Kafkas Univ Vet Fak Derg
18 (2): 337-342, 2012
DOI:10.9775/kvfd.2011.5539

RESEARCH ARTICLE

Ophthalmoscopic, Ultrasonographic and Electrophysiologic Findings of Experimentally Induced Intraocular Pressure Increase in Rabbits [1]

İrem ERGİN * Ömer BEŞALTI *

[1] *This study was summarized from the first author's PhD Thesis*
* Ankara University, Faculty of Veterinary Medicine, Department of Surgery, TR-06110 Ankara - TÜRKIYE

Makale Kodu (Article Code): KVFD-2011-5539

Summary

The aim of this study was to determine ophthalmoscopic, ultrasonographic and electrodiagnostic response of the experimentally induced increasing intraocular pressure (IOP) in 6 New Zealand rabbits. IOP was induced by cauterizing 3 vortex and 3 episcleral veins. The cases were evaluated by ophthalmoscopy, ultrasonography (USG), electroretinography (ERG) and visual evoked potentials (VEP). Significant elevation in intraocular pressure (IOP) was seen in all rabbits on the postoperative 1st day. Although IOP values did not significantly differ between treated and control eyes from the 2nd to the 4th week, exchange of cornea-anterior lens capsule and posterior lens capsule-retina measurements were persistent. In ERG, implicit time of a and b wave of the treated eyes increased significantly during 4 weeks, however, the amplitude of both waves were markedly lower than control eyes until the end of 2nd week. In VEP, the decrease in N1 wave amplitude was marked in 4th week. These results indicated that even though the increasing IOP came back to the normal limits, ERG and USG parameters did not return to baseline. As a result, in clinical cases, even if IOP return to normal limits after treatment, intraocular structures and the retina should be evaluated and treatment should be advanced in this direction.

Keywords: *Rabbit, Intraocular pressure, Tonometry, Ultrasonography, Electroretinography*

Tavşanlarda Deneysel Göz İçi Basınç Artışının Oftalmoskopik, Ultrasonografik ve Elektrofizyolojik Bulguları

Özet

Bu çalışmanın amacı, altı tavşanda oluşturulan deneysel göz içi basınç (GİB) artışının oftalmoskopik, ultrasonografik ve elektrofizyolojik bulgulara etkisinin araştırılmasıdır. Çalışmada her bir Yeni Zelanda tavşanının sol gözündeki 3 vorteks ve 3 episkleral ven koterize edilerek GİB artışı sağlanmıştır. Olgular oftalmoskopi, ultrasonografi (USG), elektroretinografi (ERG) ve görsel uyandırılmış potansiyeller (GUP) yönünden değerlendirilmiştir. Tüm tavşanlarda postoperatif 1. haftanın sonuna kadar göz içi basıncında belirgin bir artış ortaya çıkmıştır. İkinci ve 4. haftalarda GİB'deki değişim belirgin olmamış, ancak kornea-lens ön kapsülü aralığındaki artış ve lens arka kapsülü-retina aralığındaki azalmanın kalıcı olduğu görülmüştür. ERG'de a ve b dalga amplitüdlerinde 2. haftanın sonuna kadar belirgin bir düşme görülse de, dalgaların implisit zamanlarındaki artış 4 hafta boyunca sürmüştür. VEP'de ise N1 dalga amplitüdü çalışmanın 4. haftasına kadar belirgin şekilde azalmıştır. Bu bulgular artan GİB normale dönse bile ERG ve USG parametrelerindeki değişimin normale dönmediğini göstermektedir. Sonuç olarak klinik GİB artışı olgularında sağaltım sonrası basınç normale dönse dahi göz içi yapıların ve retinanın klinik olarak ERG ve USG yönünden değerlendirilmeye devam edilmesi ve sağaltımın elde edilen veriler doğrultusunda ilerletilmesi sağlanmalıdır.

