NEURAL REGENERATION RESEARCH
Volume 7, Issue 35, December 2012

www.nrronline.org

doi:10.3969/j.issn.1673-5374.2012.35.004 [http://www.crter.org/nrr-2012-qkquanwen.html]
Liu SM, Liu W, Ma YL, Liu KG, Wang MZ. Suprachoroidal injection of ketorolac tromethamine does not cause retinal damage. Neural Regen Res. 2012;7(35):2770-2777.

Suprachoroidal injection of ketorolac tromethamine does not cause retinal damage☆

Sumeng Liu[1], Wu Liu[2], Yaling Ma[1], Kegao Liu[2], Meizi Wang[2]

1 *General Hospital of Ningxia Medical University, Yinchuan 750004, Ningxia Hui Autonomous Region, China*
2 *Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University; Beijing Ophthalmology & Visual Sciences Key Lab, Beijing 100730, China*

Abstract

Rabbit right eyes were injected with 3 or 6 mg ketorolac tromethamine into the suprachoroidal space. Electroretinography results demonstrated no abnormal changes in rod cell response, maximum rod cell or cone cell mixing reaction, oscillation potential, cone cell response, waveform, amplitude, and potential of 30 Hz scintillation response in right eyes before injection, and at 1, 2, and 4 weeks after injection. There was no difference between left (control) and right eyes. Under light microscopy, the histomorphology of cells in each retinal layer was normal at 4 weeks following 6 mg ketorolac tromethamine administration. These results indicate that a single suprachoroidal injection of 3 or 6 mg ketorolac tromethamine into rabbits was safe. Suprachoroidal space injection appears to be safe.

Key Words

nonsteroidal anti-inflammatory drug; ketorolac tromethamine; segment disease; retina; suprachoroidal space; retinal toxicity; electroretinography; pharmacology; regeneration; neural regeneration

Research Highlights

(1) Previous studies have reported vitreous space injection of ketorolac tromethamine to observe neurotoxicity on the retina. However, suprachoroidal injection of ketorolac tromethamine has not been reported.
(2) A single suprachoroidal injection of 6 mg ketorolac tromethamine in rabbits showed no significant influence on electroretinograms and retinal morphological structures.
(3) Results suggested that suprachoroidal injection of 6 mg ketorolac tromethamine in rabbits is safe.

Sumeng Liu☆, Studying for doctorate, General Hospital of Ningxia Medical University, Yinchuan 750004, Ningxia Hui Autonomous Region, China

Corresponding author: Wu Liu, M.D., Professor, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University; Beijing Ophthalmology & Visual Sciences Key Lab, Beijing 100730, China; Yaling Ma, M.D., Professor, General Hospital of Ningxia Medical University, Yinchuan 750004, Ningxia Hui Autonomous Region, China
wuliubj@yahoo.com; myleye@hotmail.com

Received: 2012-08-22
Accepted: 2012-11-09
(N20120716006/YJ)

INTRODUCTION

Ketorolac tromethamine is an active nonsteroidal anti-inflammatory drug and non-narcotic analgesic with cyclooxygenase inhibitory activity. Its use does not lead to dependency[1-6]. It can be administered intramuscularly, intravenously, orally, and as eye drops as the water-soluble Trometamol salt. Ketorolac tromethamine has been widely used for the treatment of ocular inflammation, such as allergic conjunctivitis and keratitis, or as a prophylaxis to prevent post-procedure pain and cystoid macular edema[7-19]. There has been outstanding performance of ketorolac tromethamine in antiangiogenesis and in anti-proliferation in recent years[20-21]. The mechanism of action is thought to be primarily through inhibition of cyclooxygenase[22]. The most common adverse reaction of topical nonsteroidal

anti-inflammatory drugs such as ketorolac tromethamine and diclofenac is a burning and stinging sensation. Others include delayed corneal epithelial healing and conjunctival hyperemia. Serious complications such as corneal ulcer and corneal perforation have been individually reported in a few postoperative patients[23]. However, these symptoms were due to the preservative in the preparations.

