

Collagen crosslinking with photoactivated riboflavin in advanced infectious keratitis with corneal melting: Electrophysiological Study

Eman A. Awad, Mona Abdelkader, Ameera G. Abdelhameed, Walid M. Gaafar, Tharwat H. Mokbel

Ophthalmology Center, Faculty of Medicine, Mansoura University, Mansoura PO.35516, Egypt

Correspondence to: Eman A. Awad. Ophthalmology Center, Faculty of Medicine, Mansoura University, Mansoura, PO.35516, Egypt. dr_emanazmy@hotmail.com

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Abstract

• **AIM:** To assess the effect of photoactivated chromophore for keratitis crosslinking (PACK-CXL) in case of severe keratitis with melting on the electrophysiological function of the retina and the optic nerve.

• **METHODS:** The study included 32 eyes of 32 patients with smear positive severe infectious keratitis with corneal melting. The patients were randomly divided into two groups. Group I (control group) included 16 eyes received systemic and topical antimicrobial drugs guarded by culture and sensitivity test. Group II underwent CXL and then continued their antimicrobial treatment. Full field electroretinogram (ERG) and flash visual evoked potential (VEP) were done for each patient in both groups basically and then 1wk, 1 and 3mo post-treatment to assess the changes in the electrophysiological function of the retina and optic nerve.

• **RESULTS:** Healing of 10 eyes in group I in comparison to 14 eyes in group II was recorded. The mean duration of healing was 36.56 ± 5.21 d in group I vs 20.2 ± 4.4 d in group II ($P < 0.005$). In group II, ERG showed an insignificant reduction of all parameters of ERG and VEP after CXL. The amplitude of scotopic rod response, oscillatory potential amplitude, flicker amplitude and photopic cone response were insignificantly decreased ($P = 0.4, 0.8, 0.1, \text{ and } 0.3$ respectively). There were insignificant prolongation of latencies of scotopic rod, oscillatory potential, flicker and photopic cone response ($P = 0.2, 0.7, 0.5 \text{ and } 0.1$). There was slight delay in latency of VEP without a significant reduction in amplitude.

• **CONCLUSION:** CXL is an effective technique in treatment of severe infectious keratitis with melting as it halts the

melting process with acceptable safety on the retinal and optic nerve function.

• **KEYWORDS:** photoactivated chromophore for keratitis crosslinking; infectious keratitis; corneal melting; electroretinogram; flash visual evoked potential

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INTRODUCTION

The crosslinking (CXL) technique causes corneal stabilization which has an important role in patients with progressive ectatic disorders^[1]. It was found that the cross linked cornea has an increased resistance to digestive enzymes such as pepsin and collagenase which are produced by bacteria and fungi thus can prevent corneal melting^[2]. The combination of ultraviolet (UV) light and oxygen radicals induced during CXL may protect corneas with microbial keratitis by destroying microbes and protecting the collagen against destruction and melting caused by enzymes^[3-4]. Photoactivated chromophore for keratitis (PACK) is a CXL protocol applied for the treatment of infectious keratitis^[5]. The disadvantages of the application of UV were less penetration besides its strong dependence on the distance from the UV source and the corneal surface, which may cause unequal microbial inactivation. The complications related to UV light should be considered carefully in patients with corneal ulcer or corneal melting. Usually, only less than 10% of UV light penetrates the anterior chamber and reacts with the aqueous, which contains a small concentration of riboflavin. In case of corneal melting, the penetration would be more and can lead to endothelial cell loss^[4,6-9].

Alio *et al*^[8] reported that Theo Seiler (through a personal communication, April 12, 2010) suggested that the duration of UV-A application may be lengthened for infectious keratitis.

This may cause more penetration of UV-A which make the safety of the procedure on the posterior segment inquired^[9].

Full field electroretinogram (ERG) is a reflection of sum total of the retinal electrical response measured at the corneal surface. Visual evoked potential (VEP) is a gross electrical signal generated at visual cortex in response to visual stimulation. It reflects the electrical activity of central visual field of the patient. The latency of VEP provide a sensitive mean of detecting subclinical lesions of visual pathway^[10-11].

