European Journal of Ophthalmology / Vol. 14 no. 5, 2004 / pp. 394-400

The effects of cyclopentolate on intraocular pressure and retrobulbar hemodynamics in patients with pseudoexfoliation syndrome and pseudoexfoliation glaucoma

P. TANER[1], B. UNAL[2], E. DEMIRBAŞ[1], A. ERGIN[1]

[1]Ophthalmology Department
[2]Radiology Department, Kırıkkale University Faculty of Medicine, Kırıkkale - Turkey

PURPOSE. *To evaluate the changes of intraocular pressure (IOP) and retrobulbar hemodynamics after cyclopentolate administration in patients with pseudoexfoliation syndrome and pseudoexfoliation glaucoma.*

METHODS. *Eighteen patients with pseudoexfoliation syndrome and 18 patients with pseudoexfoliation glaucoma were enrolled in the study. After baseline measurements of IOP, the peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistivity index (RI) of the ophthalmic, central retinal, and posterior ciliary arteries were investigated by color Doppler imaging. Then, 1% cyclopentolate was instilled in one eye of each subject. After 45 minutes of instillation of the cyclopentolate, the measurements of IOP and retrobulbar blood flow velocities were repeated. The results were compared with those of 20 age-matched normal subjects.*

RESULTS. *Neither IOP nor retrobulbar blood flow velocities changed significantly in control subjects after cyclopentolate administration. IOP increased significantly after cyclopentolate instillation in pseudoexfoliation syndrome ($p=0.004$). Retrobulbar blood velocities did not change significantly after the cyclopentolate in this group. In pseudoexfoliation glaucoma group, it was observed that basal mean IOP showed a statistically significant increase after cyclopentolate drop ($p=0.002$). Although blood flow velocities of ophthalmic artery did not change significantly, PSV and EDV of the central retinal and posterior ciliary arteries decreased significantly ($p<0.05$) and RI of the posterior ciliary artery increased significantly ($p=0.01$) after cyclopentolate instillation.*

CONCLUSIONS. *On the basis of our findings, pseudoexfoliation appears to be a predictive factor for an IOP rise after cyclopentolate. In pseudoexfoliation glaucoma patients, an increase of IOP after cyclopentolate could lead to a decreased retrobulbar blood flow. IOP must be rechecked after cyclopentolate administration in these patients to avoid further damage to the ganglion cells. (Eur J Ophthalmol 2004; 14: 394-400)*

KEY WORDS. *Pseudoexfoliation syndrome, Pseudoexfoliation glaucoma, Cyclopentolate, Color Doppler imaging*

Accepted: April 13, 2004

1120-6721/394-07$15.00/0

INTRODUCTION

Cyclopentolate is regularly and more widely used to dilate pupils in ophthalmology practice. In 1943, Kronfeld et al (1) reported that some eyes with open angles may develop increased intraocular pressure (IOP) while under mydriasis even though no angle narrowing occurs. Gallin (2) and Harris (3) have repeatedly investigated the effects of mydriatics on IOP in normal subjects and open angle glaucoma patients. Their data indicate that the incidence of IOP elevation of 6 mmHg or more after cyclopentolate drop is 23% in a population with open angle glaucoma and only 2% in a normal population. In 1976, Valle (4) reported that significant IOP elevations (8 mmHg or more) after 1% cyclopentolate drop were encountered frequently in eyes with pseudoexfoliation. Interestingly, it was also indicated that pseudoexfoliation glaucoma was diagnosed immediately or later in all pseudoexfoliation syndrome eyes that displayed a >5 mmHg IOP elevation after cyclopentolate drops. Recently, Hancox et al (5) reported that two patients with primary open angle and pseudoexfoliation glaucoma developed a >10 mmHg sustained rise in IOP following cyclopentolate drops.

It has been suggested that acute IOP elevation that occurred artificially has direct and immediate consequences for central retinal (6) and posterior ciliary (7) arterial hemodynamics in healthy subjects. In other words, perfusion of the retina and optic nerve head critically depends on IOP. It is well recognized that an acute elevation of IOP may occur following mydriasis with cyclopentolate in patients with pseudoexfoliation. It remains unclear, however, whether retrobulbar hemodynamic alterations occur after cyclopentolate in these patients. Thus we aimed to understand whether an increase of IOP related to cyclopentolate can lead to clinical important results.