Anahtar sözcükler: *Tavşan, Göz içi basıncı, Tonometri, Ultrasonografi, Elektroretinografi*

INTRODUCTION

Resultant retina and optic nerve damage due to increased intraocular pressure (IOP) account for the most common reason of retinal ganglion cell death and loss of vision [1]. The exact mechanism for the ganglion cell death is unknown, but different hypotheses have been introduced. According to the mechanical pressure hypothesis, the

İletişim (Correspondence)
+90 312 3170315
iremerg@gmail.com

pressure on retinal layer causes deformations in optic nerve axons. To the vascular hypothesis, elevated IOP affects the retinal vascularization. This pressure causes slow blood flow and retinal ischemia [2]. Early determination of pressure elevation is essential for irreversible damage in conjunction with elevated pressure on the neurologic structures of the eye. As in human medicine, loss of vision due to elevated IOP is very common in veterinary medicine. In order to determine the damage in the eye caused by elevated IOP, several experimental models are developed [1,3-5]. In these models, the target is to block humour aquous drainage. The most commonly employed method to block humour aquous drainage is the episcleral vein cauterization model [5], which are shown on rats and mice [4]. There are many papers refer to model of acute and chronic IOP induced hyperpressure in rabbits with the use of laser induced, betamethasone, alpha-chymotrypsine, etc. [6,7]. However**,** no studies have been done about episcleral and vortex veins cauterization model in rabbits. Several ultrasonographic experiments on rats and mice have been done, in order to understand about changes in anterior chamber caused by the increased in IOP [8,9].

The aim of this study was to perform time dependant, tonometric, ophthalmoscopic, ultrasonographic and electrophysiological changes of the IOP elevation due to episcleral and vortex vein cauterization model in rabbits.

MATERIALS and METHODS

Animals

This study was approved by the Institutional Animal Ethics Committee (AU-HADYEK 2006⁄35). Six adult (two years of age) male, New Zealand rabbits (Oryctolagus cuniculus) weighing 2-2.5 kg were maintained in an environmentally controlled room with 12 h light/12 h dark daily cycles (the room light intensity is 160 lux), a temperature of 21°C, food and water provided ad libitum. This study adhered to the ARVO statement for the Use of Animals in Ophthalmic and Vision Research and was approved by Ankara University Faculty of Veterinary Medicine Ethic Committee on Animal Care.

Experimental Intraocular Pressure Model

Rabbits were anesthetized by intramuscular injection of xylazine (5 mg/kg, Alfazyne 2%, Ege Vet, Turkey) and ketamine (35 mg/kg, Ketasol 10%, Richter, Austria). The eyes were anesthetized topically with 0.5% proparacaine HCl (Alcaine®, Alcon, Belgium) eye drops. The general anesthesia lasted approximately 40 min for the complete surgical procedure. IOP was induced in the left eye of each animal and right eye was served as a control. Two millimeter incisions into the conjunctiva and *Tenon's* capsule were made on dorsal, ventral and lateral quadrants of the limbus of left eye. One dorsal episcleral vein, located near the superior rectus muscle, one temporal episcleral vein, near the lateral rectus muscle and one ventral episcleral vein, between the ventral rectus muscle and oblique muscle were isolated from the surrounding tissues. A bipolar cautery was applied to the episcleral veins in the left eye. After episcleral veins cauterization, three vortex veins, which were under the dorsal, ventral and lateral rectus muscle, were isolated from the tissues, and cauterized. Antibiotic ointment containing oxytetracycline-polymyxin B-sulfate (Terramycine®, Pfizer, Germany) was applied topically after each procedure for 5 days.

Intraocular Pressure Monitoring

The right and left eye IOP's of awake animals were measured using a digital tonometer (Tonopen Vet, Reichert Opthalmic Instruments, USA) every day for 28 days after the surgery. For IOP measurements, the eyes were anesthetized topically with 0.5% proparacaine HCl (Alcaine®, Alcon, Belgium) eye drop. All measurements were taken four times, at the same time of day in order to avoid circadian IOP changes.

Ultrasonography

B mode ultrasonography (Esaote Biomedica AU5, Genova, Italy) was performed in control and treated rabbit eye after instillation of a topical anesthetic and application of acoustic transmission gel on the 7.5-MHz linear transducer tip postoperative first day and every week after surgery. Measurements were performed by measuring the distance between the cornea (C) and the anterior lens capsule (ALC); the posterior lens capsule (PLC) and the retina (R) and overall globe size horizontally.

