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Investigating of Acute and Chronic Effects of Oxaliplatin on Rat Ocular Tissues

Akut ve Kronik Oksaliplatin Uygulamasının Sıçan Göz Dokuları Üzerindeki Etkilerinin Araştırılması

Özgün Araştırma
Research Article

Ayse Ipek Akyuz Unsal, Fadime Kahyaoglu, Ismail Saygin, Ozlem Yersal, Buket Demirci

ABSTRACT

Objective: *Visual disturbances occurring during cancer treatment with oxaliplatin (OXA) have been previously reported in some of case presentations. This study investigates the ocular toxicity of OXA on rat eye tissues by using histopathological staining. Additionally, the reversibility of findings, if there is any, were assessed in groups with waiting periods.*
Method: *Six-8 month-old rats have been separated into five groups. Acute OXA treatment (4 mg/kg) has been administered on days 1, 3 and 5th days; consequently, the eye samples were obtained on 7th and 14th days of the study. Chronic OXA treatment (4 mg/kg) has been administered for 4 weeks (two days of week); the rats were sacrificed on 28th day and 21 days after completing administration of drug. One group was used as a control.*
Results: *The most striking irreversible-features of OXA treatment were endothelial polypoid proliferation of the vessel, neo-vascularisation of cornea, capillarisation of optic nerve and, degeneration of retinal nerve fibre layer at several degrees of severity.*
Conclusion: *OXA treatment can be responsible for sight threatening side effects by influencing different parts of the ophthalmic system; therefore, oncologists and ophthalmologists should keep in mind the irreversibl-ophthalmic adverse effects of OXA treatment in oncology patients.*

Keywords: *Animal study, ophthalmology, oncology, rational drug use*

ÖZ

Amaç: *Oksaliplatin (OKSA) ile yapılan kanser tedavileri sırasında görme bozuklukları bir kaç olgu sunumunda bildirilmiştir. Bu çalışma histopatolojik boyama kullanarak sıçan göz dokularında oksaliplatinin göz toksisitesini araştırmaktadır. İlave olarak, eğer bir bulgu varsa, bulguların geri dönüşümlü olup olmadığı da bekleme süresi olan gruplarda değerlendirildi.*
Yöntem: *6-8 aylık sıçanlar beş gruba ayrıldı. Akut OKSA tedavisi (4 mg/kg) 1., 3. ve 5. günlerde verildi, sonrasında, göz dokuları 7. ve 14. günde elde edildi. Kronik OKSA tedavisi (4 mg/kg), 4 hafta boyunca (hafta da 2 gün) uygulandı; sıçanlar 28. günde ve ilaç uygulamasının sonlandırılmasını takiben 21 gün beklenerek kesildi. Bir grup kontrol olarak kullanıldı.*
Bulgular: *OKSA tedavisinin en göze çarpan geri-dönüşümsüz bulguları, damar endotelinde polipoid proliferasyon, korneada yeni damar oluşumu, optik sinir kapillerlerinde artış ve retinal sinir lifi tabakasında farklı derecelerde dejenerasyondu.*
Sonuç: *OKSA tedavisi oftalmik sistemin farklı bölümlerini etkileyerek görmeyi tehtid eden yan etkilerden sorumlu olabilir, bu nedenle onkolog ve oftalmolog OKSA ile tedavi edilen onkoloji hastalarında geri dönüşümsüz oftalmik yan etkiler olabileceğini akılda bulundurmalıdır.*

Anahtar kelimeler: *Hayvan çalışması, oftalmoloji, onkoloji, akılcı ilaç kullanımı*

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Buket Demirci
Aydın Adnan Menderes Üniversitesi, Tıp Fakültesi, Tıbbi Farmakoloji Ana Bilim Dalı, Aydın - Türkiye
✉ drbuketdemirci@gmail.com
ORCİD: 0000-0002-3442-5061

A.I. Akyuz Unsal 0000-0001-5260-647X
Aydın Adnan Menderes Üniversitesi, Tıp Fakültesi, Göz Hastalıkları Ana Bilim Dalı, Aydın, Türkiye

F. Kahyaoglu 0000-0002-5149-8051
Manisa Celal Bayar Üniversitesi, Tıp Fakültesi, Embriyoloji ve Histoloji Ana Bilim Dalı, Manisa, Türkiye