Color Doppler imaging (CDI) provides a reliable noninvasive diagnostic method for analyzing velocity of blood flow. It has been increasingly used in the assessment of many pathologies affecting orbital hemodynamics (8-10). In the present study, we aimed to investigate the changes of IOP and retrobulbar hemodynamics in patients with pseudoexfoliation syndrome and pseudoexfoliation glaucoma after topical cyclopentolate.

MATERIALS AND METHODS

Fifty-six patients entered into the study were monitored in the Ophthalmology Department of the Medical Faculty of Kırıkkale University. Of those, 18 patients had pseudoexfoliation glaucoma, 18 had pseudoexfoliative syndrome, and 20 had no ocular pathologic findings except for refractive errors as controls. The study was approved by the review board and all participants reviewed and signed informed consent statements before entering the study. A detailed medical and ophthalmic history was recorded. Each patient's age, sex, iris color, and current systemic medication were recorded. Evaluation of Snellen visual acuity test, biomicroscopy of the anterior segment, measurement of IOP with Goldmann applanation tonometry, iridocorneal angle evaluation with Goldmann three-mirror contact lenses, and funduscopic examination after dilatation of the pupils with 0.5% tropicamide using a Goldmann three-mirror contact lens were performed in all patients. Cup/disk ratio was noted. Visual field examinations were performed with program 30-2 on the Humphrey Visual Field Analyzer (Humphrey Instruments, San Leandro, CA). Patients with eye diseases other than pseudoexfoliation syndrome, pseudoexfoliation glaucoma, and mild cataract and those with uncontrolled diabetes mellitus or systemic hypertension, hypertensive or diabetic retinopathy, a history of transient ischemic attacks or stroke, a history of eye surgery, or any other pathologic findings upon ophthalmologic examination were not included in the study. Investigation of IOP and retrobulbar blood flow after cyclopentolate drops was performed on the same day and in the morning to avoid the diurnal effects of IOP.

Pseudoexfoliation syndrome was determined as the presence of pseudoexfoliation material on the anterior lens capsule or near the pupil or as presence of transillumination defects near the pupil associated with normal cup/disk ratio and visual field findings and IOP less than 21 mmHg. IOP was repeatedly measured in different days and three measurements were performed in different hours of the day. Conversely, the diagnosis of pseudoexfoliation glaucoma was made by the presence of the following criteria: pseudoexfoliation material on the anterior lens capsule or near the pupil, transillumination defects near the pupil, IOP

more than 21 mmHg, typical glaucomatous optic disk findings (e.g., thinning or notching of the neural rim in the superior or inferior temporal area), and visual field defects. Glaucomatous visual field defects were determined as a minimum presence of a cluster of three abnormal points in the same hemifield with pattern deviation less than 2% in the probability map of the Humphrey automated perimeter with at least one point less than 1%, or at least two adjacent points with pattern deviation less than 1%. In each patient, the eye that was affected in the unilaterally affected patients or the eye with more advanced glaucomatous findings in bilaterally affected patients was evaluated. In the control group, the eye was chosen randomly. Of the 18 pseudoexfoliation glaucoma patients, 8 were newly diagnosed cases and they were untreated. The other 10 patients were treated with various antiglaucomatous treatment. Four were on topical levobunolol (Betagan, Abdi Ibrahim, Turkey) and pilocarpine 2% (Pilomin, Abdi Ibrahim) and the others were on topical Cosopt (Merck-Sharp-Dohme). They were taken off all medications for 3 weeks before the study.

After initial IOP and retrobulbar blood flow velocities measurements, 1% cyclopentolate (Sikloplejin 1%, Abdi Ibrahim) was instilled in only one eye of each subject. After 45 minutes of instillation of the cyclopentolate drop, the measurements of IOP and retrobulbar blood flow velocities were repeated.

