due to the blockage of adrenergic receptors and that there is no involvement of colinergic receptors, the use of atropine does not seem entirely justified (Table 4).

Some authors believe that the use of atropine improves initial mi-diasis even though the intensity of the syndrome is not reduced.\textsuperscript{56} We must not forget that the use of atropine, above all combined with discontinuation of the drug, exposes the patient to the risk of urinary retention. An interesting study published in 2009 compared 2 pharmacological strategies for preventing the syndrome. The first included suspending the alpha blocker drug for at least 7 days prior to surgery, administering 1% atropine starting 3 days before the surgery and utilizing intracameral lidocaine. The second strategy also included suspending the use of the drug and applying a solution of adrenaline (1/12,000) and lidocaine through the intracameral pathway.\textsuperscript{57} The second strategy proved to be superior, apparently evidencing that the use of atropine does not make a significant contribution. Speculatively it could even be said that the use of atropine could be damaging because, by improving the presurgery pupil diameter but not the severity of the syndrome, the surgeon could be misled into a false feeling of safety.

**Use of intra-surgery adrenergic agonists**

As the inhibition is theoretically reversible, the injection of phenylephrine or adrenaline in high concentrations in the anterior chamber should displace tamsulosin from alpha receptors. With this measure, many times the pupil dilatation increase is not achieved although it is returned to its initial dilatation and above all the rigidity of the iris is improved, thus reducing the flaccidity and tendency toward herniation. This is probably the most efficient measure after the implant of mechanical devices.\textsuperscript{39,52,53,57–60} However, there is no absolute consensus in the literature. A recent article found a higher degree of IFIS in patients who were administered intracameral adrenaline. It is likely that this biased conclusion is due to its retrospective nature wherein the pupil diameter became a confusion factor (the surgeon decided to utilize adrenaline in patients exhibiting lower pupil diameter, who are the ones who most likely would develop a more severe form of IFIS) (Table 4).\textsuperscript{60}

The most adequate manner of preparing intracameral phenylephrine is not protocolized. Some articles proposed preparing the phenylephrine as follows: dilute 0.25 ml of 2.5% phenylephrine without preservatives in 2 ml of balanced saline solution (BSS). Other articles combine 0.25 ml with 1 ml BSS. Although some previous studies did not demonstrate that similar solutions would cause endothelial loss and given that the maximum effect is achieved in a few seconds, it is preferable to wash the solution after 30s. However, this phenylephrine preservative-free formulation is not available in the Spanish market and therefore in this country it seems more recommendable to use intracameral adrenaline.\textsuperscript{39,52,57}

In what concerns intracameral adrenaline, its use has been proposed in isolation (in a range of concentrations from 1/4000 to 1/10,000, diluting the commercial solution of 1/1000 between 4 and 10 times) as well as in combination with other substances. The use of lidocaine in these solutions is important as it relaxes the tone of the pupil sphincter muscle. A very popular solution is nicknamed epi-Shugarcaine (epi-S) and is prepared on the basis of lidocaine of 4%, epinephrine 1/1000 and BSS.\textsuperscript{58,59} The final concentration of the solution is epinephrine 0.025% and lidocaine 0.75%. A recent study demonstrated that this solution is slightly superior to the Lundberg solution (cyclopentolate 0.1, phenylephrine 1.5 and lidocaine 1%).\textsuperscript{59} The authors recorded the surgeries and subsequent measured midiasis at 4 stages thereof (beginning, minute one, after the injection of viscoelastic and at the end) and in the 4 stages the adrenaline solution was superior. The authors explained that this slightly higher efficacy of the adrenaline solution over that containing phenylephrine is because the latter is a selective agonist for alpha receptors whereas adrenaline stimulates the alpha and beta receptors, and the stimulation of the latter relaxes the pupil sphincter muscle.\textsuperscript{59} The main problem of the adrenaline solution, which is recognized by the authors of said study, is its limited stabil- ity. Catecholamines oxidize much faster than phenylephrine
Table 4 – Pharmacologically strategies applied in syndrome management.

