The effect of pseudophakia on retinal and cortical functions

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ABSTRACT

Aim To investigate the effect of pseudophakia on visual electrophysiology.

Methods Right eyes of 60 pseudophakic (study group) age- and sex-matched 60 phakic (control group) volunteers were included. Subjects without any ocular and systemic disease, who had visual acuity of ≥9/10 underwent full-field electroretinogram (ERG), pattern electroretinogram (PERG), pattern visual evoked potentials (PVEP) and electro-oculogram (EOG) recordings.

Results The P100 latency to 1°-check was significantly shorter in both pseudophakic groups (study group: 102.98±6.11, control group: 107.06±10.70, p=0.012). The P100 amplitude to 15'-check was significantly higher in the pseudophakic groups (study group: 13.96±7.01, control group: 11.60±4.69, p: 0.033). Regarding ERG, b-wave implicit time in rod response and a-wave implicit time in standard combined response (SCR) were significantly shorter in the pseudophakic group (p=0.017, and <0.001, respectively). B-wave amplitude in rod response and a-wave amplitude in SCR were significantly higher in the study group (p<0.001 for both). The P1 and N1 amplitude and implicit time differences in 30-Hz flicker response were not significant (p>0.05). Conversely, P3/P4 implicit times in oscillatory potentials (OPs) were delayed in the pseudophakic group (p=0.001, and 0.002, respectively). The P1 amplitude increase in OPs in the study group was significant (p<0.001). The N95 latency in PERG was significantly delayed (p=0.002) and P50 amplitude was increased (p=0.002) in the pseudophakics. Arden ratio in EOG was similar in both groups (p=0.961).

Conclusion Pseudophakia seems to influence ocular electrophysiological tests. Possible causes of these influences in the patients with pseudophakia should be clarified by further studies.

Key words: electrooculogram, electroretinogram, pattern electroretinogram, pattern visual evoked potentials
INTRODUCTION

The elderly population is increasing throughout the world, and senile cataract is the leading cause of preventable blindness all over the world (1). Recent developments in cataract surgery have increased the number of pseudophakic people throughout the world (2). Ocular electrophysiological tests are widely used diagnostic methods and with time, an increasing number of pseudophakic patients are undergoing quantitative electrophysiological tests especially to detect and follow up glaucoma, retinal and neuroophthalmological diseases (3). For this reason, it would be of great value to have more precise information on the effect of pseudophakia on the results of electrophysiological tests (4).

A number of studies investigated the effect of different degrees of cataract on ocular electrophysiological tests on a pre-and post-operative basis (5-9). Cataract was shown to reduce the amplitudes of the a-wave and the b-wave of the scotopic full-field electroretinogram (ERG) (4). In contrast, a normal (10) and a larger (3) than normal scotopic ERG response have also been recorded in patients with cataract. It was suggested that the latter effect might be due to the light-scattering effect of the cataract (3). Chan et al found that the central multifocal electroretinogram (mfERG) response density was reduced, but the peripheral mfERG response densities were increased under the light scattering condition (11). Cataract was also shown to reduce pattern electroretinogram (PERG) amplitude and delay pattern visual evoked potential (PVEP) latency (5,6). To our knowledge, there has been no study that investigated the influence of pseudophakia on human ocular electrophysiology although this topic has epidemiological importance.

The aim of this study was to explore the effect of pseudophakia on PVEP, PERG, full-field electroretinogram (ERG) and electrooculogram (EOG).

PATIENTS AND METHODS

This prospective, case-control study was conducted in a tertiary health center in Turkish Army. In agreement with the Declaration of Helsinki, approval from the Ethics Committee had been obtained and participants had given their informed consents in writing.

The right eyes of 60 consecutive patients with bilateral pseudophakia (study group) and 60 volunteers with bilateral phakia (control group) were included. Extracapsular cataract extraction (phacoemulsification) and posterior chamber intraocular lens (Sensar AR40e®, AMO) implantation was performed by a single experienced surgeon (FMM). Posterior capsule remained intact in all operated patients. In order to prevent a possible retinal phototoxicity due to operating microscope, the operations were performed at low illumination setting.

