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Impact of femtosecond laser-assisted in situ keratomileusis on retinal ganglion cell function

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Abstract

Purpose: To analyse the effect of femtosecond laser-assisted in situ keratomileusis (FS-LASIK) on the electrical response of retinal ganglion cells using pattern electroretinography (pERG).

Methods: This was a longitudinal, prospective, observational pilot study. We included consecutive myopic patients who underwent FS-LASIK to correct up to 6 dioptres of myopia and up to 2 dioptres of astigmatism. Patients with excessive blinking or tearing and those with Snellen uncorrected visual acuity less than 0.9 dec on postop day 1 were excluded. Diopsys NOVA® (Diopsys Inc., NJ) pERG records, using high- and low-contrast patterns, were obtained 16 h and 1 month after FS-LASIK was performed. Magnitude (μV), Magnitude D (μV), Magnitude D/Magnitude ratio and signal-to-noise ratio (dB) were analysed. Wilcoxon test for nonparametric paired data was employed.

Results: pERG data from 24 eyes were analysed from 24 patients who underwent FS-LASIK. Mean age was 35.79 ± 9.86 years. Mean preoperative refraction was −2.69 ± 7.6 D (spherical) and −0.38 ± 0.40 D (cylinder). Mean surgical time was 56.88 ± 7.6 s. No statistically significant differences were obtained for any of the studied parameters when comparing 16 h with 1 month after FS-LASIK, with the exception of Magnitude with low contrast, which increased from 1.21 ± 0.2 to 1.39 ± 0.29 μV at 16 h and 1 month postoperatively, respectively ($p = 0.03$).

Conclusions: FS-LASIK seems to induce a mild and transitory defect in retinal ganglion cell function. Only a mild decrease was detected in the magnitude value for low-contrast stimuli when pERG was performed 16 h postoperatively, and it returned to normal 1 month after surgery.

Keywords

Pattern electroretinography, retinal ganglion cells, femtosecond laser-assisted in situ keratomileusis

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Introduction

Laser-assisted in situ keratomileusis (LASIK) is one of the preferred surgical techniques for the correction of myopia. In LASIK surgery, a thin corneal layer (corneal flap) is created.[1] This corneal flap is lifted during surgery to ablate part of the underlying corneal stroma with an excimer laser to a depth that depends on the number of dioptres to be corrected. Finally, the corneal flap is repositioned over the residual stromal bed. For many years, this flap has been created using a mechanical microkeratome.[1] However, for some time, there has been the possibility of creating a corneal flap using a femtosecond laser (FSL).[2,3] This

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technology seems to create more precise and regular flaps, with a lower incidence of complications.[4]

During the creation of the flap, the eye has to be firmly held by a suction ring, which sharply increases the intraocular pressure (IOP).[5,6] After that, the device interface flattens the cornea so that the FSL can create a flap with the desired depth. This increase in IOP has been associated, occasionally and anecdotally, with posterior pole complications.[7–9]

It is known that a sustained increase in IOP, as occurs in glaucoma, leads to the apoptosis of the ganglion cells of the retina and their axons, leading to perimetric deterioration.[10] It seems that the structural changes that are recordable by means of optical coherence tomography (OCT) at the level of the retinal nerve fibre layer (RNFL) and retinal ganglion cells (RGCs) would precede the development of defects in visual function;[11] detecting a loss of the visual field would require the death of at least 30% of RGCs, affecting up to 40% of visual acuity (VA).[12,13]

However, prior to neuronal death and the aforementioned structural changes, these cells could show a malfunction in their normal electrical activity (neurapraxia), which would be measurable and could be considered to be an early indicator of neural damage, earlier even than when structurally measured by OCT. Thus, it seems that recording the electrical activity of the inner layers of the retina by means of pattern electroretinography (pERG) would be able to detect a functional alteration in patients with ocular hypertension even before OCT could detect retinal anatomic changes.[14–17]

