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Research Article

Inner Retinal Function Recovery After Vitrectomy with Epiretinal and Internal Limiting Membrane Peeling in Macular Pucker and Macular Hole: A Prospective Study of 50 Patients

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Abstract

Purpose: *To evaluate visual acuity (VA) and inner retinal function recovery using photopic negative response (PhNR) and multifocal electroretinogram (mfERG) after pars plana vitrectomy (PPV) with epiretinal membrane (ERM) and internal limiting membrane (ILM) peeling in patients with macular pucker and full-thickness macular hole (FTMH).*

Methods: *Prospective interventional case series of 50 consecutive patients (28 with macular pucker, 22 with FTMH) undergoing 25-gauge PPV with ERM/ILM peeling using Double Dyne (Trypan Blue 0.15%+Brilliant Blue G 0,05% + Lutein 2%) for visualization. Best-corrected VA (ETDRS LogMAR), PhNR, and mfERG were recorded preoperatively and at 6 months postoperatively. Primary endpoint: VA improvement. Secondary endpoints: changes in PhNR and mfERG amplitudes.*

Results: *LogMAR improved from 0.54 ± 0.14 to 0.24 ± 0.12 in macular pucker ($p < 0.001$) and from 0.54 ± 0.09 to 0.21 ± 0.09 in FTMH ($p < 0.001$). PhNR amplitude increased significantly ($p < 0.001$), with strong correlation to final VA ($r = 0.68$, $p < 0.001$).*

Conclusions: *Inner retinal recovery, particularly PhNR improvement, is a key determinant of visual success.*

Keywords: *macular hole, epiretinal membrane, macular pucker, ILM peeling, photopic negative response, multifocal ERG, inner retina.*

Introduction

Epiretinal membranes (ERM) and full-thickness macular holes (FTMH) are common vitreoretinal tractional disorders leading to macular dysfunction. ERM, or macular pucker, involves fibrocellular proliferation on the inner retinal surface, causing tangential traction, retinal distortion, and intraretinal gliosis. FTMH results from anteroposterior and tangential forces, often with cystic changes at hole edges due to altered fluid dynamics and retinal pigment epithelium pump dysfunction.

Surgical treatment via pars plana vitrectomy (PPV) with ERM and ILM peeling relieves traction and promotes anatomical restoration. While outer retinal layer integrity (ellipsoid zone [EZ], external limiting membrane [ELM]) has been emphasized in prognosis, functional recovery frequently remains incomplete despite anatomical success, suggesting a key role for inner retinal layers. Intraretinal gliosis, predominantly in the ganglion cell complex (GCC) within the first ~90 µm, disrupts Müller cell function, bipolar cell transmission, and ganglion cell signaling.

This study prospectively assesses inner retinal electrophysiological recovery (PhNR and mfERG) alongside VA in 50 patients, hypothesizing that inner retinal function restoration is central to visual outcomes.

Methods

Study design and patients

Prospective interventional case series conducted between 2018 and 2024.

Inclusion: idiopathic ERM (macular pucker) or FTMH requiring surgery. Exclusion: media opacities, glaucoma or other neurodegenerative disorders, previous vitreoretinal surgery, or significant comorbidities affecting retinal function.

Fifty patients were enrolled (28 macular pucker, 22 FTMH; mean age 70.1 ± 11.8 years).

Surgical procedure rolled (28 macular pucker, 22 FTMH; mean age 70.1 ± 11.8 years).

Surgical procedure

Standard 25-gauge PPV using the Constellation Vision System (Alcon), ERM peeling, ILM peeling assisted exclusively by Double Dyne (Alfa Intes), a lutein-based dual dye providing selective staining of both ERM and ILM with added antioxidant properties from lutein. Gas tamponade (SF_6 or C_3F_8) was used in FTMH cases as needed.

