Detection of glaucomatous damage in patients with osteo-odontokeratoprosthesis

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Abstract

Background—Osteo-odontokeratoprosthesis (OOKP) is an autologous transplantation procedure in which the cornea is replaced by an optical cylinder glued to a biological support. Patients undergoing OOKP surgery may develop a secondary glaucoma whose diagnosis, by means of standard diagnostic procedures, is often doubtful.

Methods—In the present study pattern electroretinograms (PERGs), visual evoked potentials (VEPs), contrast sensitivity, and automated threshold perimetry (Humphrey 30-2) were evaluated in 19 OOKP treated patients with postoperative visual acuities ≥ 0.8 . Nine patients had had a preoperative secondary glaucoma, while the remaining 10 had no history of glaucoma and normal posterior pole.

Results—Results were compared with those obtained from either normal control subjects or from ordinary glaucoma patients. PERG amplitudes and contrast and perimetric sensitivities were reduced in both groups of OOKP patients when compared with normal controls. However, these losses were significantly greater in OOKP patients with glaucoma compared with those with normal posterior pole. VEPs were reduced, compared with controls, only in OOKP patients with glaucoma. These VEP losses were similar to those found in ordinary glaucoma patients.

Conclusion—Among the tests employed, VEPs showed the best accuracy (79%) in discriminating between glaucomatous and non-glaucomatous OOKP treated eyes. The present results suggest a possible use of the VEP technique for detecting glaucomatous dysfunction after OOKP.

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technique,⁷ have further improved the quality of anatomical and functional results, reducing the incidence of failures to less than 10% of cases.

Postoperative visual acuity has been considered the major functional parameter to evaluate the OOKP's rate of success.³⁻⁷ However, it must be taken into account that a considerable number of patients undergoing OOKP surgery might suffer from secondary glaucoma.⁷ The development or progression of this neuro-ophthalmic complication, which is very common in eyes with physical or chemical burns, may not affect visual acuity until advanced stages are reached, and may raise important diagnostic problems, mainly related to the difficulty in obtaining reliable clinical measures (that is, IOP, visual field) from OOKP treated eyes.

In recent years, refined electrophysiological (pattern evoked retinal and cortical potentials, PERG, VEPs) and psychophysical (contrast sensitivity, automated threshold perimetry within the central 30 degrees) tests have been employed to detect the development and progression of glaucomatous disease (see Bodis-Wollner⁹ for a review). These methods can provide objective (evoked potentials) or subjective (psychophysical tests) measures of visual function that appear to be more sensitive and reliable than standard clinical tests. The use of these techniques could be of clinical value in identifying those OOKP treated patients suffering from concomitant secondary glaucoma.

In the present study we employed PERG, VEPs, contrast sensitivity, and automated perimetry to evaluate postoperatively visual function in OOKP treated patients with a recovery of Snellen acuity to normal or near to normal values. A subgroup of these patients had had a clinical history of secondary glaucoma before surgery. The results showed that both electrophysiological and psychophysical tests were able to differentiate OOKP treated patients with glaucomatous dysfunction from those with normal visual function. Among the functional tests employed, VEPs appeared to yield the best clinical discrimination between these two categories.

Materials and methods

SUBJECTS

Nineteen patients (12 males, seven females), who had been operated on for OOKP between 1988 and 1992 in the department of ophthalmology at S Camillo General Hospital (Rome, Italy), were included in the study. The

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Osteo-odontokeratoprosthesis (OOKP) is an heterotopic autograft employed for treatment of severe corneal opacities not suitable for corneal transplantation.¹ The cornea is replaced by an optical polymethylmethacrylate (PMMA) cylinder glued to a biological support (haptics), made by human living tissue (that is, an osteo-dental lamina).¹⁻⁴ The OOKP technique has been successfully employed in large series of patients.⁵⁻⁷ Long term clinical⁷ and histological⁸ results have suggested a greater stability and safety of OOKP compared with other types of keratoprostheses, whether with biological or biocompatible haptics. Recent innovative changes to the original Strampelli's

Figure 1 Representative example of an optic disc photograph taken from the right eye (through the keratoprosthesis) of one of the OOKP treated patients with a secondary glaucoma. Note the typical glaucomatous changes of the optic nerve (large cupping, reduced neuroretinal rim area).