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Author (year)</th>
<th>Design</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracameral phenylephrine</td>
<td>Manvikar (2006)</td>
<td>Prospective (no controls, no blind); 32 cases</td>
<td>The use of phenylephrine improved rigidity</td>
</tr>
<tr>
<td>Atropine</td>
<td>Bendel (2006)</td>
<td>First I without atropine, second eye with atropine. No details were given about material and methods; 14 cases</td>
<td>Effective, free of the toxicity risks of phenylephrine; midriasis maintained at 4 mm, against 2 mm of the eye untreated with atropine; surgery time reduced 50%; retractors not required</td>
</tr>
<tr>
<td>Intracameral phenylephrine</td>
<td>Gurbaxani (2007)</td>
<td>Prospective (no controls, no blind); 7 cases</td>
<td>Flaccidity improved; retractors not required</td>
</tr>
<tr>
<td>Combination of topical atropine and intracameral epinephrine</td>
<td>Masket (2007)</td>
<td>20 cases, no controls</td>
<td>Flaccidity improved; only one case required the use of retractors</td>
</tr>
<tr>
<td>Intracameral 5% adrenaline and lidocaine</td>
<td>Pérez Silguero (2009)</td>
<td>33 cases, 17 patients; comparative with the use of free surgery topical atropine</td>
<td>Slight IFIS in only 3 cases; strategy superior to suspending drug and applying topical atropine 2 days before surgery</td>
</tr>
</tbody>
</table>

and therefore the solution, once prepared, is efficient only for a few hours.59 It seems that said solutions are well tolerated and do not cause significant endothelial loss during conventional cataract surgery where most of the solution is washed almost immediately and the time of contact with the endothelium is very short. However, the toxic effect of adrenaline at a concentration of 1/10,000 has been documented in other surgeries where the immediate washing of the solution does not occur such as in intraocular lens (IOL) replacements.60

Some authors proposed the combination of both pharmacological strategies (presurgery topical atropine and intracameral phenylephrine) with nearly 100% success (19 of the 20 patients of the study did not exhibit any expression of IFIS).56 Table 4 summarizes the main pharmacological strategies utilized in the management of the syndrome.62

The use of said solutions, injected at the beginning of the surgery, is very efficient to stabilize the pupil and prevent iris herniation. Accordingly, having good clinical records showing whether the patient has consumed or is consuming said drugs is crucial. If this information is not included in the clinical records and the solution is injected in an advanced stage of the surgery after the patient has presented iris prolapse, the pupil will probably stabilize and flaccidity would improve but, due to the alteration of the herniated iris tissue, the tendency to prolapse will persist. Therefore, the preparation of an exhaustive clinical record is essential even though this is not always easy because frequently elderly patients are not fully aware of the drugs they consume and in some countries tamsulosin is sold over-the-counter, without requiring medical prescription.

Mechanical devices

Obtaining an adequate pupil surface is one of the most important factors for cataract surgery to be carried out safely. Given that the pupil area increases with the square of the pupil radius, it is easy to understand that small changes in the diameter will become significant in the pupil surface. For example, increasing the pupil diameter from 5 mm to 7 mm involves doubling the pupil area.

For the above reasons, a range of mechanical devices have been available for a number of years, some of which are quite imaginative (Table 5). These devices were designed to increase the pupil surface in patients who did not react sufficiently well to pharmacological methods. The most widely
used mechanical devices are iris retractors (Fig. 3). Other less widespread devices on the market are methacrylate rings (5 S Pupil Ring, Perfect Pupil), silicone rings (Graether silicone pupil expansion ring) and recently the foldable Malyugin ring made in polypropylene, known as the “Russian solution for poor midriasis”. It allows obtaining midriasis of 6 mm. According to Chang it is easier and faster to implant than with traditional iris hooks. As on many occasions the loss of midriasis occurs just after hydrodissection, if reasonable doubts arise the use of these devices from the beginning is recommendable. A recent article suggests the possibility of anchoring the ring with a vicryl suture to prevent its possible dislocation toward the vitreous cavity in case of posterior capsule rupture.