Only right eyes of those patients with the final best corrected visual acuity (BCVA) of 9/10 or better were included. The type and degree of lens opacification of the phakic subjects who were willing to participate in the study were evaluated by the same ophthalmologist (FMM) with dilated pupils and only the subjects with clear lenses (N0, NC0 or 1, C0, P0, Lens Opacities Classification System II) were included in the study in order to minimize the influence of cataract on electrophysiological tests. In either patients or subjects, inclusion criteria were the absence of clouding of the optic media, other eye disease such as glaucoma, age-related macular degeneration, high myopia or systemic diseases that might affect the tests, such as diabetes mellitus and systemic arterial hypertension. To ensure that all subjects were free of retinal disease, eye examination including measurement of visual acuity, intraocular pressure, slit-lamp and fundoscopic examinations was done. In addition, fast macular thickness analysis procedure by using optical coherence tomography-internal normative database (OCT Stratus, Zeiss) was performed in pseudophakic subjects in order to exclude macular edema. All subjects had less than ±2 D of spheric error and less than 1.00 D of astigmatism. Electrophysiological tests were performed at least 6 months after the surgery.

Electrophysiological tests

The Roland-Consult RetiPORT System™ (Wiesbaden, Germany) was used. All recordings were made on the basis of the International Society for Clinical Electrophysiology of Vision (ISCEV) recommendations (12-15). The room temperature was 21°C and, background illumination was below 1 cd/m² in all recordings.
Electroretinogram

The electroretinogram (ERG) is a total response for the whole retina to photopic stimuli and the record of the action potential generated at that time. The ERG represents the combined electrical activity of different cells in the retina. A standard ERG includes recording of the rod response, standard combined response, oscillatory potentials (OPs), single flash cone response and 30-Hz flicker cone response (12).

Pupil dilation was performed by instilling one drop of tropicamide 1%. To record rod ERG, SCR and OPs, all subjects were dark adapted for 30 minutes. Dawson-Trick-Litzkow (DTL) fiber electrodes were then positioned prior to recording under dim red light. A white flash of 0.0095cds/m² (25 log units below the standard flash of 3.00cds/m²) was used with an interval of 2s to obtain rod ERG. To record SCR and OPs, white standard flash (3.00cds/m²) was used with an interval of 10s and 2s, respectively. Subjects were then light adapted to a white rod saturating background (25 cd/m²) for 10-min before recording cone and 30-Hz flicker responses by white standard flash. The interval between the stimuli in recording single flash cone ERG was 2s. The responses were amplified with a gain of 10000 and recorded over a bandwidth of 100-500 Hz for OPs and 1-300 Hz for rod, SCR, single flash cone ERG and 30-Hz flicker ERG recordings. A typical ERG recording is shown in Figure 1.

Pattern visual evoked potential (PVEP)

The PVEP is a cortical response to a contrast-reversal of a checkerboard pattern. PVEP components that are commonly measured include the N75, P100 and N135 (Figure 1). P100 peak is the most stable peak between the subjects and it is the most useful parameter in clinical evaluations.

Refractions of the subjects were corrected before the PVEP recordings with trial lenses. Monocular PVEPs were recorded with gold disc surface electrodes. Active electrodes were placed on the scalp over the visual cortex at Oz with the reference electrode at Fz. The ground electrode was placed on the forehead. A 20 cm x 30 cm screen was placed 1 meter in front of the subjects. The reversal rate was 2 reversals per second. One hundred stimuli were averaged. The checkerboard stimulus subtended a visual angle of 5.7° vertically and 8.5° horizontally on either side of the fixation. Luminance was <1 cd/m² (<0.017cds/m²) for black hexagons and 115 cd/m² (1.92 cds/m²) for the white hexagons (contrast: 99%). The PVEP recordings to two check sizes (1º, 15’) were obtained.

Pattern electroretinogram (PERG)

The PERG is the retinal response to a structured stimulus, such as a reversing black-and-white checkerboard or grating. The PERG is a small response, and its recording is technically more demanding than other visual electrophysiologic tests. The waveform consists of a prominent positive component, P50 with a larger later negative component, N95 (Figure 1).

