Surgical treatment of vitreomacular diseases, assessment of anatomical and functional results

Short doctoral thesis

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Budapest
2008
Introduction

The improvement of microsurgical techniques in the last decade resulted in better anatomical and functional results in the treatment of some vitreoretinal pathologies like macular hole, diabetic macular edema, epiretial membrane and vitreal traction syndrome. One of the milestones of this development was the introduction of indocyanine green (ICG) dye in the staining of epitretinal membranes of the macula, facilitating their safe and intact peeling. After the first enthusiastic successes, however, concerns were raised because of the presumed toxicity of the dye.

As epiretinal membranes usually occur in elderly patients, there is also some degree of cataract formation present which requires combined surgical intervention involving the anterior segment as well for the good visualization of membrane removal. In order to achieve good postoperative visual acuity, accurate intraocular lens planning is required. Unfortunately, in cases accompanied by macular edema formation regular biometry methods may not be appropriate.

Aims

I. To assess the possible toxicity of ICG dye applied during macular hole surgery for the removal of the inner limiting membrane.

1. Does the dye affect anatomical success?
2. Is there any difference in postoperative visual acuity in patients where ICG dye is used compared to these where it is not?
3. Is multifocal electroretinography (mfERG) able to show the possible toxicity of the dye?
4. Are there any differences among the two groups in postoperative mfERG response densities during the follow-up period?
5. Are there any changes in response densities during the follow-up?

II. To assess the accuracy of intraocular lens planning in patients undergoing combined surgery for cataract and macular edema.

1. Are there any refractive errors postoperatively compared to calculated refraction?
2. Find a solution for the difference from the planned refraction of the patients.
Patients and Methods

I. Assessment of the possible toxicity of ICG dye applied during macular hole surgery for the removal of the inner limiting membrane.

In a prospective observational case series, 30 eyes of 29 patients (nine men and 21 women) underwent macular hole surgery at our department between May 2001 and April 2003. The ages of the patients ranged from 65 to 72 years (mean ± SD, 66.9 ± 5.7 years). Postoperative follow-up time was a minimum of 20 months. Patients with macular pathology other than macular hole, with systemic diseases affecting the eye, or with the presence of cataract, history of cataract operation, or undergoing combined (phacoemulsification and vitrectomy) operation were excluded from the study, as were those who had undergone previous retinal surgery.

The examination protocol (performed preoperatively and at three, six, 12, and 20 months after surgery) included the assessment of visual acuity (VA), slit-lamp biomicroscopy, a Watzke-Allen test, photographic documentation, optical coherence tomography (OCT), and mfERG. Before surgery, all patients noted central distortion of vision. Best-corrected visual acuity (BCVA) was determined before surgery and at three, six, 12, and 20 months after surgery. We used a standard (Snellen) VA chart, but for purposes of statistical analysis, VA results were converted to units of logarithm of minimal angle of resolution (logMAR).

Both the preoperative diagnosis and postoperative closure of the hole were confirmed by OCT (Model 2000, Zeiss-Humphrey, Dublin, California, USA).

The patients were divided into two groups according to the surgical technique: group A (n = 21) consisted of consecutive eyes that underwent ILM peeling with use of ICG staining; later, nine consecutive, unselected patients were enrolled into group B (n = 9) and underwent ILM peeling without staining. In both groups, the surgical method was otherwise similar and consisted of core pars plana vitrectomy, separation and removal of the posterior hyaloid, ILM peeling, and implantation of 14% to 16% C₃F₈ gas after air-fluid exchange. Posterior vitreous detachment was performed with a cutter unless it was already present; as much of the vitreous was removed as possible. The light source for endoillumination was a 150 W halogen lamp; no filter was used. Operations were performed by three skilled surgeons who each perform more than 100 macular hole operations a year.

The mfERG responses (first-order kernel responses) were obtained binocularly with Retiscan equipment (Roland Consult, Brandenburg, Germany). The central 30° (radius) of the retina
was stimulated by 61 black and white hexagons scaled with excentricity. The stimulus was presented on a 21-inch high-resolution monitor with a frame rate of 75 Hz, at a distance of 28 cm from the subject’s eye. The bandpass of the filter was 10 to 100 Hz.

For the intergroup comparison of patient data (age, gender, symptom duration, and stage of macular hole), the Wilcoxon rank sum test was employed. To compare the preoperative values of C1, C2, and BCVA (expressed in decimal values and in logMAR units) with all postoperative results in both groups, analysis of variance was performed, followed by Newman-Keuls post hoc analysis. To test whether there was any correlation between the 20-month postoperative logMAR VA and the response densities in the C1 and C2 regions, a linear regression was performed and the Spearman correlation coefficient determined. For statistical analysis, Statistica 6.0 software was used (Statsoft, Tulsa, Oklahoma, USA). Statistical significance was accepted at the $P < .05$ value.