The effects of medical treatments for posterior segment disease are less than satisfactory[24]. Systemic medications usually use large doses of drugs to enhance the effective drug concentration in eyes, and thus the drug inevitably has inherent side effects and contraindications are hard to be overcome[25]. Topical therapy such as retrobulbar injection achieves therapeutic drug levels too slowly, and intravitreal injection can easily lead to retina toxicity and vitreous opacity. Another option is to inject drugs into the suprachoroidal space, which is a potential cavity gap limited anteriorly in the region of the scleral spur and posteriorly by the transscleral connections of the short posterior ciliary vessels to the choroid[26]. Possible advantages of this route of drug delivery are ease of drug absorption, fast achievement of high intraocular drug concentrations after a single dose, and long duration of drug presence because of abundant vessels of the deep-seated choroid. There are many reports of suprachoroidal cavity drug administration to treat ocular perforating injury, endophthalmitis, and to repair retinal detachments[27-32]. There are also disadvantages such as suprachoroidal hemorrhage and choroidal detachment. To the best of our knowledge, the safety of suprachoroidal injection of ketorolac tromethamine has never been reported.

Thus, this study was designed to determine if ketorolac tromethamine is nontoxic to the retina when injected into the suprachoroidal space of rabbits, and to assess the safety of the drug administration route.

RESULTS

Quantitative analysis of experimental animals

A total of 12 rabbits were equally and randomly divided into 3 mg and 6 mg treatment groups. Rabbits in the 3 mg (0.05 mL) group were injected with ketorolac tromethamine in the right eye, while the dose in the 6 mg group was 6 mg (0.05 mL). The left eye was injected with 0.05 mL saline (0.9% sodium chloride solution) as a control.

Ketorolac tromethamine did not affect the appearance of rabbit retinas

All animals tolerated the injections well with no external signs of inflammation. Slit lamp biomicroscopy at baseline and 1, 2, and 4 weeks after injection revealed no intraocular inflammation or cataract formation. Indirect ophthalmoscopy of ketorolac tromethamine-injected eyes showed no signs of hemorrhage, whitening, retinal pigment epithelium loss, or optic nerve pallor.

Electroretinogram waveform appeared normal after ketorolac tromethamine injection

Representative scotopic and photopic electroretinogram waveforms are shown in Figure 1. All groups of eyes showed similar waveform patterns with clearly distinguishable a-waves and b-waves. No waveform depression was observed in eyes injected with ketorolac tromethamine.

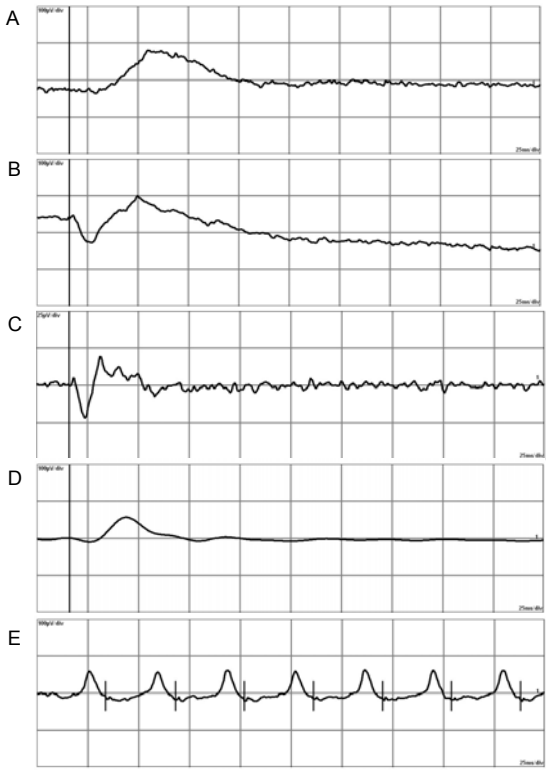


Figure 1 Electroretinogram of rabbit right eye (experimental eye) in the 6 mg treatment group.

Unit of Y-axis is mV. (A) Rod cell response; (B) cone cell response; (C) maximum rod cell-cone cell mixing reaction; (D) 30 Hz scintillation response; (E) oscillation potential.

There was no evidence that wave amplitudes produced by the standard electroretinogram differed significantly for eyes treated with 3 mg or 6 mg ketorolac tromethamine compared with saline-treated eyes (P > 0.05, Tables 1–3).

Table 1 Data from the electroretinogram of rabbit left and right eyes after right eyes were injected with 3 mg ketorolac tromethamine