In this study, assessment of the retinal and optic nerve function was performed to assess the safety of photoactivated chromophores for keratitis-crosslinking (PACK-CXL) on the posterior segment function in cases of severe infectious keratitis with corneal melting.

SUBJECTS AND METHODS

Ethical Approval In the period between April 2017 to December 2018, 32 eyes of 32 patients with smear positive severe resistant infectious keratitis with areas of corneal thinning and melting who attended Mansoura Ophthalmic Center, Outpatient Clinic were included in the study. This study followed Declaration of Helsinki and was approved by institutional research board (IRB MS.19.08.768) of Mansoura Faculty of Medicine. Informed written consent was obtained from each participant in the study after assuring confidentiality. Patients with other ocular pathologies, retinal degenerations and pregnant females and patients with systemic disorders affecting the posterior segment were excluded from the study.

A thorough work up was performed for each patient, including full history taking with detailed recording of the duration of the symptoms, history of trauma and detailed history of medications taken. Corneal examination was performed with slit lamp biomicroscopy to record the ulcer size, depth of infiltrate, endothelial plaques, satellite lesions and size of hypopyon. Horizontal and vertical axes of the ulcers were measured and recorded. Ulcers more than 6 mm in any axis with deep corneal infiltration with or without hypopyon and starting areas of thinning and melting were included in the study.

Patients were randomized into two groups, each included 16 cases. Group I (control group) received medical treatment with systemic amikacin 500 mg/12h and topical ofloxacin hourly. Natamycin 5% hourly was used if fungal keratitis was suspected. The antimicrobial was modified by the culture and sensitivity results and the clinical response. Epithelial debridement was done in only 4 cases (thick irregular margin). Group II underwent CXL treatment at time of admission and topical antimicrobial was given postoperatively (ofloxacin hourly in bacterial keratitis or natamycin 5% in fungal keratitis).

Corneal CXL was done under sterile conditions in the operating theater. After the application of topical anesthesia,

loose epithelium and debris were scraped away. The epithelium surrounding the infectious site on the cornea was removed in a 9 mm diameter ring. Riboflavin (VibexRapid, 0.1% riboflavin solution/hydroxypropyl methyl cellulose) was administered to the cornea for a period of 20-30min at intervals of 2-3min. Vega-CBM X linker (Florence, Italy) was used following the manufacturer's instructions. The surgeon checked the intensity of radiation before each treatment and the lamp was placed above the cornea at the optical focal distance. The wavelength was 370 nm and the irradiance was 3 mW/cm². The treatment time was planned to be 9min or more according to the severity of the case and the application of riboflavin topically continued during the period of treatment at 5min intervals. Antimicrobial treatment was continued after the CXL session. The patients in both groups were followed clinically 1, 2d, 1wk, 1, 3mo after treatment. We stopped treatment when there was healing of the ulcer. Healing was defined as relief of pain and ciliary injection, complete reepithelization of the corneal ulcer with more distinct margins, resolution of active corneal infiltration and stromal oedema, halting of the thinning process with scar formation and absence of anterior chamber reaction or hypopyon.

Each patient in both groups underwent flash VEP and ERG examination before starting treatment and at 1wk, 1, 3mo post-treatment. Electrophysiological testing by Roland Consult Electrophysiological diagnostic system (RETI port 21, German-made) was performed according to international standard for clinical electrophysiology and vision (ISCVS)^[10-11].

For flash VEP, standard silver chloride electrodes of 1 cm diameter was used. The midline of the head was connected to active (positive) electrode with two fingers breadth above theinion (projection at the back of the head). Ground electrode was connected in the midline of the head at the level of the ear lobule while negative electrode was connected to the middle of the forehead. The sites of electrodes were cleaned with cleaning cream before putting the electrodes. The electrodes (silver, cup-shaped) were filled with connecting gel before application. Impedance was kept below 10 kΩ and for each eye, two recordings were obtained.