Refractions of the subjects were corrected before the recordings with trial lenses. Monocular PERGs (right eye) were recorded with DTL fiber electrodes. The electrodes were placed in the lower fornix and stabilized near the lateral canthus with adhesive strips. Gold cup reference electrodes were placed at the ipsilateral outer canthi. A ground electrode was attached to the forehead. The electrical impedance for all electrodes was less than 3 kΩ. The contrast level, reversal rate and
check size were 99% (with the same luminance levels used for PVEP recording), 3 reversals per second (transient PERG). Only one check size (30') was used. The filter was set at 1-100 Hz. One hundred and fifty stimuli were averaged. Fixation was monitored closely by an experienced electrophysiology technician during PVEP and PERG recordings.

**Electrooculogram (EOG)**

The EOG records a standing or resting potential of approximately 6mV that is always present between the cornea and the back of the eye. The current flow is oriented so that voltage at the cornea is positive relative to the posterior pole.

Gold cup skin electrodes were attached with tape near the lateral and medial canthi of both eyes to record EOG. Pupil dilation with 1% tropicamide was performed. Horizontal fixation targets were 30 degrees apart. After the initial pre-adaptation period of 15-min in room light, all lights were turned off and responses from saccadic eye movements were recorded for 15-min under a dark-adapted condition (<1 cd/m²) and for 15-min under the light adapted (100 cd/m²) phase. Time interval of stimulation was 60s. The EOG data was collected for the first 12 s of every minute. The ratio of light peak to dark through (Arden ratio) was determined to evaluate the difference between the groups.

**Statistical analysis**

The difference between the data in the groups was investigated using independent samples t test. Independent samples t-test and chi-square tests were used to explore statistical significance for the variables in electrophysiologic tests and gender differences between the groups, respectively.

**RESULTS**

The difference for age, sex, best-corrected visual acuity and refraction was not significant between the groups (Table 1).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients with pseudophakia</th>
<th>Patients with phakia</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69.4±5.7</td>
<td>68.1±5.1</td>
<td>0.186</td>
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<tr>
<td>Sex (Male/Female) (No)</td>
<td>30/30</td>
<td>32/28</td>
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<tr>
<td>BCVA (metric values)</td>
<td>0.94±0.06</td>
<td>0.93±0.07</td>
<td>0.688</td>
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<td>Refraction (diopters)</td>
<td>-0.41±0.73</td>
<td>-0.32±0.74</td>
<td>0.495</td>
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</table>

Table 1. Demographic and clinical characteristics of the participants

B-wave implicit time in rod response, a-wave implicit time in SCR were significantly shorter in the patients with pseudophakia. In addition, b-wave amplitude in rod response, a-wave amplitude in SCR, and a-wave amplitude in single cone response was significantly higher in the study group (Table 3). Regarding the OPs, there was significant delay in implicit times for P₁ and P₃ waves in the study group. In addition, the patients with pseudophakia had significantly higher P₁ amplitude in the OPs (Table 4).

<table>
<thead>
<tr>
<th>Parameters</th>
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<th>Patients with pseudophakia</th>
<th>Patients with phakia</th>
<th>p</th>
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<tbody>
<tr>
<td>P100 amplitude (µV)</td>
<td>1º</td>
<td>11.8±6.1</td>
<td>10.8±3.7</td>
<td>0.264</td>
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<tr>
<td>P100 latency (ms)</td>
<td>1º</td>
<td>103.0±6.1</td>
<td>107.1±10.7</td>
<td>0.012</td>
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<td></td>
<td>15º</td>
<td>108.5±8.3</td>
<td>109.8±10.0</td>
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Table 2. P₁₀₀ amplitude and latency differences between the patients with pseudophakia and phakia