I. Saygin 0000-0002-6013-6378
Karadeniz Teknik Üniversitesi, Tıp Fakültesi, Tıbbi Patoloji Ana Bilim Dalı, Trabzon, Türkiye

O. Yersal 0000-0001-8220-4223
Aydın Adnan Menderes Üniversitesi, Tıp Fakültesi, Tıbbi Onkoloji Ana Bilim Dalı, Aydın, Türkiye

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INTRODUCTION

Third generation platinum derivative, oxaliplatin (OXA), is frequently used as a standard therapy for colorectal cancer [1]. Expectedly, chemotherapeutic agents can have potential harmful effects on healthy tissues, but drug transportation to ocular tissues is not so easy due to natural barriers such as blood-retina [2]. Ocular toxicity of cisplatin (CIS) is well described previously [3,4], but, there are very limited reports about the ocular side effects of OXA. Eye disorders including visual field defect, tunnel vision, visual field impairment, optic neuritis, papilledema and reduction in visual acuity have been reported as serious adverse effects of OXA [5,6], however there are not any histopathologic findings and detailed safety studies about it.

In this study, ocular toxicity of OXA has been histopathologically assessed for acute and chronic term. Consequently, the adverse effect of the drug if there is any, was assessed for its reversibility with waiting period.

MATERIAL AND METHODS

Animals and Experimental design

Six-8 month-old male Wistar albino rats, were obtained from Animal Care and Research Unit of University and all experiments were performed according to the principles and guidelines of Animal Ethical Committee after receival of its approval. This study was mainly planned to evaluate the ototoxic effect of OXA, but lung, heart [7] and eye tissues have been also evaluated with the aim to decrease the number of animal used in medical researches; after receiving relevant approval of the animal ethical committee (HADYEK, 64583101/2014/138). OXA (Eloxatin®, Sanofi, U.S.), the dose of 4 mg/kg has been diluted in 5% glucose solution just prior to intraperitoneal (i.p.) administration. The experimental groups were as follows:

Control: The rats in this group were administered 5% glucose solution through intraperitoneal route.

Acute OXA treatment: Animals that received OXA treatment on the 1st, 3rd and 5th days of the study, and were sacrificed on day 7.

Acute OXA treatment + waiting period: Animals that received OXA treatment on the 1st, 3rd and 5th days of the study, were sacrificed on day 14, to see the OXA effect one week later after drug cessation .

Chronic OXA treatment: OXA was administered two days a week (Monday and Thursday) for 4 weeks, then the rats were sacrificed on day 28.

Chronic OXA treatment + waiting period: OXA was administered two days a week (Monday and Thursday) for 4 weeks. Then the rats were sacrificed 21 days after the completion of the injections.

The tissue samples excised under the anesthesia of ketamine and xylazine (50 mg/kg and 5 mg/kg, respectively), were placed immediately in 10% formalin solution. After routine tissue following the obtained samples were sliced in 5 micrometer thickness and evaluated after hematoxylin-eosin (H-E) staining.

RESULTS

Histopathological analyses of all groups did not show uniform pathological phenomenon. Some photos of samples are shown in Figures 1-2, and 3. The prominent findings of the study were determined as endothelial polypoid proliferation of the vessel and neovascularisation of cornea, in addition to some degree of degeneration of retinal nerve fibre layer. Neovascularisation of cornea has increased in line with the duration of treatment. Similar pathological findings were also detected in optic nerve. Capillary vascular development was detected which increased by the duration of the treatment. The findings did not reverse properly, after