patients' mean age was 49 (range 28–65) years. Twelve patients had had unilateral and seven bilateral surgery. Only one eye for each patient was included in the study (in bilateral cases the right eye was tested). Preoperative diagnoses included severe alkali burns (seven cases), severe acid burns (seven cases), ocular pemphigoid (three cases), and stromal interstitial keratitis (two cases). Before surgery, 10 out of the 19 patients included in the study had a normal intraocular pressure (IOP), as measured by a Mackay-Marg tonometer, and no history of ocular hypertension or glaucoma, while nine patients had ocular hypertension (range 29–38 mm Hg) and a documented history of long term (15 to 26 months) IOP elevation. Most of these patients had grossly abnormal corneas with an increased central thickness, which may have led to an overestimation of the IOP.¹⁰ However, even an overestimation as large as 6.8 mm Hg (the maximum value reported by Whitacre *et al*¹⁰) may not have accounted fully for the large IOP increases found in these patients.

After surgery, in all patients the PMMA keratoprosthesis allowed the examiner clearly to visualise the fundus, under direct and indirect ophthalmoscopy, and to take colour optic disc photographs. These were examined carefully by two different observers in a masked fashion, according to the technique and grading scheme proposed by Klein *et al*.¹¹ The nine patients with a preoperative history of ocular hypertension showed typical glaucomatous changes of the optic disc (vertical elongation or notching of cupping, vertical cup/disc ratio >0.7 , reduced or absent neuroretinal rim area). Both observers agreed in judging as pathological the optic discs of these OOKP patients, who were then considered as having a secondary glaucoma. The remaining 10 patients had no apparent abnormalities of the optic nerve. An example of a glaucomatous optic disc photograph, taken from the right eye of one of our OOKP treated patients, is reported in Figure 1.

None of the patients had vitreous opacities

at the time of examination. Postoperative corrected visual acuity ranged from 0.8 to 1.0. Refractive errors were carefully corrected for the test recordings. All patients underwent electrophysiological and psychophysical tests at least 2 months after surgery.

Seventeen normal subjects (17 eyes), with an age and sex distribution comparable with that of the patients, were tested to obtain control data for PERG, VEP, and contrast sensitivity measurements. For comparison purposes with OOKP patients affected by a secondary glaucoma, eight patients with chronic open angle glaucoma were also evaluated. Their mean age was 48 (range 30–62) years. All these patients had typical optic disc and field defects, and were being treated with timolol maleate. None of them had undergone antiglaucomatous surgery.

APPARATUS AND PROCEDURE

PERG, VEPs, and contrast sensitivity

Visual stimuli employed for both electrophysiological recordings and contrast sensitivity measurements were vertical sinusoidal gratings of variable spatial frequency (between 0.6 and 4.8 c/deg), electronically generated on a high resolution (Mangoni, Pisa-I) TV monitor (24×14 cm, 85 cd/m² mean luminance) and square wave modulated in counter-phase at 8 Hz (16 reversals/second). For PERG and VEP recordings the contrast of the stimulus was maintained at 56%. For contrast sensitivity measurements a logarithmic attenuator was used to vary the contrast (in 1–10 dB steps) on the screen. Both patients and control subjects fixated monocularly at the centre of the stimulator from a distance of 57 cm. Patients viewed the stimulus through the optical PMMA cylinder, whose size was 3.5 mm. Control subjects were tested while wearing an artificial pupil of 3.5 mm, in order to match their stimulus retinal illuminance with that of patients.

PERGs were recorded by a small silver-silver chloride electrode taped over the skin of the lower eyelid. An equal electrode, placed over the eyelid of the contralateral, light tight patched eye, was used as reference (interocular ERG). With the same electrodes used for the PERG recordings, flash electroretinograms (to scotopic and photopic stimulation¹²) were also recorded in all patients and controls. In all OOKP treated patients, the amplitudes and implicit times of flash electroretinograms were comparable with those obtained in control subjects. VEPs were recorded by an active silver-silver chloride electrode placed on the midline 2 cm above theinion, and referenced to the right mastoid. The left mastoid was grounded. Retinal and cortical signals were band pass filtered between 1 and 30 Hz (–6 dB per octave), amplified (100 000 fold), and averaged (12 bit resolution, 0.5 ms sampling rate, 250 events) with artefact rejection. Discrete Fourier analysis of the resulting waveforms was performed off line in order to isolate the