The room was lit with ambient light and patients were seated in a chair with adjustment of the chin in the chin-rest to avoid muscle artifacts. The studied eye was exposed to a white stimulus given through xenon light at a distance of 30 cm, at 2 Hz frequency. The other eye was covered with an opaque patch.

Patients were asked to fix their gaze on the flash generated on the monitor. The attention lapse or gross eye movement were prevented through the procedure using monitor camera.

Each patient underwent ERG examination. Full dilatation of pupils (>7 mm) was done using 1% tropicamide and

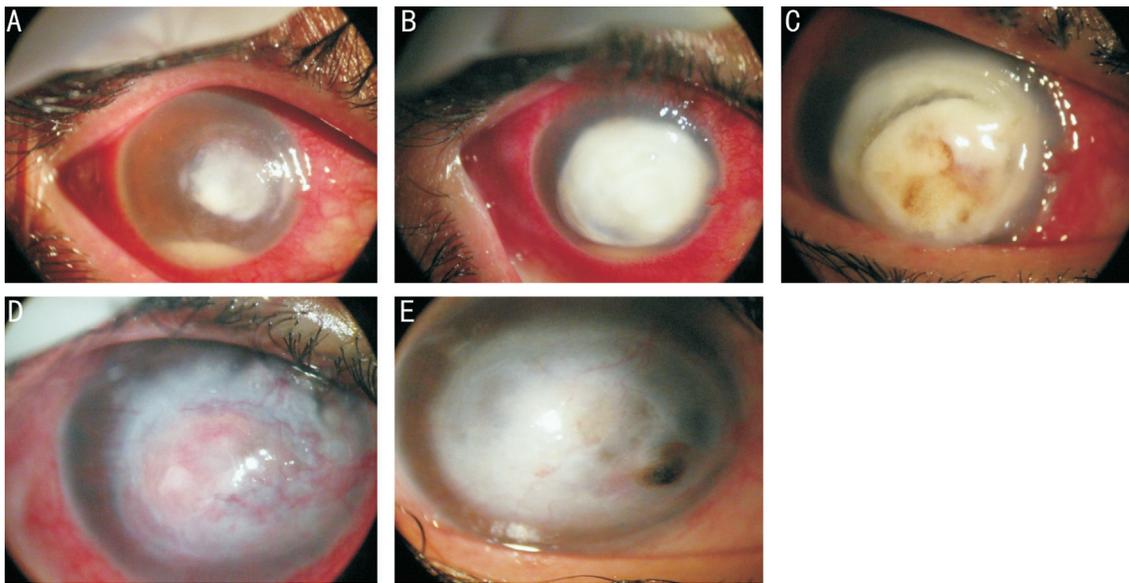


Figure 1 Slit lamp photography of a case in group II A: A case with active infection by *Aspergillus*; B: The same patient after two weeks of broad spectrum antibiotics; C: Cornea start to melt with continuation of medical therapy; D: Two days after PACK; E: The same patient after one week of PACK with halting of the melting process.

2.5% phenylephrine. After application of topical anesthesia (benoxinate hydrochloride 4%), Dawson, Trick and Litzkow (DTL) electrode (positive electrode) was placed just in contact with the corneal limbus, ground electrode was placed on the forehead and negative electrode was placed temporary near orbital rim. At first, the skin was cleaned with cleaning rub cream. The electrodes were installed under dim red light and after dark adaption for 20min. The diseased eye was tested while the other eye was covered with light pressure to suppress blinking.

The eyes fixated on red light point in the Ganzfeld globe, and then the test was started and recorded in 5 steps: scotopic rod response, scotopic combined response, oscillatory potential then light adaptation for 10min and finally photopic cone response and flicker response recording.

Data entry and statistical analysis was performed using Statistical Package of Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA). The normality of the data was first tested by a one-sample Kolmogorov-Smirnov test. The parametric data were expressed as mean±standard deviation. *P* value <0.05 was considered statistically significant. Spearman correlation coefficient was performed to correlate between variables.