Patients with IOP more than 25mm Hg after the instillation of cyclopentolate were treated with acetazolamide (Diazomid, Sanofi-Synthelabo) after the end of the test procedure. Their IOP was rechecked every 30 minutes until it began to fall below 21 mmHg.

Intraocular pressure measurements

Goldmann applanation tonometry was used to measure IOP. All readings were taken by a single observer (P.T.) after training and validation.

Color Doppler imaging

All participants underwent blood flow velocity assessment of their ophthalmic artery (OA), central retinal artery (CRA), and posterior ciliary artery (PCA) by means of CDI (Logic 400, General Electric, Milwaukee, WI) with 7.5-MHz linear phase-array transducer. All CDI measurements were performed by the same experienced radiologist (B.U.) who was masked to the clinical diagnosis. The transducer was applied gently to the closed eyelid using a coupling gel, and care was taken to avoid applying pressure to the eye during examination. Patients were in supine position, with the upper body tilted upward at about a 30-degree angle. The various vessels were examined following a standard protocol, as described previously (10). In each vessel, peak systolic velocity (PSV) and end diastolic velocity (EDV) were measured. The resistivity index (RI) was calculated as follows: (PSV–EDV)/PSV. The OA was traced approximately 10 to 15 mm behind the globe, nasal to the optic nerve after their crossing. The CRA was depicted within the anterior part of the optic nerve shadow, approximately 2 to 3 mm behind the surface of the optic disk. The PCA begin as trunks approximately 10 to 20 mm behind the globe, before they form multiple branches surrounding the optic nerve in its retrobulbar portion. This location was chosen for CDI measurements of PCA.

Statistical analysis

The data were compared with SPSS 11.0 for Windows (SPSS Inc., Chicago, IL) statistical package, statistical analyses. Differences between the means of measured parameters within the groups before and after the cyclopentolate instillation were compared by using paired samples t-test. Likelihood ratio chi-square test was performed to analyze the frequency of IOP rising ≥6 mm Hg between pseudoexfoliation syndrome and pseudoexfoliation glaucoma groups. Statistical significance was accepted at $p<0.05$.

RESULTS

Demographic features of all participants are shown in Table I. No significant differences were observed with respect to mean age or the presence of diabetes mellitus or systemic hypertension among the groups. The mean IOP was found to be significantly different among the groups ($p<0.05$).

In the pseudoexfoliation syndrome group, basal mean IOP showed a statistically significant increase after cyclopentolate drop (18.0±1.64, 19.8±2.69, respec-

TABLE I - DEMOGRAPHIC FEATURES OF PARTICIPANTS

Characteristics	Pseudoexfoliation glaucoma (n=18)	Pseudoexfoliation syndrome (n=18)	Control group (n=20)
Age, y, mean ± standard deviation	69.5±5.5	71.3±5.7	69.7±6.4
Female	8	9	9
Male	10	9	11
Systemic hypertension	8	6	6
Diabetes mellitus	4	3	4
Resting heart rate, beats/min	65	67	65
Resting blood pressure, Systolic/diastolic, mmHg	133/85	130/85	130/85