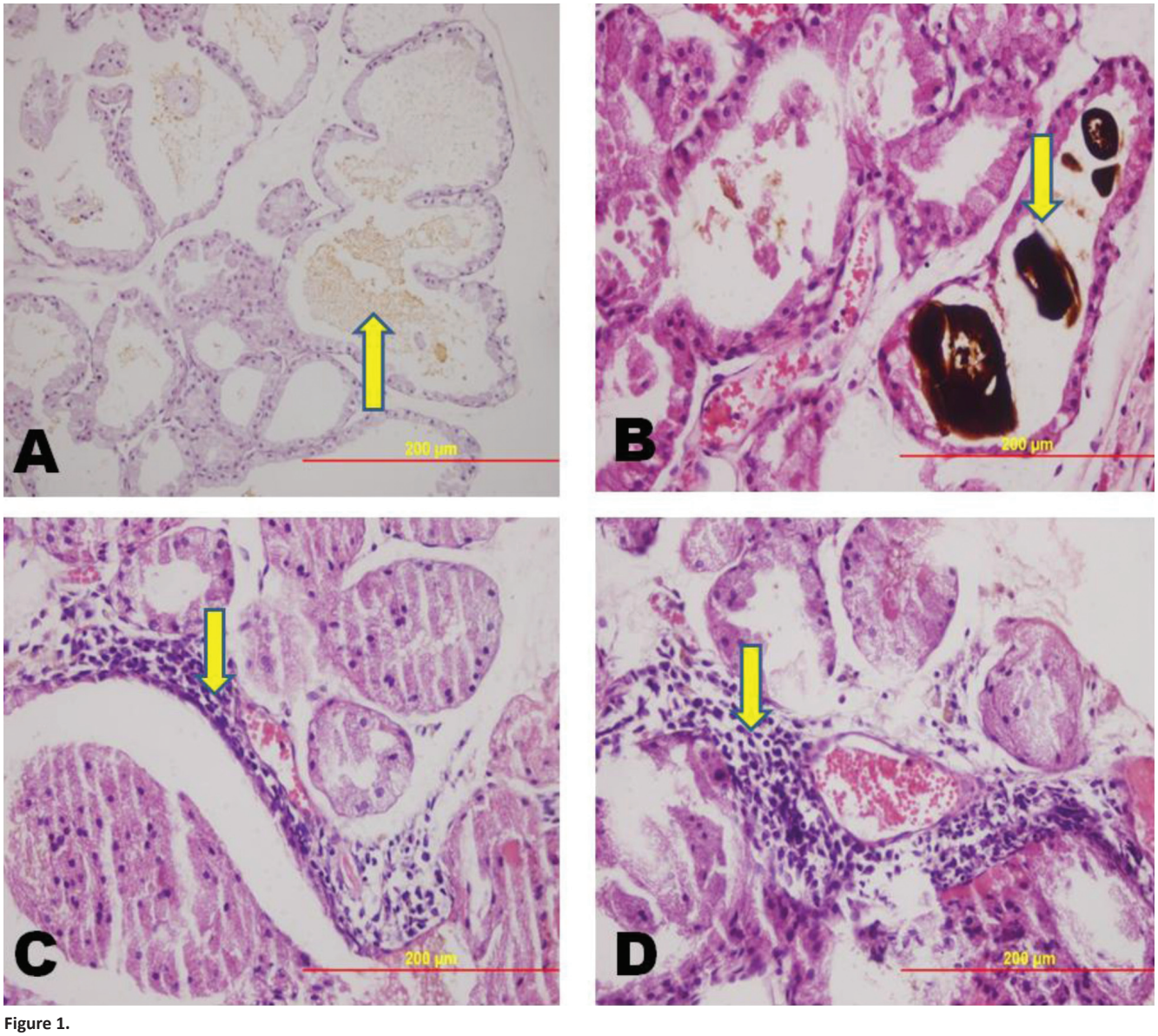


Figure 1.
A. Glandula lacrimalis cystic dilatation X40 HE (Acute OXA treatment + waiting period)
B. Glandula lacrimalis corpora amylacea X40 HE (Chronic OXA treatment + waiting period)
C. & D. Glandula lacrimalis inflammation X40 HE (Chronic OXA treatment + waiting period)