RESULTS

The study included 32 eyes of 32 patients with smear positive resistant infectious corneal ulcer associated with corneal melting. They were randomized into two groups. Group I (control group) included 8 females and 8 males. Group II included 7 females and 9 males. The mean age of patients in group I was 42.8±16.2y and in group II was 40.5±14.2y (*P*=0.9). Patients of both groups were age and gender matched. Four patients had history of cataract extraction and 2 patients

Table 1 Types of microorganisms isolated from the patients

Type of microorganisms	No. of cases
Staph aureus	8
Staph epidermidis	4
Aspergillus	6
Fusarium	4
Malbranchea saccardo	2
Colletotrichum coccodes	2
Mixed staph and aspergillus	2
No growth	4

had exposure keratitis, 10 patients had history of trauma and 8 patients were presented with dry eye, while 8 patients had no remarkable positive history. At initial presentation, all patients had best corrected visual acuity less than 1/60. The distribution of visual acuity between the two groups was statistically non-significant. The mean duration of keratitis was 15.2±3.1d in group I and 16.4±2.7d in group II (*P*>0.76).

The ulcer diameter ranged (6.1±1.6 mm)×(6.15±1.4 mm). The depth of infiltration was 32%±12%. There was no statistically significant difference in the clinical presentation of the ulcer in both groups. The results of culture outcome were illustrated in Table 1.

In group I, ten eyes (62.5%) showed healing in comparison to 14 eyes in group II (87.5%; *P*<0.005; Figure 1); in group II, the mean duration of UV exposure was 14±3.1min. Relief of pain was noted in group II in the first postoperative 24h. The time point of starting epithelization was 49.3±3.2h in group I and 26.2±2.1h in group II (*P*<0.005). The mean duration of complete epithelization of the corneal ulcer was 36.56±5.21d in group I and 20.2±4.4d in group II (*P*<0.005). Four eyes in group I failed to respond to treatment three of them

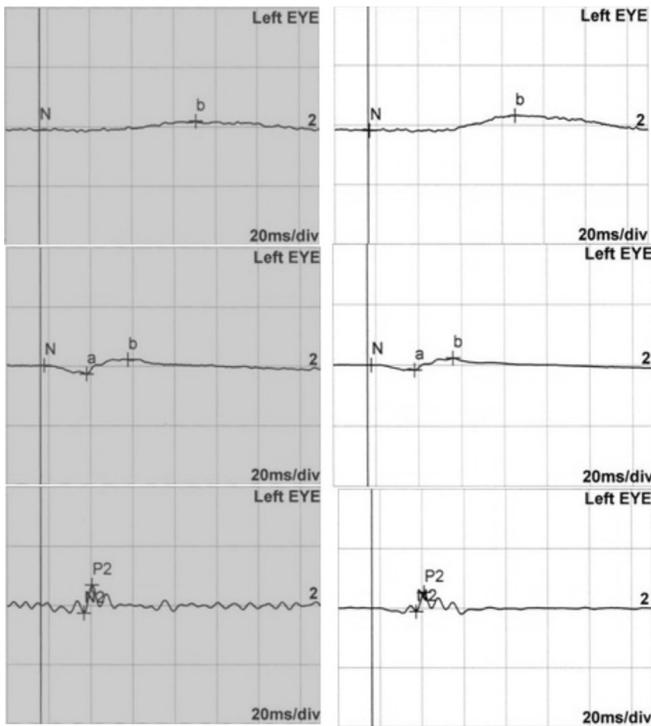


Figure 2 Scotopic ERG before and 3mo after CXL.