Figure 2 Mean (SEM) PERG amplitude and phase values as a function of spatial frequency for normal subjects, OOKP treated patients with normal posterior pole (OOKP), and OOKP treated patients with glaucoma (OOKP glaucoma).

component at the reversal frequency (16 Hz; second harmonic), whose amplitude (μV) and phase (degrees) were measured and plotted as a function of spatial frequency. The mean of at least two records was taken at each spatial frequency. The average biological noise at the second harmonic, obtained with the monitor blanked at the same mean luminance as the stimulus, was $0.09 \mu\text{V}$ for PERG and $0.2 \mu\text{V}$ for VEP in both normal subjects and patients.

Contrast sensitivity was measured in the same experimental session as the electrophysiological recordings. The method of

Figure 3 Mean (SEM) VEP amplitude and phase values as a function of spatial frequency for normal subjects, OOKP treated patients with normal posterior pole (OOKP), and OOKP treated patients with glaucoma (OOKP glaucoma).

adjustment¹³ was used to determine contrast sensitivity. Three threshold estimates were taken for each spatial frequency. The average variation of the settings did not exceed 1.5 dB and was similar in the controls and patients.

PERG, VEPs, and contrast sensitivity data obtained from patients and controls were statistically evaluated by analysis of variance (ANOVA) with post hoc adjusted *t* tests. The diagnostic sensitivity and specificity of the electrophysiological and psychophysical tests was evaluated, in the two groups of OOKP treated patients, by 2×2 contingency tables and Fisher's exact test.

Automated perimetry

Perimetric thresholds within central 30 degrees were evaluated by the Humphrey 30-2 threshold test. At least three measurements (on three separate days) were obtained from each patient. The results of the third test were considered for the purposes of the study. Perimetric indices (mean deviation (MD) corrected pattern standard deviation (CPSD) and short term fluctuation (SF)) were calculated with STATPAC software and compared with age and pupil size matched normative values. In addition, mean values of perimetric indices were compared between the OOKP patients' groups (that is, those with normal posterior pole and those with glaucoma) by unpaired *t* tests. A qualitative field evaluation for glaucomatous defects was performed following the criteria proposed by Lustgarten *et al.*¹⁴

Results

Figure 2 shows the mean (SEM) PERG amplitude and phase values as a function of spatial frequency for normal subjects, OOKP treated patients with normal posterior pole (OOKP), and OOKP patients with glaucoma (OOKP glaucoma). Mean PERG amplitudes showed a significant variation across groups (ANOVA, $F 37.8$; $df 2, 33$; $p < 0.001$), being reduced in patients in comparison with controls. Post hoc *t* test revealed significant differences, pooled across spatial frequencies, between normal subjects and both groups of patients ($p < 0.001$), and between OOKP patients with normal posterior pole and those with glaucoma ($p < 0.05$). Mean PERG phases did not change significantly across groups (ANOVA, $F 1.33$; $df 2, 33$; p not significant).

Figure 3 shows the mean (SEM) VEP amplitudes and phases as a function of spatial frequency for normal subjects, OOKP treated patients with normal posterior pole, and OOKP treated patients with glaucoma. Mean VEP amplitudes changed significantly across groups (ANOVA, $F 3.99$; $df 2, 33$; $p < 0.05$), being reduced in OOKP patients with glaucoma compared with the two other groups. Post hoc *t* test revealed significant differences, pooled across spatial frequencies, between normal subjects and OOKP patients with glaucoma ($p < 0.05$), and between OOKP patients with normal posterior pole and those

Figure 4 Mean (SEM) contrast sensitivity values (expressed in dB of attenuation from the maximum stimulus contrast available) for normal subjects, OOKP treated patients with normal posterior pole (OOKP), and OOKP treated patients with glaucoma (OOKP glaucoma).

with glaucoma ($p < 0.05$). No significant differences were found between normal subjects and OOKP patients with normal posterior pole. Mean VEP phases changed significantly across groups (ANOVA, $F 6.36$; $df 2, 33$; $p < 0.01$), showing a trend to a delay in OOKP patients compared with normal subjects. Post hoc t tests revealed significant differences only between normal subjects and OOKP patients with glaucoma ($p < 0.01$). These differences were apparent at low medium but not at higher spatial frequencies (see Fig 3).