Item	Before administration		1 week after administration		2 weeks after administration		4 weeks after administration	
	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye
Scotopic ROD								
b								
Median	177.0	166.0	263.0	141.0	190.0	133.0	164.0	173.0
Minimum value	88.9	85.3	141.0	111.0	112.0	113.0	103.0	124.0
Maximum value	205.0	245.0	279.0	197.0	220.0	155.0	168.0	191.0
Average value	157.0	165.4	227.7	149.7	174.0	133.7	145.0	162.7
Standard error	60.6	79.8	75.5	43.6	55.8	21.0	36.4	34.7
S-combined								
a								
Median	76.3	51.1	110.0	51.3	65.9	54.2	84.0	72.8
Minimum value	55.7	48.0	58.4	42.3	43.0	53.5	71.3	57.0
Maximum value	82.7	71.5	117.0	89.5	69.0	65.3	92.6	93.5
Average value	71.6	56.9	95.1	61.0	59.3	57.7	82.6	74.4
Standard error	14.1	12.8	32.0	25.1	14.2	6.6	10.7	18.3
b								
Median	212.0	160.0	273.0	146.0	220.0	171.0	175.0	194.0
Minimum value	149.0	108.0	188.0	126.0	153.0	146.0	104.0	128.0
Maximum value	238.0	275.0	298.0	209.0	238.0	172.0	190.0	203.0
Average value	199.7	181.0	253.0	160.3	203.7	163.0	156.3	175.0
Standard error	45.8	85.5	57.7	43.3	44.8	14.7	45.9	41.0
Ops								
Median	61.9	57.3	80.8	45.6	51.0	64.9	76.1	75.0
Minimum value	39.4	45.2	73.2	41.4	45.0	61.6	54.6	54.0
Maximum value	104.2	94.7	100.6	88.7	66.5	90.0	89.6	80.4
Average value	68.5	65.8	84.6	58.5	54.2	72.2	73.5	69.8
Standard error	32.9	25.8	14.1	26.2	11.1	15. 6	17.7	13.9
Photopic ROD								
a								
Median	11.2	9.6	9.3	5.5	14.5	8.1	10.8	9.2
Minimum value	8.3	5.4	4.6	3.6	8.1	3.9	8.6	8.9
Maximum value	13.8	16.9	15.0	9.3	15.8	9.8	13.1	11.0
Average value	11.1	10.6	9.7	6.1	12.8	7.3	10.8	9.7
Standard error	2.8	5.8	5.1	2.9	4.1	3.0	2.2	1.1
b								
Median	43.9	33.7	67.4	28.5	54.2	45.2	80.4	60.9
Minimum value	36.1	35.0	42.6	23.3	37.3	26.1	43.0	41.0
Maximum value	68.8	46.1	79.3	107.0	79.4	66.7	119.0	100.0
Average value	49.6	38.3	63.1	52.9	57.0	46.0	80.8	67.3
Standard error	17.1	6.8	18.7	46.9	21.2	20.3	38.0	30.0
30 Hz								
Median	34.3	35.8	38.8	34.9	31.9	35.5	56.1	36.3
Minimum value	25.5	28.8	34.6	23.2	28.9	28.4	30.4	27.7
Maximum value	53.0	41.1	55.6	71.4	45.4	35.7	81.4	44.7
Average value	37.6	35.2	43.0	43.2	35.4	33.2	56.0	36.2
Standard error	14.0	6.1	11.1	25.1	8.8	4.2	25.5	8.5

Scotopic ROD: Rod cell response; S-combined: maximum rod cell-cone cell mixing reaction; Ops: oscillation potential; photopic ROD: cone cell response; 30 Hz: 30 Hz scintillation response; a: a-wave; b: b-wave. All scotopic and photopic results are expressed in microvolts.

Ketorolac tromethamine did not affect retinal appearance

After 4 weeks, histopathological specimens were examined by light microscopy (hematoxylin-eosin staining). There were no significant differences between the histological findings of eyes injected with ketorolac tromethamine and saline as shown in Figure 2A for one rabbit injected with 6 mg, and Figure 2B for a control eye. All retinal layers, including the ganglion cell layer, inner nuclear layer, outer nuclear layer, and photoreceptor layer exhibited normal structures. The photoreceptor layer was arranged into a microgroove shape and was homogeneously stained. The cell nuclei of the other layers appeared normal.

DISCUSSION

Corticosteroids are potent anti-inflammatory medications that are widely used in treating fundus oculi disease.