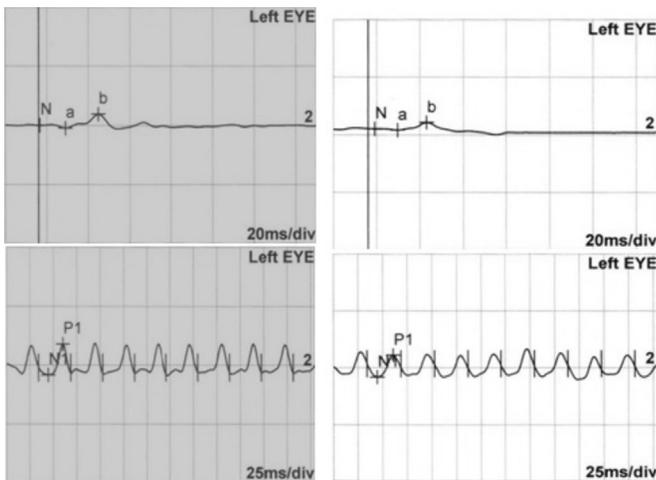


Figure 3 Photopic ERG before and 3mo after CXL.

needed amniotic membrane graft and the fourth one needed conjunctival graft. In group II, two cases were progressing and they were treated by therapeutic keratoplasty. There was no significant gain in the visual acuity in both groups due to the severity of the infection (all cases were candidates for keratoplasty).

The changes in ERG and VEP in the control group (group I) were illustrated in Table 2. Regarding the electrophysiological changes in in group II, there was an insignificant reduction in the amplitude of scotopic rod response, oscillatory potential amplitude, flicker amplitude and photopic cone response ($P=0.4, 0.8, 0.1, 0.3$ respectively) after CXL. There was delay in latencies of scotopic rod, oscillatory potential, flicker and photopic cone response ($P=0.2, 0.7, 0.5, 0.1$ respectively) after CXL (Table 3; Figures 2, 3).

Table 2 ERG&VEP in control group

ERG	Baseline	1mo	3mo	<i>P</i>
Scotopic				
Amplitude b-wave (μ V)	22 \pm 5	17 \pm 7.9	20 \pm 7	0.4
Latency b-wave (ms)	65 \pm 3	66 \pm 3.4	67 \pm 4	0.2
Combined				
b-amplitude (μ V)	103 \pm 27	100 \pm 39	99 \pm 4	0.5
b-latency (ms)	73 \pm 4.9	75 \pm 4.92	74 \pm 5	0.7
Oscillatory potential				
Amplitude (μ V)	13 \pm 5.5	12.8 \pm 5.5	12.8 \pm 5	0.8
Latency (ms)	36 \pm 4.5	36.9 \pm 4.5	36 \pm 5	0.89
Flicker				
Amplitude (μ V)	32 \pm 8.1	33.9 \pm 8.1	36 \pm 5	0.1
Latency (ms)	75 \pm 2.5	75 \pm 2.51	75 \pm 3	0.4
Photopic				
Amplitude (μ V)	28 \pm 6.5	27 \pm 6.5	28 \pm 6	0.33
Latency (ms)	36 \pm 4.5	36 \pm 4.3	37 \pm 8	0.15
VEP				
P100 amplitude	3.2 \pm 3.1	3.1 \pm 3.2	3.0 \pm 3.2	0.23
P100 latency	148 \pm 6.2	149 \pm 10.3	150 \pm 9.9	0.90

ERG: Electroretinogram; VEP: Visual evoked potential.