Ophthalmoscopy

Rabbits were anesthetized and their pupils were dilated by local application of 1% tropicamide (Tropikamid®, Roche, Germany) eye drop in order to examine the retinal and choroidal vasculature. In this way, the vasculature of control and hypertensive eyes was compared. Ophthalmoscopic examinations were performed at pretest (before the treatment), on the 1st day, in the 1st, 2nd and 4th weeks post-operatively. Flexible endoscope (VetVu, Swiss Precision Products, USA) was used for obtain eye fundus images.

Electroretinography (ERG)

To quantify potential damage to the retina due to the elevation of the IOP, electroretinography was performed at postoperative 1st day, in the 1st, 2nd and 4th weeks post-operatively in both eyes, under general anesthesia (10). The rabbits were placed on ventral recumbency, their heads were on dorsal position. An eye speculum was inserted between the lids to keep them open and to retract the nictitating membranes. 0.9% saline solution was used intermittently to keep the corneas moist. A five channels EMG⁄EP device's evoked potentials measuring

system (Medelec/Synergy Oxford, USA) was used for ERG recordings. Three stainless-steel electrodes were used for recordings. The active electrode was placed approximately 1cm below the center of the lower eyelid subcutaneously. The reference was placed ipsilateral to the active electrode and about 2 cm lateral to the outer cantus of the eye. The ground electrode was placed on the rabbit's scapular region subcutaneously. The animals were dark adapted for minimum of 15 min. ERG was performed with flashes (1 cd sec^{-1}/m^{-2}). At each stimulus intensity, the recordings were repeated (until two successive identical curves were obtained). A flash ERG routine was delivered at a 2 Hz frequency. Amplitudes and implicit times for a wave and b wave were measured. The a wave amplitude was measured from the baseline to the trough of the a wave, while the b wave measured from the trough of the a wave to the peak of the b wave. The a wave implicit time was measured from the flash onset to the a wave trough and the b wave implicit time was measured from the flash onset to the b wave peak.

Visual Evoked Potentials (VEP)

The same device was used for VEP recordings. Active electrode was placed in midline, subcutaneously, 2 cm rostral to external occipital protuberance; reference electrode was placed in midline, approximately 3 cm behind the eyes and ground electrode was placed in midline, frontal region, 2 cm in front of the eyes. VEP's were recorded using a LED goggle stimulator, to deliver 8 µsec flash duration with an intensity of 2 cd sec^{-1}/m^{-2}. For VEP recordings, responses were filtered between 1-100 Hz. Usually 200 responses were averaged in order to sufficiently improve the signal to noise ratio. More than one negative and positive deflection was noted on VEP recordings on control eyes. In order to evaluate primary cortex, only first negative (N1) and positive (P1) deflections were taken. The N1 wave amplitudes were measured from the baseline to the peak of the negative N1 wave, whereas the P1 wave amplitudes were measured from the trough of the N1 wave to the peak of the positive P1 wave. Then, the implicit times of both N1 and P1 waves were measured.

Statistical Analysis

Friedman's test was performed to the effect of time on the IOP, ERG, VEP and USG parameters which were expressed as mean ±SE. Mean data from experimental group was compared with the data from control group on each experimental time zone by using Wilcoxon test. $P<0.05$ was considered significant.

RESULTS

Tonometry

Cauterization of vortex and episcleral veins caused temporary elevation of the IOP in rabbits' treated eye. The largest increase in IOP following cauterization was observed at the next day after the surgery. At this time, all treated eyes developed significant elevation of the IOP (26.33±1.03 mmHg) compared to controls (12.00±0.63 mmHg). This significant elevation of the pressure was continued until the first week. However, a progressive and slow reduction was observed from the first week till the end of the experiment. IOP values were not significantly differing between control and treated eyes at 4 weeks postoperatively *(Fig. 1)*. Thus, the mean IOP in treated eyes at this period was close (16.65±2.4 mmHg) to the mean IOP of control eyes (12.00±0.63 mmHg).