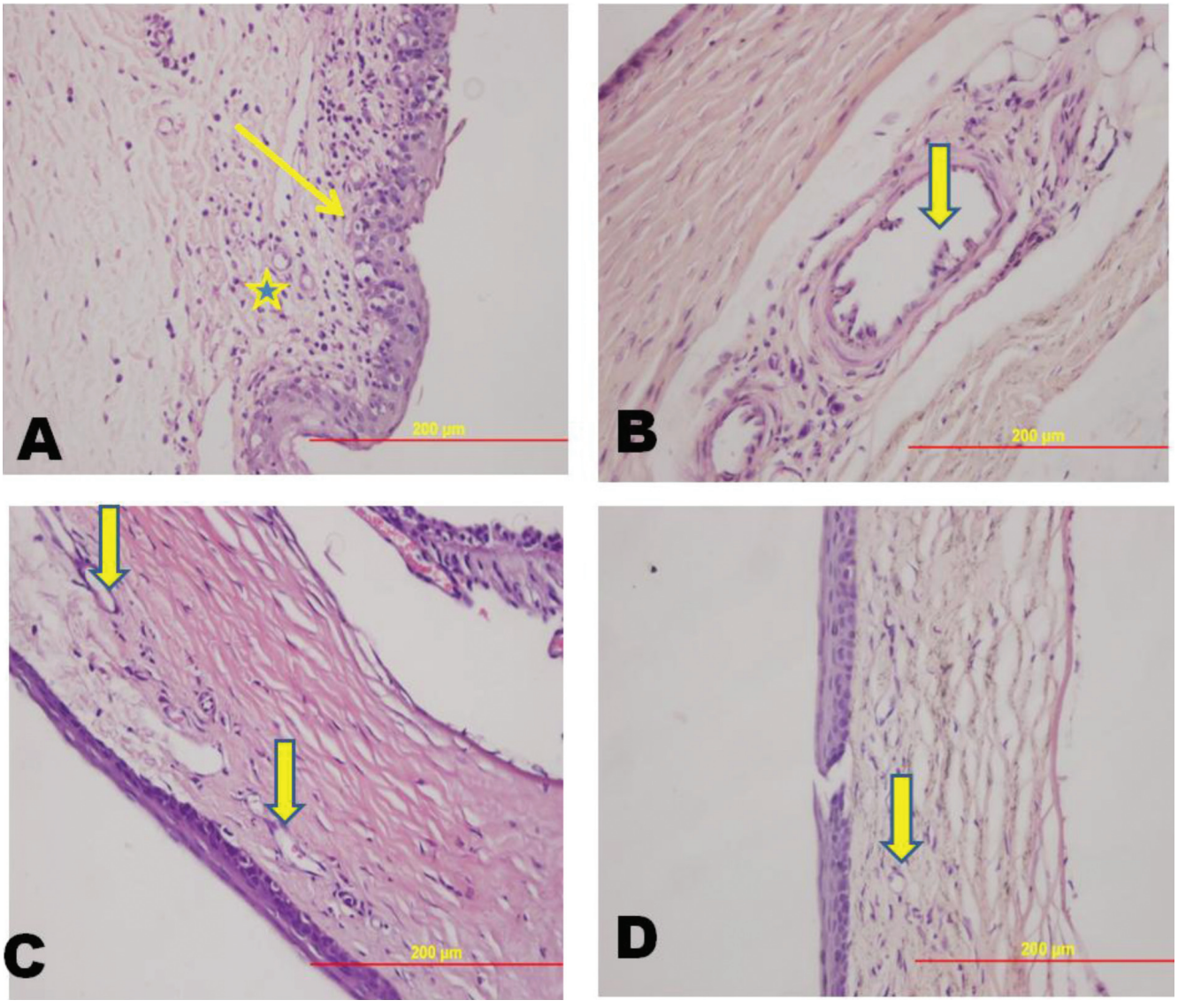


Figure 2.
A. Conjunctiva epithelial degeneration, basal vacuolar dilatation (arrow) with inflammatory cells (star) X40 HE (Chronic OXA treatment)
B. Endothelial polypoid proliferation of large vessel X40 HE (Acute OXA treatment + waiting period)
C. & D. Corneal neo-vascularisation X40 HE (Acute OXA treatment + waiting period)