The use of iris hooks also is different in the syndrome when compared to other situations. Here, the surgeon is facing a double problem (narrow pupil and flaccid iridien stroma). Placing the iris hooks following the conventional square scheme risks iris herniation because it stretches it over the area of the main incision. For this reason, the diamond shaped configuration is better. This alternative configuration has 3 advantages: firstly, it reduces the tendency to herniation because the iris is retracted behind the main incision; secondly, the phako tip does not impact against the stretched iris, and thirdly

<table>
<thead>
<tr>
<th>Device</th>
<th>Material description</th>
<th>Pupil diameter</th>
<th>Advantages</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iris retractors</td>
<td>Silastic sleeve nylon</td>
<td>Square having corneal diameter as maximum diameter</td>
<td>Easy availability, Low cost</td>
<td>Detailed manipulation, time requirement</td>
</tr>
<tr>
<td></td>
<td>Grieshaber (Kennesau, GA, USA)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>Howard Instruments (Tuscaloosa, AL, USA)</td>
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<td></td>
<td>Katena Products (Denville, NJ, USA)</td>
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<tr>
<td>Morcher Ring</td>
<td>PMMA</td>
<td>59 mm</td>
<td>Includes arm to facilitate handling</td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td>(Morcher, Stuttgart, Germany)</td>
<td></td>
<td>Does not require injector</td>
<td></td>
</tr>
<tr>
<td>Perfect pupil</td>
<td>Polyurethane</td>
<td>7.8 mm</td>
<td>Cost</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Milvella, Sydney, Australia)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graether</td>
<td>Silicone</td>
<td>7 mm</td>
<td>Elastic, more difficult to handle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(EagleVision, Memphis, TN, USA)</td>
<td></td>
<td>Requires injector</td>
<td></td>
</tr>
<tr>
<td>Malyugin</td>
<td>Polypropylene 5-0</td>
<td>6 mm</td>
<td>Easy and fast implantation and extraction</td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td>(MST, Microsurgical Technology)</td>
<td></td>
<td>Requires injector</td>
<td></td>
</tr>
<tr>
<td>Healon 5</td>
<td>Hyaluronidate 2.3%</td>
<td>Variable</td>
<td>Low cost and easy availability</td>
<td>Midriasis not stable</td>
</tr>
<tr>
<td></td>
<td>(Abbott Medical Optics)</td>
<td></td>
<td>Does not require injector</td>
<td>Not valid for very small pupils</td>
</tr>
</tbody>
</table>
the surgeon has more space for performing surgical maneuvers because the operating area is the diagonal of the square formed by the hooks.65,76 The authors of this article suggest that, in case of iris herniation occurring in the pupil having an acceptable size, a good solution could be placing a single sub-incisional iris hook.

**Which are the most appropriate parameters?**

It is likely that, from the technical viewpoint, the first priority is a good incision always in a clear and valved cornea as far as possible from the root of the iris. Although the literature does not clearly define the most appropriate phacoemulsification technique, generally the use of soft fluids is recommended (for example: <25 cm²/min; 200–250 mmHg) to reduce iris wobbling and increase the permanence time of the high-density viscoelastic. Some authors state that bimanual techniques can be superior to coaxial techniques. By separating irrigation and aspiration, the iris diaphragm is stabilized and thus the irrigation flow can be directed “against” the iris and therefore reduce its tendency toward herniation.71

It is recommendable to utilize aspiration terminals equipped with silicone sleeves in order to achieve adequate adjustment.72 In addition, it is recommended to be very careful during the IOL injection phase as it could be accidentally engaged with the herniated iris, inducing dialysis thereof.72

The use of high-density viscoelastic such as 2.3% hyaluronic acid (Healon 5®, Abbott Medical Optics)62 is also useful to stabilize the iris. In this regard, it is likely that the use of torsion devices could also be beneficial, as well as the use of capsular staining because, if the use of retractors is required at a subsequent stage, it should be easy to implant them if the edge of the capsulorhexis is stained.62 However, all these statements are merely speculative opinions based on individual complications, because there is no study that has compared various phacoemulsification techniques and such an endeavor would be exceedingly difficult.

**Conflict of interests**

No conflict of interests has been declared by the authors.

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