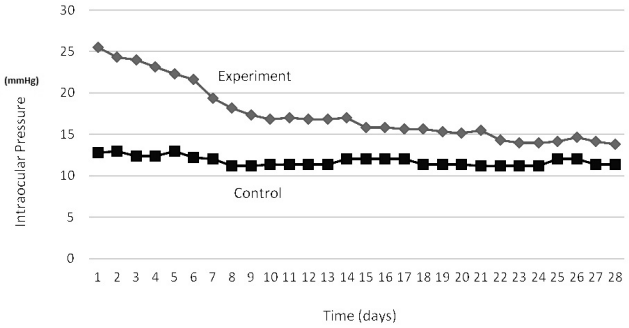

Fig 1. Mean intraocular pressure (IOP) values (±SE, n=6 rabbits)
Şekil 1. Ortalama göz içi basınç (GİB) değerleri (±SE, n=6 rabbits)

Ultrasonography

In B-mode ultrasonography, three major echoes; cornea, posterior capsule and retina were seen. The cornea was represented as a curved hyper echoic interface. Anterior chamber of the eye, lens cortex and nucleus, and the aqueous and vitreous humors were anechoic. The optic disc appeared as a hypoechoic structure in the retina. No remarkable difference was found between the eye structures taken from the left and right eyes of the rabbits.

On the postoperative first day, the distance between C-ALC in treated eyes was significantly higher than control eyes. This substantial difference lasted until the end of the postoperative 1st week. By the end of the postoperative 2nd week, measurements in treated eyes were lower than the first week. However, the measurements were still higher than those of control group. By the end of the postoperative 4th week, although the distance between C-ALC values were much lower than the values obtained on the 1st day, a significant increase was noted compared to control group ($P<0.05$). When the distance between PLC-R was evaluated, the values for treated group were markedly lower than those of control group until the end of the postoperative 4th week *(Fig. 2)*. When the horizontal length was evaluated, the value for experiment group was higher than control group ($P<0.05$). This increase lasted until the end of the postoperative 1st week. By the postoperative 2nd week, measurements in treated eyes decreased and this lasted until the end of the postoperative 4th week *(Fig. 3)*.

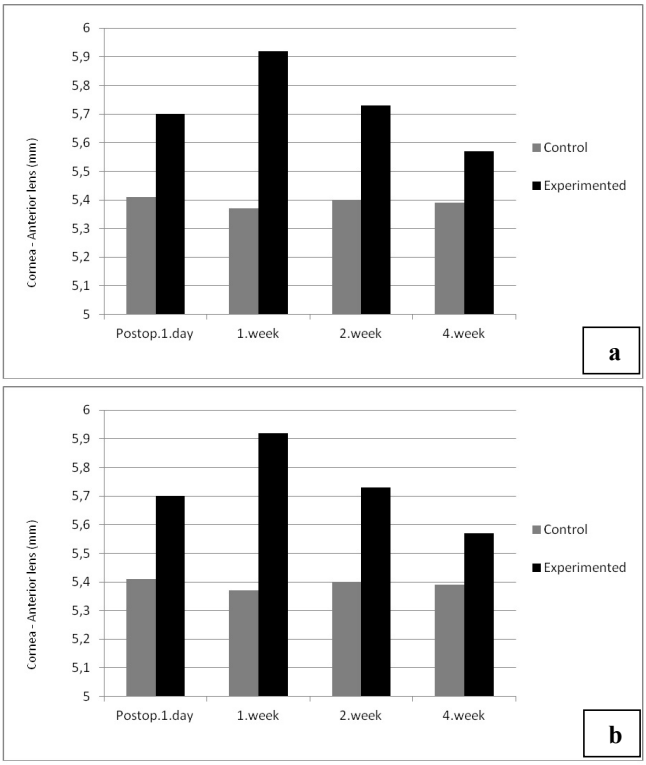

Fig 2. Mean values of control and treated eye distance between cornea-anterior lens **(a)** and between posterior lens-retina **(b)**

Şekil 2. Kontrol ve deney gözlerde kornea-lensin ön yüzü **(a)**, lensin arka yüzü-retina arası mesafe ölçümlerinin ortalama değerleri **(b)**