Conducting a pERG has historically been complex and tedious, both in its performance and in its interpretation.[18] Porciatti and Ventura[19] optimized the pERG system for glaucoma detection (PERGLA). They developed a protocol optimizing the parameters of the presented visual stimulus (alternating structured stimuli with high temporal frequency) in such a way that they obtained a steady-state response in the form of sinusoidal waves that, after applying a Fourier transformation, allowed the isolation of their harmonic component. With this protocol, it is possible to make comparisons, in terms of the amplitude and phase, with an internal normal database and enhance the signal-to-noise ratio (SNR). This makes the PERGLA recording more comfortable for the patient (the recording electrodes are placed on the skin), easier for the examiner to interpret (standardized basis) and less time consuming.[19] This PERGLA protocol has been shown to have high repeatability, reproducibility and specificity.[20–22]

Since there is scientific evidence in glaucoma supporting the usefulness of pERG for the detection of early malfunctioning RGCs prior to their apoptosis, we decided to study the electrical functionality of RGCs in eyes that have undergone femtosecond laser-assisted in situ keratomileusis (FS-LASIK) refractive surgery. For this, we used a new device with the PERGLA protocol: Diopsys NOVA® (Diopsys Inc., NJ).

Methods

This was a longitudinal, prospective and observational pilot study that recruited consecutive patients who underwent refractive surgery to correct myopia at the Novovisión clinic in Madrid, Spain. The study adhered to the tenets of the Declaration of Helsinki, and investigation review board approval was granted from CEIm-R of Madrid Community. The purpose of the study as well as the policy on the protection of personal data were explained in detail to all participants, and written informed consent was obtained.

All patients underwent a complete preoperative examination, as is usually done for these procedures. A single observer performed all the preoperative tests for all patients, including uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), subjective refraction, cycloplegic refraction, Placido disc topography (Allegro Topolyzer; Wavelight Technology AG, Alcon Laboratories, Erlanger, Germany), Scheimpflug tomography (Allegro Oculyzer; Wavelight Technologie AG, Alcon Laboratories, Erlanger, Germany), ultrasonic corneal pachymetry, infrared mesopic pupillometry (Colvard pupillometer, Oasis Medical Inc., Glendora, CA, USA) and macular and RNFL OCT (Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany). Slit lamp biomicroscopy, applanation tonometry (Goldmann type tonometer, CT-80, Topcon, Tokyo, Japan) and fundoscopy were also evaluated.

Healthy patients with up to 6 dioptres of myopia and up to 2 dioptres of astigmatism were included in the study. All of them were considered to be good candidates for FS-LASIK refractive surgery. Only one eye per patient was included (the right eye when both were eligible for the study). Eyes with uncorrected postoperative visual acuity less than 0.9 dec (Snellen) or with excessive blinking that could affect data recording were excluded. Additionally, diabetic patients or those with retinal or neuro-ophthalmological pathology were excluded. FS-LASIK surgery was performed by the same experienced surgeon (MAT). For this purpose, Intralase 60 kHz (Abott Medical Optics Inc.) FSL and a WaveLight Allegreto 400 (Acon, Fort Worth, TX, USA) excimer laser were used.

A pERG record was obtained 16 h and 1 month after surgery using a Diopsys NOVA® device (Diopsys Inc., Pine Brook, NJ). The visual stimulus used by Diopsys NOVA® was presented on a 17″ Acer V176BM LCD monitor with gamma correction. The stimulus consisted of a pattern of horizontal black and white bars (64 bars, 32 white and 32 black with 102.4 cd/m^2 of mean luminance) that alternated 15 times per second. The visual stimulus subtended an angle of 1439.90 arc minutes (24° centred on the fovea).

Each bar subtended 22.49 arc minutes. The patient fixed his gaze on a red cross that was located in the centre of the visual stimulus; this subtended 50.79 arc minutes.

The forehead skin was cleaned with NuPrep Skin Prep Gel (Weaver and Company, CO), and the lower eyelids were cleaned with OCuSOFT Lid Scrub Original (OCuSOFT Inc., TX) to ensure good and stable electrical conductivity. Then, the electrodes were placed: one under each lower eyelids (near the eyelid margins) and the third on the forehead. A 'ground' electrode (EEG Diopsys NOVA® electrode) was placed in the central area of the forehead with conductive paste (Ten20, Weaver and Company). An optimal prescription for a 60-cm reading distance was used, and the subjects sat in front of the stimulus monitor.