Table 2 Data from the electroretinogram of rabbit left and right eyes after right eyes received 6 mg of ketorolac tromethamine injection

Item	Before administration		1 week after administration		2 weeks after administration		4 weeks after administration	
	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye
Scotopic ROD								
b								
Median	245.0	123.0	196.0	136.0	123.0	137.0	167.0	128.0
Minimum value	173.0	100.0	143.0	135.0	120.0	104.0	166.0	126.0
Maximum value	276.0	145.0	451.0	210.0	263.0	268.0	208.0	168.0
Average value	231.3	122.7	263.3	160.3	168.7	169.7	180.3	140.7
Standard error	52.8	22.5	164.7	43.0	81.7	86.7	24.0	23.7
S-combined								
a								
Median	70.3	53.4	69.0	53.0	46.9	55.8	64.5	48.2
Minimum value	48.3	50.1	62.2	47.7	45.1	53.0	45.1	46.5
Maximum value	77.1	59.2	146.0	71.1	76.3	63.8	70.1	99.4
Average value	65.2	54.2	92.4	57.3	56.1	57.5	59.9	64.7
Standard error	15.0	4.6	46.5	12.3	17.5	5.6	13.1	30.1
b								
Median	272.0	152.0	241.0	164.0	134.0	164.0	205.0	137.0
Minimum value	187.0	117.0	165.0	158.0	113.0	154.0	113.0	111.0
Maximum value	302.0	170.0	465.0	234.0	187.0	168.0	220.0	199.0
Average value	253.7	146.3	290.3	185.3	144.7	162.0	179.3	149.0
Standard error	59.6	27.0	156.0	42.2	38.1	7.2	57.9	45.2
Ops								
Median	57.4	65.1	59.1	56.6	37.3	63.7	54.0	46.1
Minimum value	47.6	54.6	56.8	55.8	34.3	56.6	34.3	36.6
Maximum value	61.8	74.4	95.0	76.1	79.5	71.0	62.4	86.4
Average value	55.6	64.7	70.3	62.9	50.7	63.8	50.3	56.4
Standard error	7.2	9.9	21.4	11.5	25.3	7.2	14.4	26.4
Photopic ROD								
a								
Median	5.5	6.5	15.6	11.7	4.1	6.4	4.1	6.8
Minimum value	5.0	4.4	5.0	6.5	1.3	3.1	3.9	4.7
Maximum value	8.3	11.9	17.1	14.9	7.5	11.7	5.9	14.6
Average value	6.3	7.6	12.6	11.0	4.3	7.0	4.6	8.7
Standard error	1.8	3.9	6.6	4.2	3.1	4.4	1.1	5.2
b								
Median	45.8	59.1	74.5	35.9	22.0	33.3	45.1	37.3
Minimum value	41.2	52.9	33.0	33.3	20.8	30.7	20.8	31.7
Maximum value	48.3	61.8	80.1	73.6	64.1	55.5	59.6	58.6
Average value	45.1	57.9	62.5	47.6	35.6	39.8	41.8	42.5
Standard error	3.6	4.6	25.7	22.6	24.7	13.6	19.6	14.2
30 Hz								
Median	37.9	36.1	61.1	33.6	43.8	32.9	35.6	32.6
Minimum value	36.9	29.7	24.5	32.9	23.8	29.3	23.8	25.0
Maximum value	46.9	36.7	75.9	36.2	93.8	36.7	55.6	54.3
Average value	40.6	34.2	53.8	34.2	53.8	33.0	38.4	37.3
Standard error	5.5	3.8	26.5	1.7	36.0	3.7	16.1	15.2

Scotopic ROD: Rod cell response; S-combined: maximum rod cell-cone cell mixing reaction; Ops: oscillation potential; photopic ROD: cone cell response; 30 Hz: 30 Hz scintillation response; a: a-wave; b: b-wave. All scotopic and photopic results are expressed in microvolts.

However, the side effects and the risk-benefit ratio preclude their use in some patients. A growing body of scientific evidence supports the use of nonsteroidal anti-inflammatory drugs in improving the treatment of diseases such as cystoid macular edema, diabetic macular edema, neovascularization, uveitis, and even age-related macular degeneration[33-37]. In this report, we examined the safety of one such nonsteroidal anti-inflammatory drug, ketorolac tromethamine. The combination of electroretinogram and histopathological analyses demonstrated that a suprachoroidal dose as high as 6 mg of ketorolac tromethamine was well tolerated and safe in the rabbit retina.

Komarowska *et al* [38] reported that repeated intravitreal injections of commercial ketorolac preparations (3 mg, with preservative) at 2-week intervals induced local histological damage but was not sufficient to affect the electroretinogram data. A previous study showed that doses as high as 4 mg of ketorolac tromethamine injected into adult human eyes was nontoxic tromethamine[39]. However, eyes injected intravitreally

with 6 mg of ketorolac tromethamine demonstrated a 10% amplitude decrease at 4 weeks and a 20–30% decrease at 8 weeks. Based on our results, it can be assumed that administration of 3 and 6 mg ketorolac tromethamine may not damage the retina. The differing results of our study may be due to the different routes of administration. Possible advantages of suprachoroidal injection are ease of drug absorption and fast achievement of high intraocular drug concentrations after a single dose because of abundant vessels of the deep-seated choroid in this region. This injection route is obviously better tolerated than intravitreal injection.