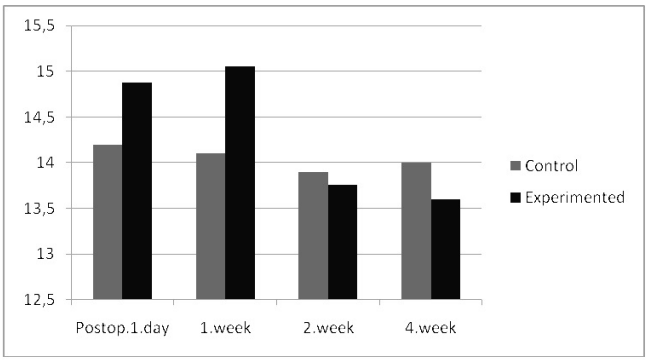

Fig 3. Mean values of horizontal length of control and treated eye

Şekil 3. Kontrol ve deney gözlerin horizontal çap ölçüm değerleri

Ophthalmoscopy

In the ophthalmoscopic examination of the control group, we observed healthy eye merangiotic fundus structures *(Fig. 4a)*. However in the treated eyes, non-vascularized areas were noted. Vascular congestions were seen in cauterized areas *(Fig. 4b)*. In the 2nd week fundus examination collateral vein formations in different parts of nonvascularized areas were noted. By the end of the postoperative 4th week, treated eye's fundus had the same structures as the control group.

Electroretinography (ERG)

The amplitude of a and b wave of the treated eyes was

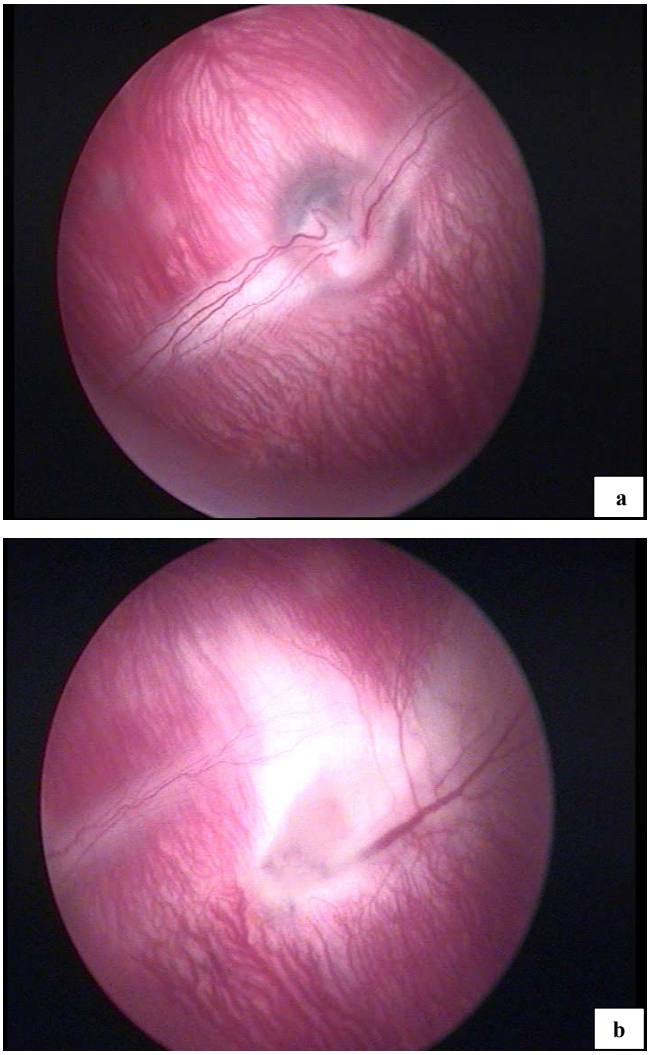

Fig 4. a. Merangiotic fundus structures in control eyes, **b.** In treated eye fundus, nonvascularized area and vascular congestions on postoperative 1st day after cauterization

Şekil 4. a. Kontrol gözlerde merangiotik fundus yapısı, **b.** Koterizasyon işleminden sonraki 1. gün göz fundusundaki damarsız bölgenin ve damar konjesyonlarının görüntüsü

low compared to control eyes until the end of the study, but the difference between the groups was marked by the end of 2nd week. In treated eyes, a and b wave implicit time was significantly higher than control eyes from the postoperative 1st day to the 4th week (*Table 1* and *2*).

Visual Evoked Potentials (VEP)

The decrease in N1 wave amplitude in treated group compared to control group was marked on the post-operative 1st day and the 1st week, until the end of the postoperative 4th week. The implicit time of N1 wave was elongated in treated group compared to control group until the end of 4th week, however, the difference between time zones and control eyes was not significant *(Table 3)*. The changes for amplitude and implicit time of P1 wave was not significant between treated and control eyes *(Table 4)*.