The pERG examination was performed in a dark room, free from visual and auditory distractions. The record was obtained by an experienced examiner, stimulating each eye separately (monocular). The 'Contrast Sensitivity Protocol' was carried out as it was specifically designed to obtain the electrical function of RGCs. This protocol performs two measurements of each eye, one with high contrast (Hc) (85%) and the other with low contrast (Lc) (15%), each with a duration of 25 s. If more than four blinks were recorded during the test, the test was aborted. Therefore, patients were advised to reduce the blink rate to reduce artefacts.

After performing the test, the device offers an easy-to-interpret record sheet (Figure 1). It shows an image of the morphology of the recorded waves with high- and low-contrast stimuli, a colour interpretation of the signal quality and a table with results of different parameters registered with a colour code with respect to the normality database (for values recorded with high contrast). The colour code (green, yellow and red) facilitates the interpretation of the results since it analyses them according to the normative database: green for values that are within the normal range and that correspond to 96% of the reference population, yellow for 'limit' values, and red for 'abnormal' values corresponding to 2% of the reference population.

From the parameters recorded and analysed and according to the manufacturer's instructions: the total magnitude ('Mag') (μv) represents the maximum amplitude of the wave generated by RGCs; the magnitude D ('MagD') (μv) is the amplitude of the wave resulting from averaging all the 200-ms sections during the 25 s that the test lasts (125 sections), in such a way that lower values correspond to asynchronous waves since 'MagD' evaluates both the magnitude and the phase of the averaged waves; the 'MagD/Mag ratio' (from 0 to 1) shows the repeatability in the phase of the wave, in such a way that lower values correspond to waves more out of phase in the recording time, indicating a greater probability of the dysfunction of RGCs; and SNR (dB) corresponds to the strength of the 15 Hz signal compared to the electrical noise in the room, in such a way that high values correspond to the absence of noise and reliability in the signal collected. Only measurements with good signal quality were analysed.

In the present study, the analysed variables were 'Mag', 'MagD', the 'MagD/Mag ratio' and SNR in Hc and Lc after performing FS-LASIK. Values obtained at 16 h and 1 month postoperatively were compared. The data were collected in a Microsoft Excel spreadsheet. The descriptive statistics are expressed as the mean value ± standard deviation (SD). Statistical analysis was performed with StatView SE + Graphics software (Abacus Concepts, Berkeley, CA) on a Macintosh PowerBook 1400 cs/117 (Apple Computer, Cupertino, CA). Statistical analysis was carried out, in case of the normality of the sample, with Student's *t* test of paired data (or Wilcoxon signed-rank test, otherwise), and a value of $p < 0.05$ was considered statistically significant.

Results

A total of 24 eyes of 24 healthy myopic patients who underwent FS-LASIK were included. Among the patients, 41% were men and 59% were women. The mean age of the patients was 35.79 ± 9.86 years, with a mean of treated myopia of −2.69 ± 0.9 D and astigmatism of −0.38 ± 0.4 D. The mean time of the FS-LASIK intervention was 56.88 ± 7.6 s.