Table 3 Difference of control eyes and right eyes treated with 3 mg or 6 mg of ketorolac tromethamine (*P* value)

Item	Statistical difference between left and right eyes after right eye treated with 3 mg of ketorolac tromethamine	Statistical difference between left and right eyes after right eye treated with 6 mg of ketorolac tromethamine
Scotopic ROD		
b	0.619	0.847
S-combined		
a	0.810	0.135
b	0.532	0.166
Ops	0.866	0.594
Photopic ROD		
a	0.448	0.405
b	0.537	0.947
30 Hz	0.955	0.097

Scotopic ROD: Rod cell response; S-combined: maximum rod cell-cone cell mixing reaction; Ops: oscillation potential; photopic ROD: cone cell response; 30 Hz: 30 Hz scintillation response; a: a-wave; b: b-wave. The method of generalized estimating equations for correlation analysis of repeated-measures data was used to account for the repeated measurements within subjects.

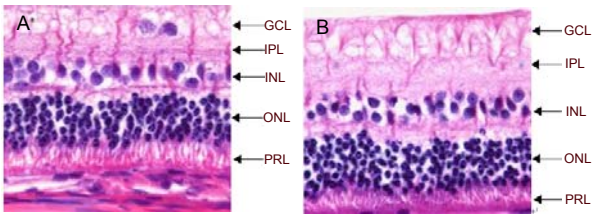


Figure 2 Light microscopy of the retina at 4 weeks after injection of 6 mg of ketorolac tromethamine (A) or saline (B) (hematoxylin-eosin staining, × 400).

Ganglion cells, inner plexiform layer, inner nuclear layer, outer nuclear layer, and photoreceptor layer exhibited normal structure after injection with 6 mg of ketorolac tromethamine.

GCL: Ganglion cell layer; IPL: inner plexiform layer; INL: inner nuclear layer; ONL: outer nuclear layer; PRL: photoreceptor cell layer.

There are increasingly more reports of administration of drugs into the suprachoroidal space. Olsen *et al* [40] demonstrated the safety and feasibility of such administration experimentally, and proved that it was an effective method to deliver targeted drugs into the posterior segment. Wang *et al* [41] reported that suprachoroidal injection of ketorolac tromethamine could achieve an effective drug level in the retina/choroid. The mean maximum concentration of ketorolac tromethamine in the retina/choroid was 56.71 ± 22.64 μg/g (at 0.5 hours) after suprachoroidal injection of 250 μg ketorolac tromethamine. Our findings clarify and further expand upon these results.

In conclusion, ketorolac tromethamine, a nonsteroidal anti-inflammatory drug, is nontoxic to the retina when injected into the suprachoroidal space of rabbits. The results are promising. However, this study has limitations because of the low number of eyes injected and the limited number of doses used.

MATERIALS AND METHODS

Design

A randomized, controlled animal experiment.

Time and setting

Experiments were performed in Capital Medical University, China between February and September 2011.

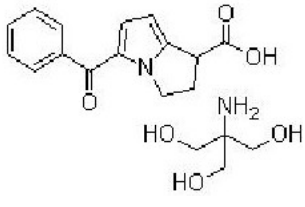
Materials

Animals

Twelve 6-month-old, healthy, specific pathogen free, male adult albino rabbits weighing 2.0 kg each were housed in separate cages and maintained in a controlled environment for these experiments. Animals were provided by the Animal Care Department of the Capital Medical University, license No. SCXK (Jing) 2007-0001. All experimental use of animals complied with the *Guidance Suggestions for the Care and Use of Laboratory Animals*, issued by the Ministry of Science and Technology of China[42].

Drug

The ketorolac tromethamine chemical formula is $C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$, and the chemical structural formula is as follows:



It was acquired in powder form (Ketorolac tris salt; Weidu Medical Technology Chemical Co., Ltd., Jinan, China) and dissolved in saline (0.9% sodium chloride solution) under sterile conditions.