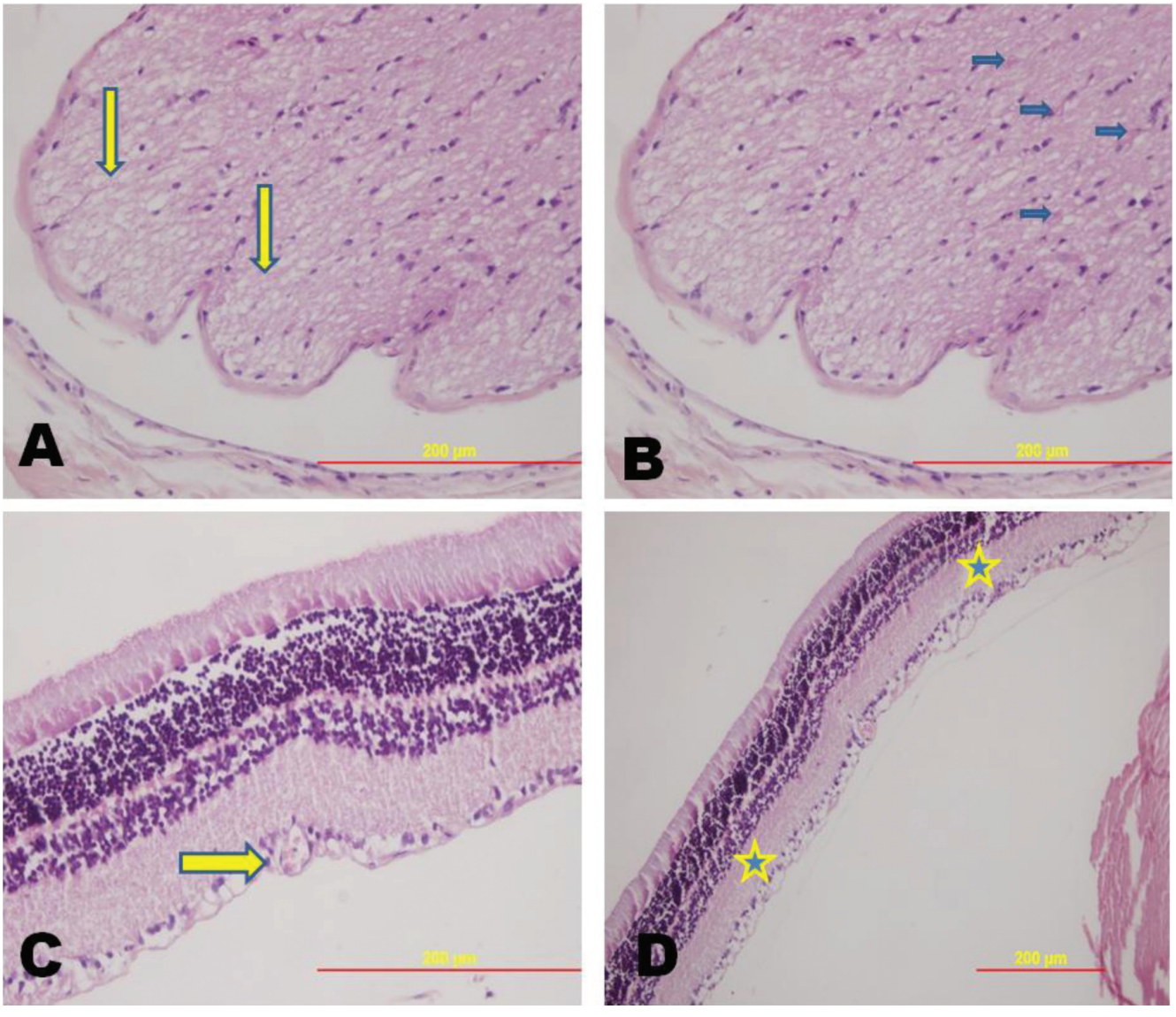


Figure 3.
A. Optic nerve vacuolar degeneration X40 HE (Acute OXA treatment)
B. Optic nerve capillarisation X40 HE (Acute OXA treatment).
C. Retinal nevre fibre layer degeneration X40 HE (Chronic OXA treatment)
D. Retinal nevre fibre layer vascularisation X20 HE (Chronic OXA treatment)

Table 1. The histopathological findings of all experimental groups, number of pathologic sample/number of evaluated preparation.

Findings	Control	Acute OXA treatment	Acute OXA treatment + waiting period	Chronic OXA treatment	Chronic OXA treatment + waiting period
Cornea					
Neovascularization	0/4	4/9	3/8	6/8	6/8
Conjunctiva					
Epithelial degeneration	0/4	0/9	1/8	2/8	0/8
Retina					
Degeneration of retinal nerve fibre layer	0/4	2 M, 2 S/9	3M, 1 S/8	5 M, 3 S/8	3M, 2 S/8
Vessel					
Endothelial polipoid proliferation	0/4	3/9	2/8	4/8	3/8
Glandula Lacrimalis					
Corpora amylacea	3/4	4/7	2/4	1/2	5/7
Cystic dilatation	0/4	2/7	0/4	0/2	1/7
Inflammatory cells	0/4	0/7	0/4	0/2	1/7
Optic Nerve					
Inflammatory cells	0/3	0/6	0/4	0/6	0/5
Necrosis	0/3	0/6	0/4	0/6	0/5
Oedema	0/3	0/6	0/4	0/6	0/5
Number of seen capillary	6-3-4	3-4-3-3-0-0	7-3-5-6-3	4-4-6-8-9-3	5-3-9-7-4
Vacuolar degeneration	0/3	2/6	1/5	0/6	0/5