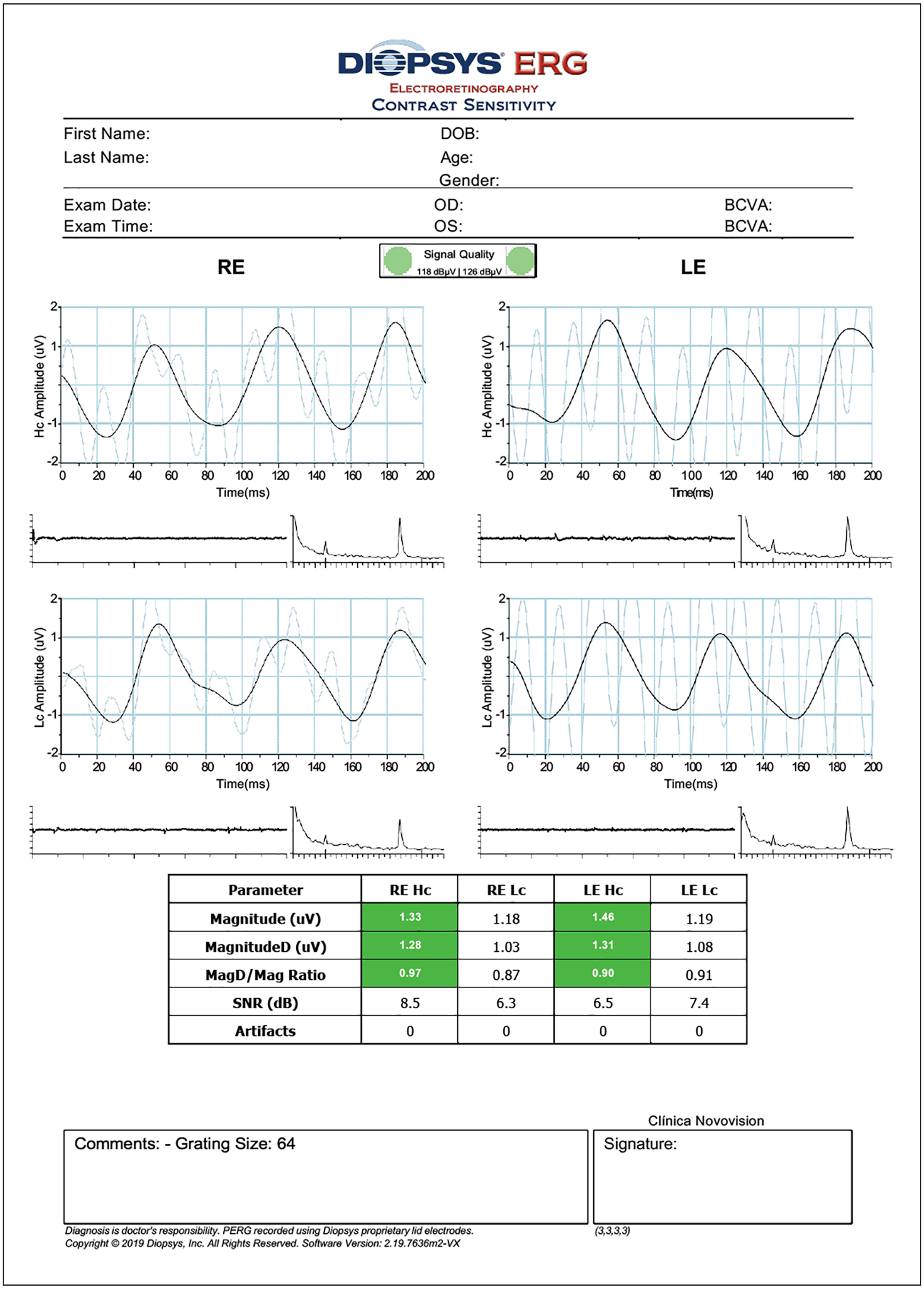
Good quality records were obtained in all patients for whom the test was carried out, which allowed the interpretation of results, so no subject had to be excluded from the study for this reason. The results obtained for the studied parameters ('Mag', 'MagD', the 'MagD/Mag ratio' and 'SNR') at 16 h and 1 month after FS-LASIK are shown in Tables 1 and 2.

When comparing the records obtained for the different studied parameters in Hc and Lc, at 16 h and 1 month after FS-LASIK, no statistically significant differences were found in any of the analysed variables, except for 'Mag' in Lc, which increased from 1.21 ± 0.21 μV (16 h) to 1.39 ± 0.29 μV (1 month) ($p = 0.03$).

Discussion

This pilot study analysed the electrical function of RGCs as measured by pERG (Diopsys NOVA®), which have been exposed to stress by an acute increase in IOP secondary to the suction ring and applanation cone (patient interface) during FS-LASIK treatment for moderate myopia. An abnormality as found in the electrical activity of RGCs in the immediate postoperative period, which was mild in intensity and transient.