Methods

Ketorolac tromethamine administration in the suprachoroidal space

Animals were first anesthetized with an intramuscular injection of 50 mg/kg of ketamine hydrochloride and 20 mg/kg of xylazine hydrochloride. Before all suprachoroidal space injections, the eyes were treated with several drops of 0.5% proparacaine hydrochloride (Alcon, Inc., Brussels, Belgium), and tropicamide-phenylephrine ophthalmic solution (Santen Pharmaceutical Co., Ltd., Suzhou, China) was applied to dilate the pupils. Then, a conjunctival peritomy was made on the superonasal quadrant, exposing clear access to the sclera. A parallel 2 mm scleral tunnel incision was made with a blade about 4 mm away from the inferior limbus to expose bare choroid. Before injection, 0.1 mL of aqueous humor was drained to minimize the leakage and to reduce the intraocular pressure. Viscoelastic materials (Bausch & Lomb Surgical, Inc., Beijing, China) were injected into the suprachoroidal space to facilitate the drug's delivery. A volume of 0.05 mL was then slowly injected by a 0.1 mL-syringe with a special needle (32 G, 0.22 mm × 5 mm, Beijing Brightway Medical Instruments Co., Ltd., Beijing, China). According to previously reported procedures[38-39], the right eyes of each animal in the 3 mg treatment group and 6 mg treatment group were given a single injection into the suprachoroidal space, with 3 mg/0.05 mL, and 6 mg/0.05 mL of ketorolac tromethamine. Left eyes were given a single injection into the suprachoroidal space with 0.05 mL of saline, as a control.

Electroretinography of retina functions in rabbits

All animals underwent electroretinography exams prior to injections and exams were repeated at 1, 2, and 4 weeks after drug delivery. Standard dark-adapted and light-adapted electroretinography was performed after anesthesia as discussed above, and pupillary dilation was induced by topical tropicamide. Electroretinography responses were recorded in the dark-adapted animals after 1 hour of dark equilibration. The recording electrode (Eye Institute of Tongren Hospital, Beijing, China) was positioned on the cornea. The reference electrode (Eye Institute of Tongren Hospital) was inserted into the lip and the ground electrode was placed subcutaneously in the ipsilateral leg. All procedures were carried out under dim red light at the end of the adaptation period. Full-field stimulation was used in the experiments. The flash stimuli were 0.01 cd·s/m^2 for rod stimulation, 3.0 cd·s/m^2 for all other standard responses, and 30 cd·s/m^2 for light adaptation and background luminance. Electroretinography analysis was based on the amplitude of a-wave, b-wave, and the total amplitudes of oscillatory potentials (Ops), as well as the average amplitude of 30 Hz flicker. According to the ISCEV Standard[43], results were designated as Dark-adapted 0.01 electroretinography (rod response, Rod-R), Dark-adapted 3.0 electroretinography (standard combined response, S-combined), Dark-adapted 3.0 oscillatory potentials (oscillatory potentials, Ops), Light-adapted 3.0 electroretinography (photopic response, phot.R), and Light-adapted 3.0 flicker electroretinography (30 Hz), respectively. The a-wave reflects the function of the inner segment of the photoreceptors, and the b-wave reflects the activity of the Muller cells and the bipolar cells. Electroretinography responses of the experimental eyes (right eye) were compared with electroretinography responses of the control eyes (left eye) in each wave study.

Light microscopic observation of rabbit retinal tissue morphology

After the electroretinography test, at 4 weeks, the rabbits were euthanatized with an intravenous injection of air. The eyes were immediately enucleated and fixed in a solution of glacial acetic acid, formaldehyde, and ethanol, provided by the Peking University People's Hospital for light microscopy methods (Zeiss, Oberkochen, Germany). After embedding, the eyes were sliced into 7 μm thick coronal sections, and stained with hematoxylin-eosin. The light microscopy magnification was × 400.

Statistical analysis

The data were analyzed using SPSS 17.0 software (IBM, New York, USA, serial No. 4625180487). The method of general linear model-repeated measures was used to account for the repeated measurements within subjects.

Acknowledgments: The authors would like to thank Haiting Cheng from the General Hospital of Ningxia Medical University in China for excellent assistance with laboratory procedures.

Author contributions: Sumeng Liu participated in the experimental operation, data analysis, statistical processing, and manuscript writing and was in charge of all experiments. Wu Liu and Yaling Ma were responsible for the study design, study supervision, and manuscript preparation. Wu Liu contributed in the animal surgery. Kegao Liu participated in all aspects of the electroretinography tests. Meizi Wang

participated in data collection. All authors approved the final version of the manuscript.

Conflicts of interest: None declared.

Ethical approval: Animal care and experimental procedures were approved by the Animal Care Department of the Capital Medical University in China.

Author statements: The manuscript is original, has not been submitted to or is not under consideration by another publication, has not been previously published in any language or any form, including electronic, and contains no disclosure of confidential information or authorship/patent application disputations.