No differences were significant

TABLE II - INTRAOCULAR PRESSURE AND RETROBULBAR BLOOD FLOW VELOCITIES BEFORE AND AFTER THE CYCLOPENTOLATE DROP

Artery		Basal	After cyclopentolate	p value
Ophthalmic				
PSV	PXG	35.10±4.33	35.18±4.34	0.600
	PXS	36.90±3.82	36.67±3.93	0.532
	Control	36.56±5.03	35.98±5.18	0.123
EDV	PXG	7.58±0.46	7.71±1.31	0.314
	PXS	7.43±0.89	7.33±1.31	0.651
	Control	8.20±1.23	7.94±1.31	0.078
RI	PXG	0.77±0.02	0.77±0.02	0.936
	PXS	0.78±0.02	0.80±0.02	0.057
	Control	0.76±0.02	0.77±0.02	0.088
Central retinal				
PSV	PXG	10.46±1.38	9.73±2.11	0.014
	PXS	10.56±1.71	10.33±1.86	0.398
	Control	10.52±1.64	10.58±1.51	0.620
EDV	PXG	2.96±0.58	2.64±0.72	0.015
	PXS	3.16±0.66	3.08±0.82	0.562
	Control	3.63±0.50	3.53±0.50	0.076
RI	PXG	0.71±0.04	0.72±0.04	0.106
	PXS	0.69±0.05	0.69±0.04	0.828
	Control	0.64±0.02	0.65±0.01	0.059
Posterior ciliary				
PSV	PXG	13.68±1.46	12.62±1.74	0.001
	PXS	13.28±1.75	13.01±1.97	0.181
	Control	15.53±1.47	15.83±1.19	0.062
EDV	PXG	4.54±0.53	4.02±0.66	0.002
	PXS	4.69±0.85	4.46±0.98	0.117
	Control	5.16±0.72	5.12±0.71	0.558
RI	PXG	0.65±0.03	0.67±0.04	0.01
	PXS	0.66±0.03	0.67±0.04	0.148
	Control	0.66±0.02	0.67±0.03	0.159
IOP	PXG	25.7±2.29	28.7±4.0	0.002
	PXS	18.0±1.64	19.8±2.69	0.004
	Control	16.4±1.9	16.6±1.9	0.606

Values are mean ± standard deviation. PSV = Peak systolic velocity; PXG = Pseudoexfoliation glaucoma; PXS = Pseudoexfoliation syndrome; EDV = End-diastolic velocity; RI = Resistive index; IOP = Intraocular pressure

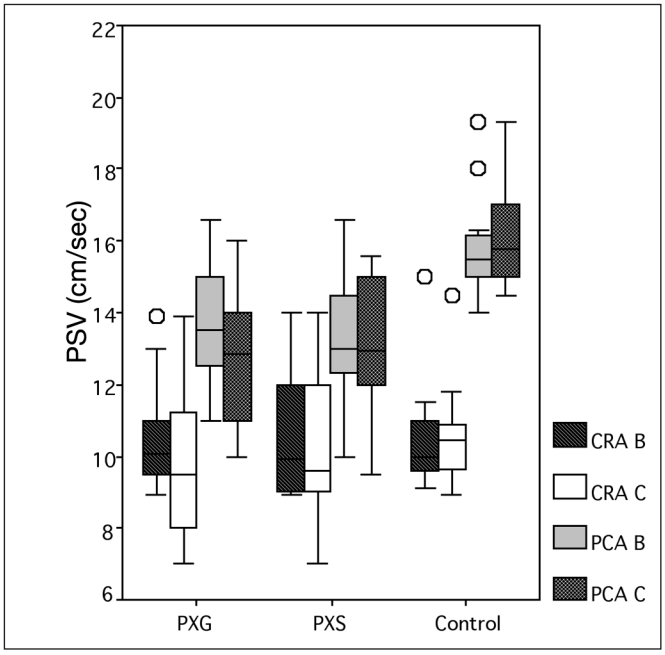

Fig. 1 - *Distribution plot of the peak systolic velocity (PSV) of central retinal (CRA B: baseline, CRA C: after cyclopentolate) and posterior ciliary arteries (PCA B: baseline, PCA C: after cyclopentolate). PXG = Pseudoexfoliation glaucoma; PXS = Pseudoexfoliation syndrome; O = Extreme values.*