Table 3 ERG before and after CXL

ERG	Baseline	1wk	1mo	3mo	<i>P</i>
Scotopic					
Amplitude b-wave (μ V)	20 \pm 5.9	15 \pm 5.8	17 \pm 7.9	20 \pm 7	0.4
Latency b-wave (ms)	67 \pm 3.4	70 \pm 4.5	66 \pm 3.4	67 \pm 4	0.2
Combined					
b-amplitude (μ V)	100 \pm 27.9	90 \pm 38	95 \pm 37.9	99 \pm 4	0.8
b-latency (ms)	75 \pm 4.9	77 \pm 5	75 \pm 4.92	76 \pm 5	0.87
Oscillatory potential					
Amplitude (μ V)	10 \pm 5.5	7 \pm 5.6	9.8 \pm 5.5	8.8 \pm 5	0.8
Latency (ms)	35 \pm 4.5	39 \pm 5.5	37.9 \pm 4.5	36 \pm 5	0.7
Flicker					
Amplitude (μ V)	35 \pm 8.1	33 \pm 6.1	35.9 \pm 8.1	36 \pm 7	0.1
Latency (ms)	72 \pm 2.5	75 \pm 2.5	75 \pm 2.51	75 \pm 3	0.5
Photopic					
Amplitude (μ V)	25 \pm 6.5	20 \pm 3.9	22 \pm 6.5	28 \pm 6	0.3
Latency (ms)	35 \pm 4.5	40 \pm 4.9	39 \pm 4.3	38 \pm 8	0.1

ERG: Electroretinogram; CXL: Crosslinking.

There was statistically insignificant delay in latency of VEP after CXL (Table 4; Figure 4). There was insignificant differences in ERG&VEP parameters between control and study groups preoperative and after 1, 3mo ($P=0.33, 0.67, 0.23$ respectively).

The increase in the duration of UV was accompanied with reduction in all ERG&VEP parameters. However, it is statistically insignificant (Table 5).

DISCUSSION

The clinical use of photo-activated riboflavin for treatment of corneal melting was first recorded in 2000 by Schnitzler

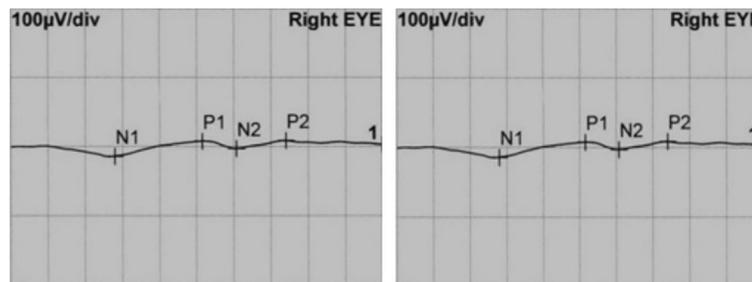


Figure 4 VEP before and after CXL.

Table 4 VEP changes before and after CXL

VEP parameters	P100 amplitude (µV)	P100 latency (ms)
Before CXL	2.6±3.5	150.5±10.6
After CXL	2.1±3.9	151±9.9
<i>P</i>	0.34	0.65

CXL: Crosslinking; VEP: Visual evoked potential.

Table 5 Correlation between ERG&VEP and duration of UV

Parameters	After 1mo		After 3mo	
	<i>R</i>	<i>P</i>	<i>R</i>	<i>P</i>
ERG parameters				
Scotopic ERG amplitude	-0.4	0.343	-0.31	0.415
Photopic ERG amplitude	-0.2	0.876	-0.11	0.9
VEP parameters				
P100 amplitude	-0.23	0.89	0.-24	0.6
P100 latency	0.4	0.71	0.39	0.18

VEP: Visual evoked potential; UV: Ultraviolet.

et al^[12]. They used CXL in the treatment of four patients with non-infectious corneal melting. The rationale was that the technique increases the covalent bond among the collagen molecules so it help to stabilize the disease^[12].

In this study 32 eyes with smear positive severe resistant microbial keratitis with corneal melting were randomly divided into two groups (each included 16 patients). Group I was control group who received their antibiotic treatment according to culture and sensitivity test, group II underwent CXL and then continue their antibiotic treatment as group I.

In our study, the mean duration of treatment was significantly shorter in group II (20.2±4.4d) in comparison to group I (36.56±5.21d). This is in agreement with Bamdad *et al*^[13] who reported shorter duration of treatment in CXL group versus the control group. However, their study was limited to cases of moderate bacterial keratitis. On contrary Said *et al*^[14] assigned 40 patients with severe infectious keratitis and in their comparative study they recorded insignificant change in the average time of healing between the two groups.