During the process of creating the flap in refractive surgery for the treatment of myopia using FS-LASIK, it is necessary to create a vacuum by applying a suction ring. This represents a sharp and large increase in IOP.[5,6] Although it is well known that this elevation in IOP is



DIOPSYS ERG
Electroretinography
Contrast Sensitivity

First Name: DOB:
Last Name: Age:
Gender:

Exam Date: OD: BCVA:
Exam Time: OS: BCVA:

RE Signal Quality 118 dBµV | 126 dBµV LE

Hc Amplitude (uV)
Time(ms)
Lc Amplitude (uV)
Time(ms)

Parameter	RE Hc	RE Lc	LE Hc	LE Lc
Magnitude (uV)	1.33	1.18	1.46	1.19
MagnitudeD (uV)	1.28	1.03	1.31	1.08
MagD/Mag Ratio	0.97	0.87	0.90	0.91
SNR (dB)	8.5	6.3	6.5	7.4
Artifacts	0	0	0	0

Clínica Novovision

Comments: - Grating Size: 64
Signature:

Diagnosis is doctor's responsibility. PERG recorded using Diopsys proprietary lid electrodes.
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Figure 1. pERG Diopsys NOVA® record sheet from a healthy patient. The upper part shows the details of the patient (name, age, date of birth, sex, exam date, refraction and BCVA), followed by the quality of the signal (colour-coded) and four waves corresponding to the right eye (RE) and left eye (LE) after stimulation with Hc in the upper part and Lc in the lower part. Below each wave, there are two graphs that allow the detection of artefacts, as they show variations in signal and frequency during recording. Finally, it shows a table with the values for each eye of each of the main parameters measured under conditions of Hc and Lc: Magnitude (Mag), Magnitude D (MagD), MagD/Mag ratio, signal-to-noise ratio (SNR) and the number of artefacts. High contrast values are shown colour-coded after comparison with normal values: green ('normal'), yellow ('borderline') and red ('abnormal').

Table 1. pERG values obtained with a high contrast stimulus at 16 h and 1 month after FS-LASIK (mean ± standard deviation).

	Magnitude (μV)	MagnitudeD (μV)	MagD/Mag ratio	SNR (db)
16 h	1.51 ± 0.37	1.30 ± 0.42	0.86 ± 0.11	5.41 ± 2.86
1 month	1.82 ± 0,59	1.56 ± 0.58	0.85 ± 0.10	6.24 ± 2.09

FS-LASIK: femtosecond-LASIK; pERG: pattern electroretinogram; SNR: signal to noise ratio.

Table 2. pERG values obtained with a low contrast stimulus at 16 h and 1 month after FS-LASIK (mean ± standard deviation).

	Magnitude (μV)	MagnitudeD (μV)	MagD/Mag ratio	SNR (db)
16 h	1.21 ± 0.21	0.99 ± 0.26	0.81 ± 0.11	3.74 ± 2.49
1 month	1.39 ± 0.29	1.12 ± 0.35	0.80 ± 0.12	3.58 ± 1.69

FS-LASIK: femtosecond-LASIK; pERG: pattern electroretinogram; SNR: signal to noise ratio.

not followed by a structural deterioration in RNFL thickness as measured by OCT,[23] it is known that this acute increase in IOP would have an impact on RGCs, especially in more vulnerable eyes such as myopic eyes that could go unnoticed if just the structure is analysed using OCT. Although it is difficult to determine the true prevalence of glaucoma in the myopic population, it is clear that myopic eyes, especially when they exceed 4 dioptres of myopia, are more susceptible to glaucoma than nonmyopic eyes.[24] Morphological and structural differences in the ocular layers of myopic eyes could have a lower resistance to the harmful effect of IOP.

The deleterious effect of IOP on vulnerable RGCs could go unnoticed if just the structure is analysed using OCT. However, it is possible that the analysis of the electrical activity of RGCs using pERG could allow the earlier detection of a negative effect on neural cell functions when they are exposed to stress. Thus, it has been reported that some eyes from patients with ocular hypertension could present changes in their pERG, even though this defect could not be identified through the structural analysis of the RNFL or RGCs.[25,26]

Devices that provide functional or electrical information about the retina are based on electroretinography (ERG). Specifically, in pERG, the stimulation of the retina with a structured visual stimulus using a reversible pattern and constant luminance allows better isolation of the electrical signal generated by the cells of the inner layers of the retina, so this type of recording is the one that is especially focussed on the functional study of RGCs. A decrease in the amplitude of the electrical response of the retina, as measured by pERG, could be due to the death of RGCs and/or their electrical dysfunction. However, the type of stimulus used with the PERGLA strategy allows the possibility of registering an asynchrony in the phase of the waves (delay in the latency of its response), and that could allow it to isolate cases in which RGCs survive although they respond more slowly (dysfunctional).[27]