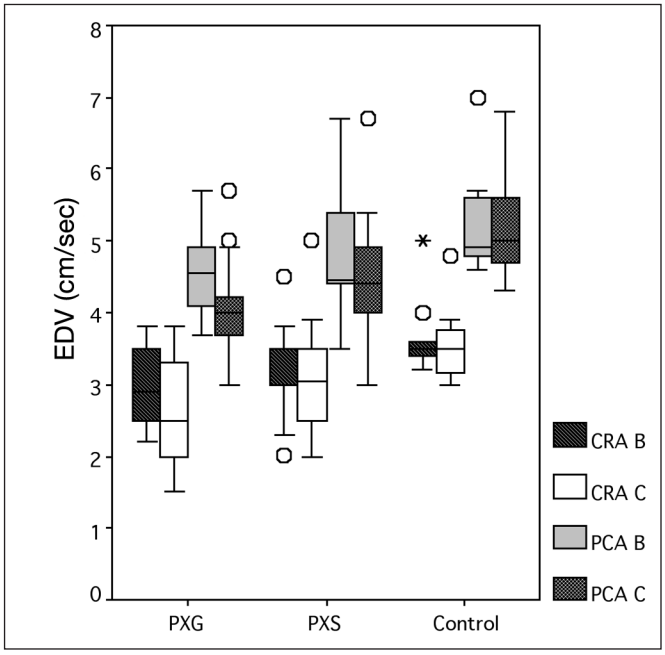

Fig. 2 - *Distribution plot of the end diastolic velocity (EDV) of central retinal (CRA B: baseline, CRA C: after cyclopentolate) and posterior ciliary arteries (PCA B: baseline, PCA C: after cyclopentolate). PXG = Ppseudoexfoliation glaucoma; PXS = Pseudoexfoliation syndrome; O = Extreme values.*

tively, p=0.004) (Tab. II). Blood flow velocities of OA, CRA, and PCA did not change after cyclopentolate drop administration (p>0.05) (Tab. II, Figs. 1-3). In this group, 1 patient (5.6%) had an acute IOP rise of 6 mmHg or more.

In the pseudoexfoliation glaucoma group, it was observed that basal mean IOP showed a statistically significant increase after cyclopentolate drop (25.7±2.29, 28.77±4.05, respectively, p=0.002) (Tab. II). Although blood flow velocities of OA did not change significantly after cyclopentolate instillation (p>0.05), PSV and EDV of the CRA and PCA decreased significantly (p<0.05). RI of the PCA showed a statistically significant increase (p=0.01) (Tab. II, Figs. 1-3). In this group 7 patients had an abrupt rise of IOP (6 mm Hg or more). The frequency of IOP rise ≥ 6 mmHg was significantly higher in this group than in pseudoexfoliation syndrome (p=0.002).

In the control group, no significant changes were observed in IOP and blood flow velocities of retrobulbar arteries after cyclopentolate administration (Tab. II, Figs. 1-3).

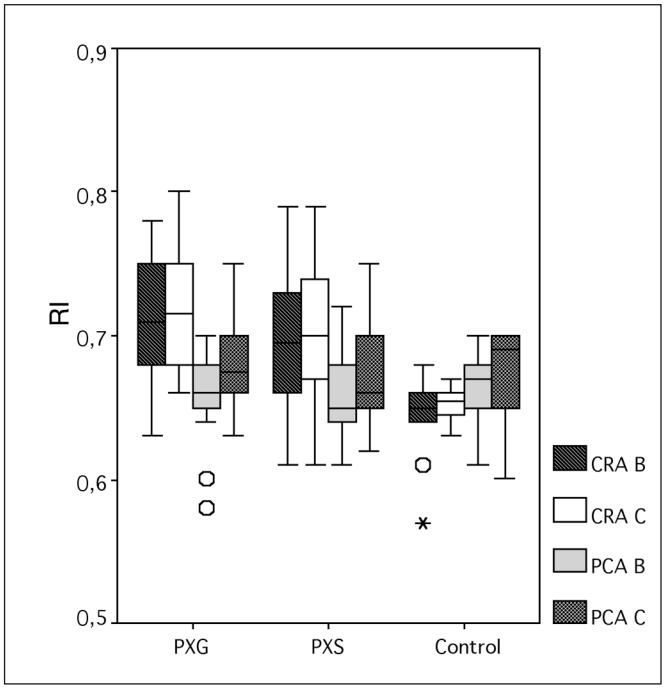

Fig. 3 - *Distribution plot of the resistive indices (RI) of central retinal (CRA B: baseline, CRA C: after cyclopentolate) and posterior ciliary arteries (PCA B: baseline, PCA C: after cyclopentolate). PXG = Pseudoexfoliation glaucoma; PXS = Pseudoexfoliation syndrome; O = Extreme values.*

DISCUSSION

Pseudoexfoliation manifests clinically as characteristic fibrillar protein deposits in the anterior segment of the eye (11). It is definitively established that subjects with pseudoexfoliation syndrome have an increased risk of glaucoma (12).