REFERENCES

[1] Sivaprasad S, Bunce C, Wormald R. Non-steroidal anti-inflammatory agents for cystoid macular oedema following cataract surgery: a systematic review. Br J Ophthalmol. 2005;89(11):1420-1422.

[2] Lynn AM, Bradford H, Kantor ED, et al. Ketorolac tromethamine: stereo-specific pharmacokinetics and single-dose use in postoperative infants aged 2-6 months. Paediatr Anaesth. 2011;21(3):325-334.

[3] Attar M, Schiffman R, Borbridge L, et al. Ocular pharmacokinetics of 0.45% ketorolac tromethamine. Clin Ophthalmol. 2010;4:1403-1408.

[4] Lin TF, Lin FS, Chou WH, et al. Compatibility and stability of binary mixtures of ketorolac tromethamine and tramadol hydrochloride injection concentrate and diluted infusion solution. Acta Anaesthesiol Taiwan. 2010;48(3): 117-121.

[5] Salaris M, Nieddu M, Rubattu N, et al. Acid and base degraded products of ketorolac. J Pharm Biomed Anal. 2010;52(2):320-322.

[6] Sinha VR, Kumar RV, Singh G. Ketorolac tromethamine formulations: an overview. Expert Opin Drug Deliv. 2009; 6(9):961-975.

[7] Rifkin L, Schaal S. Shortening ocular pain duration following intravitreal injections. Eur J Ophthalmol. 2012; 22(6):1008-1012.

[8] Sivaprasad S, Bunce C, Patel N. Non-steroidal anti-inflammatory agents for treating cystoid macular oedema following cataract surgery. Cochrane Database Syst Rev. 2005;(1):CD004239.

[9] Yilmaz T, Cordero-Coma M, Gallagher MJ. Ketorolac therapy for the prevention of acute pseudophakic cystoid macular edema: a systematic review. Eye (Lond). 2012; 26(2):252-258.

[10] Despriet DD, Klaver CC, Witteman JC, et al. Complement factor H polymorphism, complement activators, and risk of age-related macular degeneration. JAMA. 2006;296(3): 301-309.

[11] Joussen AM, Poulaki V, Mitsiades N, et al. Nonsteroidal anti-inflammatory drugs prevent early diabetic retinopathy via TNF-alpha suppression. FASEB J. 2002;16(3): 438-440.

[12] Zanetti FR, Fulco EA, Chaves FR, et al. Effect of preoperative use of topical prednisolone acetate, ketorolac tromethamine, nepafenac and placebo, on the maintenance of intraoperative mydriasis during cataract surgery: a randomized trial. Indian J Ophthalmol. 2012; 60(4):277-281.

[13] Kim SJ, Doherty TJ, Cherney EF. Intravitreal ketorolac for chronic uveitis and macular edema: a pilot study. Arch Ophthalmol. 2012;130(4):456-460.

[14] Snyder MB, Bregmen DB. SPRIX (ketorolac tromethamine) nasal spray: a novel nonopioid alternative for managing moderate to moderately severe dental pain. Compend Contin Educ Dent. 2012;33 Spec No 1(1):2-11.

[15] Sivaprasad S, Bunce C, Crosby-Nwaobi R. Non-steroidal anti-inflammatory agents for treating cystoid macular oedema following cataract surgery. Cochrane Database Syst Rev. 2012;2:CD004239.

[16] Turan-Vural E, Torun-Acar B, Acar S. Effect of ketorolac add-on treatment on intra-ocular pressure in glaucoma patients receiving prostaglandin analogues. Ophthalmologica. 2012;227(4):205-209.

[17] Gianesello L, Pavoni V, Barboni E, et al. Perioperative pregabalin for postoperative pain control and quality of life after major spinal surgery. J Neurosurg Anesthesiol. 2012; 24(2):121-126.

[18] Wang XJ, Wong SH, Givergis R, et al. Evaluation of analgesic efficacy of bromfenac sodium ophthalmic solution 0.09% versus ketorolac tromethamine ophthalmic solution 0.5% following LASEK or Epi-LASIK. Clin Ophthalmol. 2011;5:1451-1457.

[19] Hungund S, Thakkar R. Effect of pretreatment with ketorolac tromethamine on operative pain during periodontal surgery: A case-control study. J Indian Soc Periodontol. 2011;15(1):55-58.

[20] Wilkinson-Berka JL. Vasoactive factors and diabetic retinopathy: vascular endothelial growth factor, cycoloxygenase-2 and nitric oxide. Curr Pharm Des. 2004;10(27):3331-3348.

[21] Kim SJ, Toma HS, Barnett JM, et al. Ketorolac inhibits choroidal neovascularization by suppression of retinal VEGF. Exp Eye Res. 2010;91(4):537-543.