That is, finding abnormalities in the PERGLA registry in the absence of structural damage in the RNFL could suggest a neural alteration known as neurapraxia, meaning that there is early functional damage of RGCs, but they remain viable. In fact, recent studies employing this strategy have shown a different adaptive response of RGCs when they are subjected to a stress situation.[28–30]

In our sample, the PERGLA (Diopsys NOVA®) record in Hc conditions did not show significant differences when comparing the values of the parameters ('Mag', 'MagD', the 'MagD/Mag ratio', and 'SNR') obtained at 16 h and 1 month after treatment with FS-LASIK. When an Lc stimulus was used, we found a significant increase in the Mag value 1 month postoperatively, which went from 1.21 ± 0.2 μV (16 h) to 1.39 ± 0.29 μV (1 month) ($p = 0.03$).

The fact that the 'Mag' value was lower for Lc stimuli at 16 h after the operation (and that it recovered a month after the surgery) should be interpreted with caution. On the one hand, the 'Mag' values (as well as those of 'MagD' and the 'MagD/Mag ratio') obtained by pERG Diopsys NOVA® when Lc stimuli were used did not have a normalized database for comparison, as is available for Hc stimuli, so the results obtained at 16 h after surgery, even though they were lower than those obtained at 1 month, were not significantly different from normal values. Despite this, and although this change was small in intensity, the fact that there is a statistically significant increase 1 month after surgery highly suggests the existence of a real functional alteration in the immediate postoperative period.

We only found one study using the same device for pERG (Diopsys NOVA®) where the repeatability and reliability of the data were analysed in healthy Caucasian patients (40 eyes of 20 patients).[18] Gillmann et al. found that the values of 'Mag', 'MagD' and the SNR were highly reproducible and repeatable when the stimulus was Hc. Of all the parameters recorded in Hc stimuli, the 'MagD/Mag ratio' was the least repeatable and reproducible. It has been suggested that the increase in the variability in this parameter could be due to the dysfunction of RGCs, which is why it has been proposed for monitoring during follow-up for glaucomatous disease. However, the fact that the repeatability and reproducibility of these values were low in a group of healthy subjects, without known comorbidities, challenges the theory that directly links variability with disease progression. Another interesting fact that these authors found was that this same value in Lc was highly repeatable, possibly because in Lc, the collected amplitude was smaller, masking the discrepancies between 'Mag' and 'MagD'.

To our knowledge, this is the first study to evaluate the electrical function of RGCs after FS-LASIK surgery. Based on our results, FS-LASIK surgery appears to induce a mild and transient defect in RGC function in healthy myopic eyes. It is possible that different RGCs of the same individual or of different individuals require a variable level of stress to become dysfunctional, and being able to identify eyes that are most vulnerable to damage would offer an advantage in the therapeutic approach for glaucoma. Thus, classic provocation tests in the diagnosis of glaucoma, such as the inverted position (head down), have shown that the behaviour of pERG registered in each patient could be an early marker for the future development of glaucoma.[28] In the same way, we could infer from the results of our pilot study that myopic eyes that exhibit greater changes in pERG after being subjected to the stress of the sudden increase in IOP in FS-LASIK surgery could indicate a greater vulnerability of their RGCs for damage, and this perhaps has some predictive value for future damage.

One of the main limitations of our study was the number of eyes evaluated: it is possible that a larger sample size could yield more robust conclusions and detect differences in a greater number of pERG parameters. However, we believe that the present study allows us to get a rough idea about the function situation of RGCs after FS-LASIK surgery. Another limitation of this study was the time in which the measurements were made (16 h and 1 month), since they involve a short follow-up. Therefore, more in-depth studies are required with a greater number of eyes and longer follow-up over time to be able to evaluate the evolution in the changes in the electrical function of RGCs after being subjected to acute stress, such as a sudden increase in IOP during FS-LASIK surgery.

Declaration of conflicting interests

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