Cyclopentolate is in extensive clinical use both as a cycloplegic for the examination of refraction and as mydriatic for examination of the fundus of the eye or preoperatively before cataract surgery. Cycloplegic agents can cause a rise in IOP and the exact mechanism is insufficiently known. It may be related to decreased aqueous outflow, resulting from decreased pull on the trabecular meshwork due to ciliary muscle paralysis (11). On the other hand, an acute rise of IOP after cyclopentolate drops was significantly more common in eyes with pseudoexfoliation (4, 14). It was suggested that pigment liberation in the aqueous after cyclopentolate drop was more frequent in eyes with pseudoexfoliation (15). Valle noted that pigment liberation may have caused transient blocking of the trabecular meshwork, obstruction of aqueous outflow, and elevation of IOP (15). In our study, in contrast to the control subjects, in pseudoexfoliation syndrome and pseudoexfoliation glaucoma groups, mean IOP values increased statistically after the cyclopentolate drops. These increases were associated with a decrease of blood flow velocities of central retinal and posterior ciliary arteries in the pseudoexfoliation glaucoma group. Optic nerve head received arterial from posterior ciliary and central retinal arteries. In an eye already compromised by pseudoexfoliation glaucoma, an acute rise in IOP related to cyclopentolate may cause further damage in ganglion cells. It is recommended that the IOP be rechecked following cyclopentolate drop in eyes with pseudoexfoliation, especially those with glaucoma. Patients with significant rises in IOP should be treated immediately to decrease the risk of damage to the optic nerve.

In contrast to the pseudoexfoliation glaucoma group, increase in mean IOP that occurred following cyclopentolate in the pseudoexfoliation syndrome group did not lead to a decrease of retrobulbar circulation. This may be related to the number of patients with sharp increase in IOP. The number of patients with IOP rise ≥6 mmHg in the pseudoexfoliation syndrome group was significantly lower than in the pseudoexfoliation glaucoma group. Moreover, it has been suggested that patients with pseudoexfoliation glaucoma have more prominent abnormalities in retrobulbar circulation than patients with pseudoexfoliation syndrome (16). Thus, a higher sensitivity of retrobulbar circulation to fluctuations of IOP may exist in eyes with pseudoexfoliation glaucoma.

We observed an increase of IOP after mydriasis with cyclopentolate in eyes with pseudoexfoliation. However, it is unknown whether physiologic mydriasis has a similar effect on IOP in eyes with pseudoexfoliation. Further studies are needed to elucidate whether an increase of IOP occurs in physiologic mydriasis.

Two human studies have suggested that an artificially increased IOP affects the hemodynamics of central retinal and posterior ciliary arteries, while sparing the hemodynamics of the ophthalmic artery (6, 7). Both of these studies were experimental studies on healthy subjects. However, no report has been published regarding the effects of acute rise of IOP on retrobulbar hemodynamics in patients with glaucoma. In the present study, we demonstrated an acute rise of IOP leading to a decrease in blood flow velocities of CRA and PCA in patients with pseudoexfoliation glaucoma. Conversely, similar to that of healthy subjects, no significant change was observed in the blood flow velocities of OA.

It has been suggested that retrobulbar blood flow can be affected by several factors, including age, topical antiglaucomatous treatment, systemic blood pressure, blood viscosity, and stenosis of the carotid artery (17-19). We could not find any significant differences with respect to age, the presence of systemic hypertension, or diabetes mellitus among the patients with pseudoexfoliation glaucoma and pseudoexfoliation syndrome and the control participants. Similarly, to avoid the effects of topical antiglaucomatous drops on retrobulbar hemodynamics, our pseudoexfoliation glaucoma patients were taken off the therapy before 3 weeks of the study. Thus, in our study, many possible factors that could alter the retrobulbar hemodynamics could be eliminated.

In our study, we found that maximum pressure rise was observed at 45 minutes after the cyclopentolate drops. This finding is consistent with studies that have reported that the rise in IOP reaches its peak at 45 minutes after diagnostic mydriasis with cyclopentolate (3).