<table>
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<th>Patients with phakia</th>
<th>p</th>
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<tr>
<td>Rod response</td>
<td>b wave (ms)</td>
<td>78.8±6.6</td>
<td>81.6±6.2</td>
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<td>b wave (µV)</td>
<td>88.1±26.5</td>
<td>72.5±13.2</td>
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<td>Standard combined response</td>
<td>a wave (ms)</td>
<td>18.9±2.5</td>
<td>22.9±1.7</td>
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<tr>
<td></td>
<td>b wave (ms)</td>
<td>44.5±4.2</td>
<td>45.6±3.8</td>
<td>0.127</td>
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<td>Cone response</td>
<td>a wave (µV)</td>
<td>121.6±32.9</td>
<td>96.6±22.5</td>
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<td>b wave (µV)</td>
<td>200.5±50.3</td>
<td>189.6±32.6</td>
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<td>a wave (ms)</td>
<td>15.5±1.5</td>
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<td></td>
<td>b wave (ms)</td>
<td>33.5±1.7</td>
<td>33.4±1.7</td>
<td>0.626</td>
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<tr>
<td>30-Hz flicker response</td>
<td>P1 (ms)</td>
<td>29.0±1.8</td>
<td>29.4±1.9</td>
<td>0.160</td>
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<tr>
<td></td>
<td>P1 (µV)</td>
<td>61.7±19.0</td>
<td>59.0±11.9</td>
<td>0.346</td>
</tr>
<tr>
<td></td>
<td>P3 (µV)</td>
<td>23.4±7.7</td>
<td>21.6±7.4</td>
<td>0.206</td>
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</tbody>
</table>

Table 3. Electroretinogram differences between the patients with pseudophakia and phakia
The significant differences in PERG between the groups were observed in N95 implicit time and P50 amplitude. N95 implicit time was delayed and P50 amplitude was higher in the study group (Figure 2). N95/P50 ratio was significantly lower in the patients with pseudophakia (2.01±0.17), comparing to the patients with phakia (1.88±0.23) (p<0.001).

The Arden ratios in the study group and control group were 2.368±0.431 and 2.381±0.522, respectively. The difference was not significant (p=0.961).

DISCUSSION

Cataract extraction and IOL implantation is currently the only way for the treatment of cataract, the most significant cause of preventable blindness over the world (16). Although most IOLs provide a reasonable imitation of the spectral characteristics of the natural human lens, the balance is a little less optimal than in the natural lens (17).

A study showed that VEPs recorded on the first day after removal of a longstanding, dense, unilateral cataract showed a marked delay to stimulation of the operated eye compared to the unoperated eye, delays in the VEP returned to normal within approximately 3 months after the surgery, suggesting the sensitiveness of the adult central visual system to visual deprivation caused by longstanding, dense cataract (6). Semenicki et al. (18) observed a shortening of the N2 latency of flash VEP after cataract extraction and IOL implantation. To the best of our knowledge, there has been no study that investigated the PVEP difference between the pseudophakic subjects and age- and sex-matched controls. Cataract decreases the contrast of the objects on the retina (19). For this reason, the latency shortening after cataract extraction that was found in previous studies is rather logical (6, 18). However, in this study, we showed that there was still a significant shortening of P100 latency in the pseudophakics with respect to age-matched phakics, even after at least 6 months of cataract surgery. Although the mean age of both patient groups in the present study was similar, a slightly significant decrease in contrast perception due to age-related changes of the lens of phakic subjects may cause this difference. However, this assumption needs to be confirmed. A second possible cause for PVEP and also ERG results according to the results of the present study may be related to the light scattering effect of intraocular lenses. A study showed that intraocular light scatter in pseudophakic eyes increase by a factor of 2 with respect to age-matched normal eyes (20). Light scattering by the intraocular lens causes the stimulation of a retinal area many times, and this may result in amplitude increase and latency shortening in ERG and PVEP. The supranormal ERG amplitude increase and latency shortening in ocular albinism are also caused by this mechanism (21).

The results of this study have shown that OPs were a series of wavelets superimposed on the ascending limb of the ERG b-wave after stimulation by an intense light flash. The cellular origin of OPs in the retina is somewhat uncertain (22). Current information supports the conclusion that cells of the inner retina supplied by the retinal circulation, such as the amacrine or possibly interplexiform cells, are the generators of these potentials (23, 24). Reduction of amplitude of OPs becomes apparent in patients with diabetic retinopathy, central retinal vein occlusion, sickle cell retinopathy, X-linked juvenile retinoschisis, and in some patients with congenital stationary night blindness (25). This study found significantly delayed implicit times (P3, P4) and lower P1 amplitude in OPs in the pseudophakic group. This result may be interpreted as reduced OPs in the pseudophakic subjects.