Table 1. *Mean first negative peak (a) amplitudes and implicit time values. a,b: groups in the same row with different letters are different (- : P>0.05)*
Tablo 1*. İlk negatif dalga (a) amplitüd ve implisit zaman ortalama değerleri. a,b: aynı sırada farklı harfleri taşıyan gruplar farklıdır (- : P>0.05)*

a Wave	Postoperative 1st Day		Postoperative 1st Week		Postoperative 2nd Week		Postoperative 4th Week	
	Control	Treated	Control	Treated	Control	Treated	Control	Treated
Amplitude, μV	1.39 ± 0.55^{a}	0.41 ± 0.17^{bA}	1.45 ± 0.44^{a}	0.69 ± 0.31^{bB}	1.22 ± 0.44^{a}	0.9 ± 0.39^{bC}	$0.98\pm0.51^{-}$	0.86 ± 0.57^{-C}
Implicit time, ms	15.5 ± 3.38^{a}	19.3 ± 3.56^{bA}	13.96 ± 2.91^{a}	16.8 ± 2.45^{bB}	15.20 ± 3.72^{a}	18.15 ± 2.9^{bC}	12.24 ± 4.49^{a}	19.7 ± 2.15^{bA}

Table 2. *Mean first positive peak (b) amplitudes and implicit time values. a,b: groups in the same row with different letters are different. - : P>0.05*
Tablo 2*. İlk pozitif dalga (b) amplitüd ve implisit zaman ortalama değerleri. a,b: aynı sırada farklı harfleri taşıyan gruplar farklıdır. - : P>0.05*

b Wave	Postoperative 1st Day		Postoperative 1st Week		Postoperative 2nd Week		Postoperative 4th Week	
	Control	Treated	Control	Treated	Control	Treated	Control	Treated
Amplitude, μV	23.31 ± 7.36^{a}	15.86 ± 6.18^{bA}	23.1 ± 5.60^{a}	18.7 ± 9.24^{bB}	22.3 ± 10.43^{a}	19.1 ± 9.18^{bC}	$22.96\pm5.85^{-}$	22.08 ± 6.4^{-D}
Implicit time, ms	23.05 ± 4.34^{a}	29.03 ± 7.0^{bA}	23.15 ± 5.2^{a}	28.0 ± 2.39^{bA}	23.55 ± 2.06^{a}	30.15 ± 8.0^{bA}	22.86 ± 2.05^{a}	25.9 ± 1.06^{bB}

Table 3. *Mean first negative peak (N1) amplitudes and implicit times values. a,b: groups in the same row with different letters are different. - : P>0.05*
Tablo 3*. İlk negatif dalga (N1) amplitüd ve implisit zaman ortalama değerleri. a,b: aynı sırada farklı harfleri taşıyan gruplar farklıdır. - : P>0.05*

N1 Wave	Postoperative 1st Day		Postoperative 1st Week		Postoperative 4th Week	
	Control	Treated	Control	Treated	Control	Treated
Amplitude, μV	3.12 ± 2.71^{a}	1.92 ± 0.61^{bA}	2.74 ± 2.56^{a}	0.72 ± 0.21^{bB}	1.63 ± 0.83^{a}	1.50 ± 0.0^{bC}
Implicit time, ms	$24.10\pm8.74^{-}$	$25.00\pm9.49^{-}$	$24.20\pm6.94^{-}$	$26.01\pm3.20^{-}$	$23.26\pm8.72^{-}$	$24.00\pm6.27^{-}$

Table 4. *Mean first positive peak (P1) amplitudes and implicit times values. a,b: groups in the same row with different letters are different. - : P>0.05*
Tablo 4. *Ilk pozitif dalga (P1) amplitüd ve implisit zaman ortalama değerleri. a,b: aynı sırada farklı harfleri taşıyan gruplar farklıdır. - : P>0.05*

P1 Wave	Postoperative 1st Day		Postoperative 1st Week		Postoperative 4th Week	
	Control	Treated	Control	Treated	Control	Treated
Amplitude, μV	$8.02\pm3.51^{-}$	$6.16\pm3.78^{-}$	$6.78\pm1.62^{-}$	$5.63\pm3.24^{-}$	$6.76\pm2.04^{-}$	$4.5\pm2.82^{-}$
Implicit time, ms	$13.00\pm2.78^{-}$	$14.94\pm7.92^{-}$	$12.41\pm4.14^{-}$	$14.82\pm4.12^{-}$	$13.46\pm6.38^{-}$	$15.3\pm6.36^{-}$