On the basis of our findings, pseudoexfoliation appears to be a predictive factor for IOP rise after cyclopentolate. In pseudoexfoliation glaucoma patients, an increase of IOP after cyclopentolate could lead to a decreased retrobulbar blood flow. IOP must be rechecked after cyclopentolate administration in these patients to avoid further damage to the ganglion cells.

ACKNOWLEDEGMENTS

The authors acknowledge the help of Fikriye Yılmazbas.

Reprint requests to:
Pelin Taner, MD
Konutkent 1 Sitesi, F 2 Blok No:14
Cayyolu, Ankara, Turkey
pelintaner@hotmail.com

REFERENCES

1. Kronfeld PC, McGarry HI, Smith H. The effect of mydriatics upon the intraocular pressure in primary wide angle glaucoma. Am J Ophthalmol 1943; 26: 245-52.
2. Galin MA. The mydriasis provocative test. Arch Ophthalmol 1961; 66: 353-5.
3. Harris LS. Cycloplegic induced intraocular pressure elevations. Arch Ophthalmol 1968; 79: 242-6.
4. Valle O. The cyclopentolate provocative test in suspected or untreated open-angle glaucoma. Acta Ophthalmol 1976; 54: 473-90.
5. Hancox J, Murdoch I, Parmar D. Changes in intraocular pressure following diagnostic mydriasis with cyclopentolate 1%. Eye 2002; 16: 562-6.
6. Harris A, Joos K, Kay M, et al. Acute IOP elevation with scleral suction: effects on retrobulbar hemodynamics. Br J Ophthalmol 1996; 80: 1055-9.
7. Ioos KM, Kay MD, Pillunat LE, et al. Effect of acute intraocular pressure changes on short posterior ciliary artery haemodynamics. Br J Ophthalmol 1999; 83: 33-8.
8. Williamson TH, Harris A. Color Doppler ultrasound imaging of the eye and orbit. Surv Ophthalmol 1996; 40: 225-67.
9. Galassi F, Nuzzaci G, Sodi A, et al. Color Doppler imaging in evaluation of optic nerve blood supply in normal and glaucomatous subjects. Int Ophthalmol 1992; 16: 273-6.
10. Atilla H, Arslanpençe A, Batioglu F, et al. Effect of hormone replacement therapy on ocular hemodynamics in postmenopausal women. Eur J Ophthalmol 2001; 11: 277-80.
11. Netland PA, Ye H, Streeten BW, Hernandez MR. Elastosis of the lamina cribrosa in pseudoexfoliation syndrome with glaucoma. Ophthalmology 1995; 102: 878-86.
12. Mitchell P, Wang JJ, Hourihan F. Blue Mountains Eye Study. The relationship between glaucoma and pseudoexfoliation. Arch Ophthalmol 1999; 117: 1319-24.
13. Velasco CJ, Eiroa MP, Garcia SJ, et al. Changes in intraocular pressure due to cycloplegia. CLAO J 1998; 86: 111-4.
14. Valle O. The cyclopentolate provocative test in suspected or untreated open-angle glaucoma. Acta Ophthalmol 1976; 54: 654-64.
15. Valle O. Effect of cyclopentolate on the aqueous dynamics in incipient or suspected open-angle glaucoma. Acta Ophthalmol 1973; 21: 52-9.
16. Yüksel N, Karabaş L, Arslan A, Demirci A, Çağlar Y. Ocular hemodynamics in pseudoexfoliation syndrome and pseudoexfoliation glaucoma. Ophthalmology 2001; 108: 1043-9.
17. Costa VP, Kuzniec S, Molnar LJ, et al. Clinical findings and hemodynamic changes associated with severe occlusive carotid artery disease. Ophthalmology 1997; 104: 1994-2002.
18. Williamson TH, Lowe GD, Baxter GM. Influence of age, systemic blood pressure, smoking and blood viscosity on orbital blood velocities. Br J Ophthalmol 1995; 79: 17-22.
19. Ewans DW, Haris A, Chung HS, et al. Effects of long-term hypotensive therapy with nonselective beta-blockers on ocular hemodynamics in primary open-angle glaucoma. J Glaucoma 1999; 8: 12-7.