II. Evaluation of the accuracy of intraocular lens planning in patients undergoing combined surgery for cataract and macular edema.

Current ultrasonographic techniques permit an accuracy of 0.1 mm or less in axial length measurement. According to the relevant formula for sample size calculation for a power of 80%, at least nine patients are required to detect a difference of 0.2 mm in the case of a 0.15 mm standard deviation. In order to exceed the minimum number required, 12 eyes of 12 patients (nine women, three men; aged 72.42 ± 1.73 years) who underwent combined phacoemulsification, IOL implantation and vitreoretinal surgery for epiretinal membrane or diabetic macular oedema at our department were enrolled in this prospective, observational case series study. Patients with previous intraocular surgery were not admitted. The indication for cataract surgery was visually significant cataract that precluded sufficient visualization for vitreoretinal surgery. Indications for pars plana vitrectomy included epiretinal membrane (eight cases) and macular oedema (four cases), demonstrated by optical coherence tomography (OCT-2; Zeiss-Humphrey Instruments, San Leandro, CA, USA).

The preoperative clinical data obtained for each patient included age, measurement of macular thickness by OCT in the central 3.5-mm area and determination of the ultrasound axial length (UAL). Immersion axial length measurements were performed with the same equipment (Ultrascan; Alcon Laboratories Inc., Fort Worth, TX, USA) by two different examiners with substantial experience in ultrasound biometry. Intraocular lens power was calculated using the SRK/T formula according to the patient's requirements and ametropia in the fellow eye. In addition to the routine follow-up, patients were called in for examination at 6 months.
postoperatively, as resolution of macular oedema can be accurately assessed 6 months after ILM peeling. Ultrasound axial length was measured by setting the ultrasound device in ‘acrylic pseudophakic eye’ mode, and macular thickness and refraction error (Tomey RT-6000 autorefractometer; Tomey Corp., Nagoya, Japan) were assessed at the same time.

Operating procedure

The cataract removal and vitrectomy in the combined procedure were performed by the same, experienced surgeon. Cataract surgery was performed using the phacoemulsification technique through a 3.2-mm clear-corneal incision followed by intracapsular implantation of a foldable acrylic posterior chamber IOL (Alcon MA60AC; Alcon Laboratories Inc.). In all cases the diameter of the continuous curvilinear capsulorhexis was smaller than the optics of the IOL. Following temporary suturing of the corneal wound, a standard 20-gauge, three-port pars plana vitrectomy was performed. After peeling of the posterior hyaloidal surface, tripan-blue assisted membranectomy (in the cases of epiretinal membrane) or indocyanine-green assisted ILM peeling (in the cases of macular oedema) was performed and the vitreous cavity was filled with sterile balanced salt solution. At the end of the operation the vitrectomy sites were closed and the corneal sutures were removed.

Statistical analysis

Data were expressed as mean ± standard error of the mean (SEM) and analysed using Statistica 6.0 software (StatSoft Inc., Tulsa, OK, USA). Normality of data was checked with Shapiro–Wilk’s W-test. As data did not follow normal distribution, the pre- and postoperative UAL, macular thickness and the planned refraction and achieved refraction were compared with Wilcoxon’s matched pairs test. Regression analysis was applied by determining the p- and r-values to analyse the relationship between pre- and postoperative variables. In all cases p < 0.05 was considered statistically significant.

Results

I. Assessment of the possible toxicity of ICG dye applied during macular hole surgery for the removal of the inner limiting membrane.

Preoperatively, there was no significant difference in VA, stage of macular hole, duration of the symptoms, and age of the patients. In all eyes, a closure of the macular hole was noted on clinical examination, and the anatomical success was confirmed by OCT. In both the C1 and C2 areas, retinal response densities decreased at three and six months after the operation; an
increase was noted at 12 months. At the 20-month follow-up examination, the b-waves in the central retinal area showed a marked increase in both patient groups. However, in group B, the increase was more pronounced; the C1 values for group B were much higher than those for group A. Similar changes were observed in both groups in the perimacular response densities for the C2 area; however, although an increase was observed in group B at the 20-month follow-up, the values were not markedly different from the baseline values.

II. Evaluation of the accuracy of intraocular lens planning in patients undergoing combined surgery for cataract and macular edema.