Degeneration of retinal nerve fibre layer has been scored as medium (+, M) and serious (++, S). Capiller vascular number of each evaluated preparation given on the table (X40 magnification for evaluation.)

ceasing the treatment. All of the findings are summarized in Table 1.

DISCUSSION

The aim of the study was to investigate the safety of short-, and long-term OXA treatment on ocular tissues. Additionally, if there is any tissue damage, reversibility of the findings during waiting periods has been also investigated.

One of the advantages of animal studies is that only the effect of the suspected drug is evaluated. Considering many drugs taken altogether in a treatment regime, it is highly difficult to distinguish which one of them is responsible from the harmful effect. Also, synergistic effects of drugs can increase the number of unexpected adverse effects. In addition, the progression of cancer in the body can mimic or facilitate development of symptoms due to increased permeability of tissue barriers etc. While deciding the dose and duration of OXA in our animal study, we have taken previous literatures [8-11], on OXA's animal neurotoxic study doses into account. Similar to our previous study [2], we have evaluated all ocular tissue layers. Histopathological evaluation revealed many different pathological alterations in all parts of the ocular tissues; neo-vascularisation of cornea, endothelial polypoid proliferation of vessel and degeneration of retinal nerve fibre layer were important findings. These findings did not regress after discontinuation of OXA.

Noguchi et al., [6] reported that the adverse effects of OXA frequently affect Japanese patients. Some of the symptoms appear at the early period of treatment that are reversible and mild in most cases. A 64-year-old woman developed blurred vision, transient bilateral temporal hemianopsia and progressive visual loss just three hours after administration of the drug and all of the visual symptoms were transient [1]. As, our study is an animal study, we could not describe any clinical findings such as blurred vision and pain, watering eyes; but, we could demonstrate histopathological findings of serious side effects of OXA on ophthalmic tissues. A case report of a 52 year-old woman describing visual loss, altered color vision and neurological symtoms under the advanced colorectal treatment, supports the findings of our study [12]. Her electrooculogram test revealed

severe impairment of the retinal pigment epithelium and even after 8 months, electrooculogram remained abnormal. Park et al. have reported another 43-year-old woman, after one cycle of chemotherapy. This patient developed bilateral concentric field defect and electroretinogram revealed marked reduction of responses at both eyes and 3 months later electroretinogram still remained abnormal [1]. At some point, degeneration of retinal nerve fibre layer detected in this experimental study could explain the reported clinical findings.

Alterations in vascular cells were another remarkable finding of this study. The alterations have been determined as neo-vascularisation on cornea, endothelial polypoid proliferation of the vessel and increased capillary vessels of the optic nerve. Cisplatine induced neo-vascularization has been reported previously [3]; as another member of platinum derivatives OXA, induces neo-vascularisation irreversibly on eye tissues even during the acute-short term treatment.

The findings of glandula lacrimalis were not considered to be important because the development of corpora amylacea was also seen in the control group.

We preferred to describe the raw data of the each group on the Table 1; Statistical evaluation was not possible due to low number of preparations which could be evaluated. Hence, the changes of vascular cells and degeneration of retinal nerve fibre layer can be easier to follow in the different groups. This study is limited to one kind of staining technique, therefore it give us a general structural idea about the OXA side effects and its irreversible pattern on eye tissues in the studied posology. Additionally, except limited number of case reports, there is not any detailed study about the ocular effects of OXA, therefore we were unable to discuss our results from histopathological perspective. In other words, our study will shed the light on the future studies.

CONCLUSION

Ocular toxicity findings of OXA such as retinal nerve fibre degeneration and vascular alterations should be kept in mind in the clinical practice, during any treatment regimen. An irreversible damage on the ocular tissues may occur, if there is any suspicion, the patient should be referred to the ophthalmologist. Detailed reports also needed to clarify the severity and frequency of the ocular toxic effects of OXA.

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