In this study, healing of 14 eyes in group II (treated with CXL) versus 10 eyes in group I was recorded. This can be explained by the fact that PACK-CXL can cause release of free oxygen radicals which can cause damage of the pathogen. It also inhibits the pathogen replication^[5].

This is not in agreement with the finding of Vajpayee *et al*^[2] who reported that retrospectively reviewed patients with mycotic keratitis treated with PACK-CXL and intensive topical antifungal therapy didn't show significant difference from antifungal alone. However, we believe that corneal melting in our study caused thinning of the cornea which allows the treatment to reach the effective depth.

Richoz *et al*^[15] suggested that short term and marked inflammation in patients of microbial keratitis can occur after PACK-CXL due to sudden release of foreign fungal antigen which was concentrated in the deeper layer of the cornea and this facilitates corneal melting. This observation was not noticed in our patients.

In our study, the participants were treated by accelerated technique (9-14min) treatment as learnt from Theo Seiler who advised that longer treatment duration was recommended for infectious keratitis^[8]. This does not go in agreement with Bäckman *et al*^[16] who found that accelerated treatment was less effective in treating certain bacterial infections. However, Richoz *et al*^[17] found that accelerated treatment can kill 93% of bacteria.

As regard the safety of CXL, it is known that UV-A could damage intraocular structures. The expected damage was reported by Spoerl *et al*^[3]. During standard CXL of a cornea with a 400 µm thickness, the irradiances of the UV light reaching the lens, and retina are of smaller magnitude than the damage thresholds, and the cells liable for damage are the microbes, the corneal endothelium, and the keratocytes.

However, in our study, this longer time of application besides the advanced thinning due to melting of the cornea increase our concern about the safety of the procedure and the toxicity on the retina.

To the best of our knowledge this is the first study to assess the functional effect of the PACK-CXL on optic nerve and retinal function. It is well known that full field ERG gives information about general retinal function. Under scotopic condition, the wave is directly generated by bipolar cell^[18]. On the other hand, under photopic condition, several types of neurons contribute to its generation^[19]. Oscillatory potential are four to six low amplitude, high frequency wavelets superimposed on the

ascending limb of ERG-b-wave. The oscillatory potential are thought to result from a feedback between the amacrine cells and the bipolar cell and/or feedback from ganglion cells to amacrine cell^[20]. As regard to full field Ganzfeld ERG, in this study there was statistically insignificant reduction in scotopic and photopic responses.

There was no observed reduction in oscillatory potential amplitude and flicker response in our patients. Regarding VEP, there were statistically insignificant delay latency or reduction in amplitude.

In conclusion, PACK-CXL is an effective technique in treatment of severe infectious keratitis with melting as it halts the melting process with acceptable safety on the retinal and optic nerve function.

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Conflicts of Interest: Awad EA, None; Abdelkader M, None; Abdelhameed AG, None; Gaafar WM, None; Mokbel TH, None.