DISCUSSION

In this experimental study, episcleral vein and vortex vein cauterization was employed in combination to form a chronic pressure elevation in six adult (2 years of age) male, New Zealand rabbit eyes. Prominent elevation in IOP values in treated eyes nearly continued 2 fold of control eyes during postoperative 1st week. Changes in IOP in this study were similar with the previous study employed with rat model [10,11]. The gradual decrement in IOP values was reached to what's noted in control eyes at the end of 4th week. This decrement should be compensated by the changes in C-ALC, PLC-R and horizontal length.

Retinal circulation is weak in rabbits, and choroidal vessels are very important for the metabolic requirement of the retina [12]. Vein cauterization model can cause some serious damage in choroidal circulation, and the function of retinal cells, especially photoreceptors will be affected. In one study suggests that changes in a and b waves of ERG are resultant of loss of function in retinal cells due to damage in choroidal circulation [11]. However, even if vein cauterization model causes damage in choroidal circulation, this will not affect the ERG traces completely [10]. In the present study, the changes in ERG parameters were in the same time changes with IOP. Because of the disruption of choroidal circulation and resultant increasing IOP, retinal function should be affected. The values obtained from ERG recordings revealed that the retinal function has not come back to the normal.

Serious damage to choroidal veins in cauterized area was seen in postoperative 1st day to the 1st week. Starting from 1st week of onset of decrease in pressure, collateral veins started forming in nonvascularized areas. At the end of the study, all treated eyes mean IOP measurements were the close to the control eye measurements, and the collateral vein network occupied the whole non-vascularized area. In contrast, the retinal veins look normal at the first day when the IOP was at the highest level. Alterations in the fundus of some animals and changes in IOP levels dependant on time being parallel with supported previous studies.

Elevated IOP, besides its effects on retina and optic

nerve, causes numerous structural changes in the eye. In an ultrasonographic study which is the same model we used for rabbits in rats [13], during the time zone with marked elevation in IOP levels, it was observed that no changes took place in depth of anterior camera. In the present study, differences of the distance between C-ALC, and PLC-R were persistent for 4 week. In addition Horizontal length of the eye had increased until first week and decreased gradually as IOP. During the observation period, treated eye's IOP measurements being higher than control group just at the first week, not at the 2nd and 4th weeks.

Increasing the distance of C-ALC and decreasing the distance of PLC-R were persistent, and the values were significantly different than control eyes. However, the increasing IOP was stayed at the significantly highest level at 1st week, and get at the level of control eyes for the later periods. These findings can be explained as; increasing IOP has been compensated by the moving of the lens or attached structures (zonular fibers, corpus ciliare, iris) backwards.

When the photoreceptors of the retina are stimulated by light, phototransduction, which is the conversion of the energy of light into a neuroelectrical response, occurred in the cells. The information from the photoreceptors is then processed through the retina, and finally, retinal ganglion cells are stimulated. This processing of visual information in the retina results in electrical changes in the tissue that can be recorded as a mass potential called the electroretinogram. Each retinal ganglion cell relays that information to higher visual centers. The visual evoked potentials however, is a gross electrical potential recorded from the visual cortex in response to a visual stimulus from the retina. That is a visual stimulus results in the excitation of many cells in the cortex and the summed activity of these cells is recorded as the VEP on the scalp [14].

In a study, which was given Ringer's solution to the anterior chamber of the rabbit eyes to increase IOP, changes in VEP parameters were monitored [15]. In VEP recordings, decrease in N1 wave amplitude with elongation of implicit time was determined in treated eyes. In the present study, postoperative first day at which IOP is significant, decrease in the amplitude of both waves, as well as elongation in the implicit time was concluded. The time periods in which increase IOP is significant, as a result of increase in pressure of retinal cells damages occurs, and it was thought that in ganglion cells electrical stimulation is not transmitting in a normal limit. In this experiment, the persistent change in ERG was not in the same line with VEP except for amplitude of N1 wave.