Figure 4 shows mean (SEM) contrast sensitivity values (expressed in dB of attenuation from the maximum stimulus contrast available) for normal subjects, OOKP treated patients with normal posterior pole, and OOKP treated patients with glaucoma. Mean contrast sensitivities changed significantly across groups (ANOVA, $F 55.5$; $df 2, 33$; $p < 0.001$), being reduced in patients compared with controls. Post hoc t test revealed significant differences, pooled across spatial frequencies, between normal subjects and both groups of patients ($p < 0.001$), and between OOKP patients with normal posterior pole and those with glaucoma ($p < 0.05$).

Table 1 reports the mean (SEM) values of perimetric indices recorded in OOKP treated patients with normal posterior pole and in those with glaucoma. In both groups of patients, the MD and CPSD were, on average, significantly different (lower and larger, respectively) than normal values. By contrast, the SF mean values were within the range of normal variability. Unpaired t test showed that, on average, MD was significantly lower, and CPSD significantly larger, in OOKP patients with glaucoma compared with those with normal posterior pole ($p < 0.05$). Most of the OOKP treated patients (either with or

Table 1 Mean values (SD) of perimetric indices recorded in OOKP treated patients with normal posterior pole and in those with secondary glaucoma

	OOKP	OOKP (glaucoma)
Mean deviation (dB)	-14.9 (1.9)	-19.1 (5.2)
Corrected pattern standard deviation	8.4 (1.8)	11.8 (1.7)
Short fluctuation	1.6 (0.5)	1.9 (0.5)

Figure 5 Mean (SEM) PERG (A) and VEP (B) amplitudes and contrast sensitivity (C) values, as a function of spatial frequency, for normal subjects and control glaucoma patients. Note (see Fig 3 for comparison) that VEP losses in glaucoma patients are similar to those of OOKP treated patients with glaucoma and greater than those of OOKP patients with normal posterior pole.

without glaucoma) had a generalised depression of sensitivity across their visual fields, which made an assessment for localised glaucomatous defects difficult. However, in four out of the nine OOKP patients with glaucoma, a localised, typical glaucomatous defects (arcuate scotoma, nasal step, or para-central scotoma) was found, while such defects were not observed in the OOKP patients with normal posterior pole.

Figure 5 shows the results obtained with PERG, VEPs, and contrast sensitivity (mean values (SEM)) in the control groups of chronic open angle glaucoma patients and normal subjects. When compared with normal subjects, glaucoma patients had significant reductions in the mean PERG ($F 28.6$, $df 1, 23$, $p < 0.01$) and VEP ($F 8.7$, $df 1, 23$, $p < 0.01$) amplitudes, as well as in the mean contrast sensitivity values ($F 181.8$, $df 1, 23$, $p < 0.01$). The PERG and contrast sensitivity losses found in the control glaucoma patients did not differ significantly from those of OOKP treated patients, either with normal posterior pole or with glaucoma (see, for comparison, Figs 2 and 4). By contrast, the VEP amplitude losses of the control glaucoma patients were significantly greater than those of OOKP treated patients with normal posterior pole, and similar to those

of OOKP treated patients with glaucoma (see, for comparison, Fig 3).

Individual electrophysiological (PERG and VEPs amplitudes and phases) and psychophysical (contrast sensitivities and perimetric indices) results obtained from OOKP treated patients were analysed in order to determine which of the tests employed in this study was able to best discriminate between glaucomatous and non-glaucomatous patients. To this goal, the data obtained from each patient were compared with the corresponding 95% confidence limits (that is, plus or minus 2 SD) established for normal subjects. An individual patient's value was defined as abnormal when outside these limits. The number of abnormal results obtained with each test was then compared in non-glaucomatous and glaucomatous OOKP treated patients. We found that VEPs to 1.4 c/deg spatial frequency stimuli were abnormal (in amplitude, phase, or both) in one out of 10 (10%) OOKP patients with normal posterior pole, and in six out of nine (67%) OOKP patients with glaucoma. The difference between the two patient groups was statistically significant (Fisher's exact test: $p=0.02$), and corresponded to a 75% test sensitivity, 85% specificity, and 79% total accuracy. Other tests yielded poorer clinical discriminations (Fisher's exact test: p not significant) between the two patient groups. For both PERG and contrast sensitivity the best discriminating responses were those to 4.8 c/deg spatial frequency stimuli. With these responses, PERG had 61% test sensitivity, 66% specificity, and 63% total accuracy, while contrast sensitivity had 100% test sensitivity, but only 53% specificity and 57.8% of total accuracy.