The preoperative refraction error was $0.66 \pm 0.41$ D. Visual acuity was better after 6 months (preoperative VA $0.22 \pm 0.05$ versus postoperative VA $0.48 \pm 0.12$, $p = 0.028$), whereas keratometric values did not change (preoperative $43.78 \pm 0.42$ D versus postoperative $43.82 \pm 0.44$ D, $p > 0.05$). The UAL increased (preoperative $23.32 \pm 0.23$ mm versus postoperative $23.52 \pm 0.25$ mm, $p = 0.023$), whereas macular thickness decreased (preoperative $430 \pm 30.39$ µm versus postoperative $288.08 \pm 36.17$ µm, $p = 0.002$). No statistically significant difference was observed in axial length changes between patients operated on for epiretinal fibrosis or diabetic macular oedema. Achieved ametropia ($-0.16 \pm 0.48$ D) was measured in the minus direction compared with preoperatively planned ametropia ($0.63 \pm 0.38$ D), demonstrating an average myopic shift of $-0.79 \pm 0.24$ D ($p = 0.034$). The preoperative macular thickness and the postoperative dioptic shift correlated ($r = 0.76$, $p = 0.004$). Case-to-case comparison of the corrected preoperative axial length (axial length plus the change in macular thickness) and the postoperative axial length showed no difference ($23.46 \pm 0.23$ mm versus $23.51 \pm 0.25$ mm, $p > 0.05$) due to the strong correlation ($r = 0.94$, $p < 0.001$) between results, showing a close degree of correspondence between the increase in UAL and the decrease in macular thickness.

Finally, the adjusted planned ametropia was determined by substituting the full axial length and the implanted IOL power into the SRK/T formula. This full axial length was determined in each case by adding the difference between the normal value of macular thickness ($0.65696-0.2029 \times \text{UAL}$) and results of OCT scans to the UAL. Case-to-case comparisons revealed differences between planned and adjusted planned postoperative ametropia ($0.63 \pm 0.38$ D versus $0.03 \pm 0.48$ D, $p = 0.005$), and correlation analysis of data showed a significant relationship between measured and adjusted planned postoperative ametropia ($r = 0.93$, $p < 0.001$).
Conclusions

I. Assessment of the possible toxicity of ICG dye applied during macular hole surgery for the removal of the inner limiting membrane.

1. Postoperative results were not affected by the application of ICG as holes closed in both groups.
2. The significantly better visual acuities in the unstained group 20 months postoperatively may show the toxicity of the dye.
3. Multifocal electoretinography may be an objective method capable of detecting damage to the finite neural elements of the retina and thus we believe it is capable for the mapping of possible functional alterations caused by ICG.
4. The evidence of higher response densities in C1 and C2 rings observed in the unstained group may also point on the possible toxicity of the ICG dye.
5. According to the continuous increase observed in the mfERG parameters retinal function may improve even 20 months postoperatively and therefore long-term follow-up of patients might be of importance.

II. Evaluation of the accuracy of intraocular lens planning in patients undergoing combined surgery for cataract and macular edema.

1. Using the SRK/T formula for the preoperative planning of the IOL by ultrasonography there was a difference in the planned and achieved postoperative visual acuity with a shift towards myopia.
2. There is a correlation between preoperative macular thickness and postoperative refractive difference. The reason for this difference is the shorter axial length measurement as the photoreceptor layer is hypothesized to be more anteriorly than its actual position. This fact should be taken into consideration during preoperative IOL planning.
3. When calculating the IOL refractive power the modified axial length should be used which equals the measured axial length by ultrasound added to the difference between actual macular thickness and the average macular thickness used for the SRK/T formula.
4. In the absence of OCT the average macular thickness in the case of macular edema needing surgical intervention should be calculated as 400-500 microns and thus it is advised to reduce the refractive power of the implanted IOL with 1.0 Diopter.

**New results described by the present work:**

1. For the first time in the currently available literature, we reported the use of mfERG for the possible assessment of retinal toxicity by the applied ICG dye in patients undergoing macular hole surgery with the removal of the ILM.
2. We reported decreased response densities in the two central rings 20 months postoperatively in eyes undergoing ILM peeling with the use of ICG dye.
3. According to our knowledge, it is the longest mfERG follow-up applied in patients undergoing vitrectomy for macular hole formation. The importance of long follow-up is underlined by the fact that parameters of retinal function were still improving after 20 months.
4. We were the first to show that postoperative refraction may be shifted towards myopia in patients undergoing combined surgical intervention due to cataract and macular edema.
5. We introduced and published in the international literature the phenomenon of *corrected axial length* and its calculation which helps the planning of postoperative refraction in patients undergoing combined cataract extraction and operation for macular edema. The prerequisites of the method are preoperative axial length assessment by ultrasound, macular thickness measurement by OCT and IOL planning by the SRK-T formula.
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