In conclusion, marked elevation of IOP until the 1st postoperative week was in consistence with alterations in USG, ERG and VEP (N1 amplitudes) parameters. Even though the increasing IOP came back to the normal limits, ERG parameters and measurements between C-ALC and PLC-R did not return to normal limits. As a result, in clinical cases, even if IOP return to normal limits after treatment, intraocular structures and the retina should be evaluated and treatment should be advanced in this direction.

Acknowledgements

I gratefully thank Prof. Dr. Bahattin KOÇ and Prof. Dr. Perran GÖKÇE for their supports and comments of the manuscript and Assoc. Prof.Dr. Safa GÜRCAN for his contributions to statistical analysis.

REFERENCES

1. Ederra JR, Verkman AS: Mouse model of sustained elevation in intraocular pressure produced by episcleral vein occlusion. *Exp Eye Res,* 82, 879-884, 2006.

2. Siliprandi R, Bucci MG, Canella R, Carmignoto C: Flash and pattern electroretinograms during and after acute intraocular pressure elevation in cats. *Invest Ophthalmol Vis Sci,* 29 (4): 558-565, 1988.

3. Gelatt KN: Animal models for glaucoma. *Invest Ophthalmol Vis Sci,* 16, 592-596, 1977.

4. Morrison JC, Moore CG, Deppmeier LM, Gold BG, Meshul CK, Johnson EC: A rat model of chronic pressure-induced optic nerve damage. *Exp Eye Res,* 64 (1): 85-96, 1997.

5. Shareef SR, Valenzuela EG, Salierno A, Walsh J, Sharma SC: Chronic ocular hypertension following episcleral venous occlusion in rats. *Exp Eye Res,* 61, 379-382, 1995.

6. Gross RL, Chang P, Pennesi ME, Yang Z, Zhang J, Wu SM: A mouse model of elevated intraocular pressure: Retina and optic nerve findings. *Trans Am Ophthalmol Soc*, 101, 163-169, 2003.

7. Lim KS, Wickremasinghe SS, Cordeiro MF, Bunce C, Khaw PT: Accuracy of intraocular pressure measurements in New Zealand white rabbits. *Invest Ophthalmol Vis Sci,* 46, 2419-2423, 2005.

8. Aihara M, Lindsey JD, Weinreb RN: Experimental mouse ocular hypertension: establishment of the model. *Invest Ophthalmol Vis Sci,* 44, 4314-4320, 2003.

9. Nyland TG, Mattoon JS: Ocular ultrasonography. **In**, Nyland TG, Mattoon JS (Eds): Veterinary Diagnostic Ultrasound. 1st ed., pp. 178-197. W.B. Sounders Company Ltd, Philadelphia, 1995.

10. Grozdanic SD, Betts DM, Sakaguchi DS, Kwon YH, Kardon RH, Sonea IM: Temporary elevation of the intraocular pressure by cauterization of vortex and episcleral veins in rats causes functional deficits in the retina and optic nerve. *Exp Eye Res,* 77, 27-33, 2003.

11. Mittag TW, Danias J, Pohorenec G, Yuan HM, Burakgazi E, Redman RC, Podos SM, Taton WG: Retinal damage after 3 to 4 months of elevated intraocular pressure in a rat model of glaucoma. *Invest Ophthalmol Vis Sci,* 41 (11): 3451-3459, 2000.

12. Kiel JW, Shepherd AP: Autoregulation of choroidal blood flow in the rabbit. *Invest Ophthalmol Vis Sci,* 33 (8): 2399-2410, 1992.

13. Nissirios N, Chanis R, Johnson E, Morrison J, Cepurna WO, Jia L, Mittag T, Danias J: Comparison of anterior segment structures in two rat glaucoma models: An ultrasaund biomicroscopic study. *Invest Ophthalmol Vis Sci,* 49 (6): 2478-2482, 2008.

14. Sawada A, Neufeld AH: Confirmation of the rat model of chronic, moderately elevated intraocular pressure. *Exp Eye Res,* 69, 525-531, 1999.

15. Okuno T, Oku H, Sugiyama T, Yang Y, Ikeda T: Evidence that nitric oxide is involved in autoregulation in optic nerve head of rabbits. *Invest Ophthalmol Vis Sci,* 43 (3): 784-789, 2002.