Discussion

A stable recovery in visual acuity to normal or near normal values (0.8–1.0) is frequently reported in eyes that have received OOKP surgery for severe corneal opacities not treatable by perforating keratoplasty (56.6% of 134 eyes in the series reported by Falcinelli *et al*).⁷ However, a significant proportion of those OOKP treated eyes may develop a secondary glaucoma, which can be considered the most frequent complication in OOKP.⁷ Glaucoma may induce a subtle and progressive visual dysfunction that is not reflected, unless in advanced stages, by changes in visual acuity. Reliable and sensitive methods for glaucoma diagnosis in OOKP treated eyes are therefore needed. In this respect, standard clinical measures may not be adequate. IOP is difficult to measure reliably either in diseased corneas before surgery, or after OOKP has been implanted. Peripheral visual fields, determined by Goldmann kinetic perimetry, may be significantly affected by the relatively small diameter of the optical PMMA cylinder.¹⁵

In the present study, we evaluated the possible use of some tests of central visual functioning (PERGs, VEPs, contrast sensitivity, and automated perimetry) for detecting glaucomatous dysfunction in OOKP treated eyes. We tested two groups of those eyes, one

with normal posterior pole and no history of glaucoma and the other with clinical signs and a history indicative of preoperative secondary glaucoma. The results from these two groups were also compared with those from unoperated control eyes, either normal or glaucomatous. We found that both electrophysiological and psychophysical tests were altered, compared with controls, in both normal and glaucomatous OOKP treated eyes. Indeed, PERG amplitudes as well as contrast and perimetric sensitivities were reduced, and VEP phases were delayed, in both groups of patients in comparison with controls. These changes may be at least in part related to a reduced optical quality (that is, reduced effective retinal size¹⁵) of visual stimuli viewed through the PMMA cylinder, whose length and refractive power are 7.2 mm and 55 dioptres, respectively. A reduction in the effective retinal contrast of visual stimuli may also have occurred in patients, because of possible changes in the eyes' modulation transfer functions induced by the optical PMMA prostheses. The large losses in psychophysical sensitivities (about 15 dB for both contrast sensitivity and automated perimetry) found in non-glaucomatous OOKP patients might give an indication of the amount of contrast attenuation through OOKP prosthesis. However, PERG, VEPs, contrast sensitivity, and perimetric losses were significantly more marked in OOKP operated eyes with glaucoma compared with those with normal posterior pole, indicating the presence of glaucoma related changes in both electrophysiological and psychophysical variables. This is also supported by the finding that, in the unoperated control eyes with glaucoma, PERG, VEP, and contrast sensitivity were reduced in comparison with normal eyes. Interestingly, VEP losses of glaucoma control eyes were similar to those found in OOKP treated eyes with glaucoma, and greater than those of OOKP eyes with normal posterior pole.

Among the tests employed in this study, we found that VEP responses to medium spatial frequencies (1.4 c/deg) yielded the best discrimination, in terms of sensitivity and specificity, between glaucomatous and non-glaucomatous OOKP eyes. Although this finding needs to be confirmed in a larger series of patients, it suggests that VEPs may have a specific clinical value for diagnosis of glaucomatous damage in OOKP treated patients.

Abnormalities in electrophysiological and psychophysical tests have been typically reported in previous functional studies on glaucoma.^{9 14 16 17} It is also known⁹ that these tests may be of clinical value for monitoring the progression of glaucomatous damage. This suggests a possible use of the techniques employed in the present study for postoperative longitudinal evaluation of glaucomatous OOKP patients. Preliminary results of an ongoing follow up study, which will be the object of a separate report, are encouraging in this respect.

In conclusion, our results indicate that both

electrophysiological methods and psychophysical measures employed for glaucoma diagnosis might be helpful for the postoperative assessment of visual function in OOKP patients who are being suspected of having a secondary glaucoma. In clinical setting, VEPs appear to give the best sensitivity and specificity for detecting a glaucomatous dysfunction after OOKP.

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