REFERENCES

- 1 Tabibian D, Mazzotta C, Hafezi F. PACK-CXL: corneal cross-linking in infectious keratitis. *Eye Vis (Lond)* 2016;3:11.
- 2 Vajpayee RB, Shafi SN, Maharana PK, Sharma N, Jhanji V. Evaluation of corneal collagen cross-linking as an additional therapy in mycotic keratitis. *Clin Exp Ophthalmol* 2015;43(2):103-107.
- 3 Spoerl E, Mrochen M, Sliney D, Trokel S, Seiler T. Safety of UVA-riboflavin cross-linking of the cornea. *Cornea* 2007;26(4):385-389.
- 4 Iseli HP, Thiel MA, Hafezi F, Kampmeier J, Seiler T. Ultraviolet A/riboflavin corneal cross-linking for infectious keratitis associated with corneal melts. *Cornea* 2008;27(5):590-594.
- 5 Price MO, Price FW Jr. Corneal cross-linking in the treatment of corneal ulcers. *Curr Opin Ophthalmol* 2016;27(3):250-255.
- 6 Makdoui K, Mortensen J, Sorkhabi O, Malmvall BE, Crafoord S. UVA-riboflavin photochemical therapy of bacterial keratitis: a pilot study. *Graefes Arch Clin Exp Ophthalmol* 2012;250(1):95-102.
- 7 Khan YA, Kashiwabuchi RT, Martins SA, Castro-Combs JM, Kalyani S, Stanley P, Flikier D, Behrens A. Riboflavin and ultraviolet light a therapy as an adjuvant treatment for medically refractive Acanthamoeba keratitis: report of 3 cases. *Ophthalmology* 2011;118(2):324-331.
- 8 Alio JL, Abbouda A, Valle D, del Castillo JM, Fernandez JA. Corneal cross linking and infectious keratitis: a systematic review with a meta-analysis of reported cases. *J Ophthalmic Inflamm Infect* 2013;3(1):47.
- 9 Jiang LZ, Qiu SY, Li ZW, Zhang X, Tao XC, Mu GY. Therapeutic and inducing effect of corneal crosslinking on infectious keratitis. *Int J Ophthalmol* 2016;9(12):1820-1823.
- 10 McCulloch DL, Marmor MF, Brigell MG, Hamilton R, Holder GE, Tzekov R, Bach M. ISCEV Standard for full-field clinical electroretinography. *Doc Ophthalmol* 2015;130:1-12
- 11 Odom JV, Bach M, Brigell M. ISCEV standard for clinical visual evoked potentials (2016 update). *Doc Ophthalmol* 2016;133:1-9.
- 12 Schnitzler E, Spörl E, Seiler T. Irradiation of cornea with ultraviolet light and riboflavin administration as a new treatment for erosive corneal processes, preliminary results in four patients. *Klin Monbl Augenheilkd* 2000;217(3):190-193.
- 13 Bamdad S, Malekhosseini H, Khosravi A. Ultraviolet A/riboflavin collagen cross-linking for treatment of moderate bacterial corneal ulcers. *Cornea* 2015;34(4):402-406.
- 14 Said DG, Elalfy MS, Gatziofufas Z, El-Zakzouk ES, Hassan MA, Saif MY, Zaki AA, Dua HS, Hafezi F. Collagen cross-linking with photoactivated riboflavin (PACK-CXL) for the treatment of advanced infectious keratitis with corneal melting. *Ophthalmology* 2014;121(7):1377-1382.
- 15 Richoz O, Moore J, Hafezi F, Moore T. Corneal cross-linking as an adjuvant therapy in the management of recalcitrant deep stromal fungal keratitis: a randomized trial. *Am J Ophthalmol* 2015;160(3):616-617.
- 16 Bäckman A, Makdoui K, Mortensen J, Crafoord S. The efficiency of cross-linking methods in eradication of bacteria is influenced by the riboflavin concentration and the irradiation time of ultraviolet light. *Acta Ophthalmol* 2014;92(7):656-661.
- 17 Richoz O, Kling S, Hoogewoud F, Hammer A, Tabibian D, Francois P, Schrenzel J, Hafezi F. Antibacterial efficacy of accelerated photoactivated chromophore for keratitis-corneal collagen cross-linking (PACK-CXL). *J Refract Surg* 2014;30(12):850-854.
- 18 Hood DC, Birch DG. Beta wave of the scotopic (rod) electroretinogram as a measure of the activity of human on-bipolar cells. *J Opt Soc Am A Opt Image Sci Vis* 1996;13(3):623-633.
- 19 Robson JG, Frishman LJ. Photoreceptor and bipolar cell contributions to the cat electroretinogram: a kinetic model for the early part of the flash response. *J Opt Soc Am A Opt Image Sci Vis* 1996;13(3):613-622.
- 20 Sieving PA, Murayama K, Naarendorp F. Push-pull model of the primate photopic electroretinogram: a role for hyperpolarizing neurons in shaping the b-wave. *Vis Neurosci* 1994;11(3):519-532.