The PERG is a powerful clinical tool, allowing both an objective evaluation of macular function and a direct assessment of retinal ganglion cell function. P50 and N95 may be selectively affected in macular and optic nerve (and ganglion cell) disease, respectively (26, 27). Previous studies showed that chemical mediators such as, cytokines and prostaglandins, increase in the

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<tbody>
<tr>
<td>OP1 Amplitude (µV)</td>
<td>22.7±10.2</td>
<td>16.2±4.5</td>
<td>&lt;0.001</td>
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<tr>
<td>Implicit time (ms)</td>
<td>19.6±1.7</td>
<td>19.4±1.0</td>
<td>0.349</td>
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<tr>
<td>OP2 Amplitude (µV)</td>
<td>44.6±13.7</td>
<td>44.8±9.1</td>
<td>0.909</td>
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<tr>
<td>Implicit time (ms)</td>
<td>26.6±2.4</td>
<td>26.7±1.1</td>
<td>0.733</td>
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<tr>
<td>OP3 Amplitude (µV)</td>
<td>7.2±4.4</td>
<td>6.2±3.9</td>
<td>0.210</td>
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<tr>
<td>Implicit time (ms)</td>
<td>36.8±4.8</td>
<td>34.4±1.3</td>
<td>&lt;0.001</td>
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<tr>
<td>OP4 Amplitude (µV)</td>
<td>6.3±3.2</td>
<td>6.5±3.2</td>
<td>0.703</td>
</tr>
<tr>
<td>Implicit time (ms)</td>
<td>50.9±9.5</td>
<td>46.9±2.5</td>
<td>0.002</td>
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</table>

Table 4. Oscillatory potential differences between the patients with pseudophakia and phakia
intraocular environment after phakoemulsification surgery and this results in the disruption of blood-aqueous and blood-retina barrier (28). The pathophysiology of the postoperative cystoid macular edema is explained with this theory (29). In addition, it is probable that these chemical mediators affect not only the macula but also may affect the peripheral retina (28). Supporting this assumption, Teresaki et al (30) reported significant amplitude reductions and implicit time delay in OPs in patients with aphakic and pseudophakic cystoid macular edema. The patients in this study had neither cystoid macular edema nor increased macular thickness with respect to normative OCT database, but we had reduced OPs and N95 latency delay in pseudophakic patients. These PERG and OPs results may show an irreversible or long-lasting functional impairment in the inner retina due to intraocular inflammation after the phakoemulsification surgery. There are various reports describing retinal and macular changes, remaining stable for at least 6 months after cataract surgery (31, 32). The effect of cataract surgery on retinal and macular functions needs to be clarified by retinal electrophysiological and structural studies.

The EOG response has two components: one light-insensitive other light-sensitive. It is a widely used test which measures the light response of the retinal pigment epithelium, but it is not a pure test of RPE function since retinal photoreception is required in the light-sensitive component (33). The light-insensitive component depends on the integrity of the retinal pigment epithelium. This component, accounting for the dark through, is not influenced by previous retinal illumination and it is thus independent of the functional status of the retinal photoreceptors (33). The light sensitive component appears to be generated by a depolarization of the basal membrane of the RPE (34). Intact photoreceptor cells are, however, also necessary to generate this response (33, 35). Arden ratio difference between the pseudophakic and phakic subjects in this study was not significant. This insignificant EOG difference between the groups may mean that the possible functional impairment in the inner retina because of the increased inflammatory mediators may possibly not affect the outer retina.

In conclusion, significant differences in ERG, PVEP and PERG responses in pseudophakics may possibly be related to the differences in optical performance of IOLs and natural human lens or the inflammatory response of ocular tissues after cataract surgery. However, further studies are necessary to clarify possible causes of the influence of pseudophakia on electrophysiological tests.

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TRANSPARENCY DECLARATIONS
Competing interests: None to declare.

REFERENCES