[22] Rooks WH 2nd. The pharmacologic activity of ketorolac tromethamine. Pharmacotherapy. 1990;10(6 (Pt 2): 30S-32S.

[23] Gaynes BI, Fiscella R. Topical nonsteroidal anti-inflammatory drugs for ophthalmic use: a safety review. Drug Saf. 2002;25(4):233-250.

[24] Paliwal SK, Chauhan R, Sharma V, et al. Entrapment of ketorolac tromethamine in polymeric vehicle for controlled drug delivery. Indian J Pharm Sci. 2009;71(6): 687-691.

[25] Kompella UB, Kadam RS, Lee VH. Recent advances in ophthalmic drug delivery. Ther Deliv. 2010;1(3):435-456.

[26] Emi K, Pederson JE, Toris CB. Hydrostatic pressure of the suprachoroidal space. Invest Ophthalmol Vis Sci. 1989; 30(2):233-238.

[27] Poole TA, Sudarsky RD. Suprachoroidal implantation for the treatment of retinal detachment. Ophthalmology. 1986;93(11):1408-1412.
[28] Witkin AJ, Fineman M, Ho AC, et al. A novel method of draining intraoperative choroidal detachments during 23-gauge pars plana vitrectomy. Arch Ophthalmol. 2012; 130(8):1048-1050.
[29] Patel SR, Berezovsky DE, McCarey BE, et al. Targeted administration into the suprachoroidal space using a microneedle for drug delivery to the posterior segment of the eye. Invest Ophthalmol Vis Sci. 2012;53(8): 4433-4441.
[30] Tetz M, Rizzo S, Augustin AJ. Safety of submacular suprachoroidal drug administration via a microcatheter: retrospective analysis of European treatment results. Ophthalmologica. 2012;227(4):183-189.
[31] Jackson TL, Hussain A, Salisbury J, et al. Transscleral albumin diffusion and suprachoroidal albumin concentration in uveal effusion syndrome. Retina. 2012; 32(1):177-182.
[32] Rizzo S, Ebert FG, Bartolo ED, et al. Suprachoroidal drug infusion for the treatment of severe subfoveal hard exudates. Retina. 2012;32(4):776-784.
[33] Margalit E, Kugler LJ, Brumm MV, et al. The safety of intraocular ketorolac in rabbits. Invest Ophthalmol Vis Sci. 2006;47(5):2093-2099.
[34] Maldonado RM, Vianna RN, Cardoso GP, et al. Intravitreal injection of commercially available ketorolac tromethamine in eyes with diabetic macular edema refractory to laser photocoagulation. Curr Eye Res. 2011; 36(8):768-773.
[35] Giannantonio C, Papacci P, Purcaro V, et al. Effectiveness of ketorolac tromethamine in prevention of severe retinopathy of prematurity. J Pediatr Ophthalmol Strabismus. 2011;48(4):247-251.
[36] Margalit E, Boysen JL, Zastrocky JP, et al. Use of intraocular ketorolac tromethamine for the treatment of chronic cystoid macular edema. Can J Ophthalmol. 2010; 45(4):409-410.
[37] Kim SJ, Toma HS. Inhibition of choroidal neovascularization by intravitreal ketorolac. Arch Ophthalmol. 2010;128(5):596-600.
[38] Komarowska I, Heilweil G, Rosenfeld PJ, et al. Retinal toxicity of commercially available intravitreal ketorolac in albino rabbits. Retina. 2009;29(1):98-105.
[39] Kim SJ, Adams NA, Toma HS, et al. Safety of intravitreal ketorolac and diclofenac: an electroretinographic and histopathologic study. Retina. 2008;28(4):595-605.
[40] Olsen TW, Feng X, Wabner K, et al. Cannulation of the suprachoroidal space: a novel drug delivery methodology to the posterior segment. Am J Ophthalmol. 2006;142(5): 777-787.
[41] Wang M, Liu W, Lu Q, et al. Pharmacokinetic comparison of ketorolac after intracameral, intravitreal, and suprachoroidal administration in rabbits. Neurosurgery. in press.
[42] The Ministry of Science and Technology of the People's Republic of China. Guidance Suggestions for the Care and Use of Laboratory Animals. 2006-09-30.
[43] Marmor MF, Fulton AB, Holder GE, et al. ISCEV Standard for full-field clinical electroretinography (2008 update). Doc Ophthalmol. 2009;118(1):69-77.

(Edited by Tu QY, Bai H/Qiu Y/Song LP)