Examinations

Best-corrected VA (ETDRS chart, converted to LogMAR), spectral-domain OCT, full-field ERG including PhNR, and mfERG (ISCEV standards) were performed preoperatively and 6 months postoperatively.

Statistical analysis

Paired t-tests or Wilcoxon signed-rank tests for pre/post changes; one-way ANOVA for group comparisons; Pearson correlation for associations. Sample size (n=50) provided >90% power to detect ≥25% amplitude changes (α=0.05). Amplitudes were age-normalized and log-transformed where appropriate.

Results

Overall (Tab.1), VA improved by ≈3.0 ETDRS lines ($p < 0.0001$). PhNR and mfERG amplitudes increased significantly in both groups ($p < 0.001$ for PhNR overall; $p = 0.002$ for mfERG). Postoperative PhNR correlated strongly with final LogMAR ($r = -0.68$, $p < 0.001$).

Parameter	Macular Pucker (n=28) Mean ± SD	Macular Hole (n=22) Mean ± SD	p-value (post-op between groups)
Age (years)	68.8 ± 12.5	72.0 ± 10.2	0.31
LogMAR pre-op	0.54 ± 0.138	0.544 ± 0.088	0.89
LogMAR post-op (6 mo)	0.24 ± 0.124	0.211 ± 0.093	0.28
mfERG amplitude pre (µV)	1.61 ± 0.21	1.53 ± 0.17	-
mfERG amplitude post	2.13 ± 0.34	2.16 ± 0.21	0.72
PhNR amplitude pre (µV)	1.56 ± 0.23	1.70 ± 0.14	-
PhNR amplitude post	2.15 ± 0.22	2.37 ± 0.23	0.011

Table 1. Baseline and postoperative characteristics

Discussion

This study demonstrates that PPV with ERM/ILM peeling yields significant VA gains and robust inner retinal functional recovery, as measured by PhNR and mfERG, in both macular pucker and FTMH. The strong correlation between PhNR amplitude improvement and final VA ($r = 0.68$, $p < 0.001$) highlights the fundamental role of inner retinal restoration in visual prognosis.

The photopic negative response (PhNR) is a slow negative component following the b-wave of the photopic full-field ERG, primarily generated by the spiking activity of retinal ganglion cells (RGCs) and their axons, with secondary contributions from amacrine cells and Müller glia.[1,2] According to the ISCEV extended protocol, the most reliable recording uses a red flash on a blue background to maximize PhNR amplitude and reproducibility.[3] The PhNR (measured baseline-to-trough) is currently the most specific non-invasive electrophysiological biomarker of RGC function available in clinical practice.

In tractional maculopathies such as idiopathic ERM and FTMH, chronic tangential traction induces reactive gliosis predominantly within the ganglion cell complex (GCC) in the innermost 90 µm of the retina.[4] This gliosis impairs RGC and bipolar cell function, resulting in reduced preoperative PhNR amplitude. Postoperative increase in PhNR amplitude (from 1.56–1.70 µV to 2.15–2.37 µV) reflects successful reversal of reversible intraretinal gliosis after traction relief. This functional recovery of the inner retina frequently precedes or exceeds complete outer retinal restoration (EZ/ELM) and correlates strongly with BCVA improvement.

Importantly, our results contrast with earlier reports showing selective PhNR reduction after macular hole surgery, particularly when indocyanine green (ICG) was used for ILM staining combined with prolonged gas tamponade.[5] In our cohort, employing a lutein-based dual dye and limited gas use, we observed clear recovery rather than further decline, suggesting that the benefit of traction removal outweighs potential iatrogenic damage when a minimally traumatic technique is adopted.

Compared with mfERG (which primarily reflects mid-retinal cone–bipolar activity) and pattern ERG (which requires good fixation), PhNR offers the advantage of being full-field, less dependent on central fixation, and more specific to RGC function [6]. Its integration with OCT-derived GCC thickness and microperimetry could provide a multimodal prognostic model for timing of surgery and expected visual recovery 7.

Limitations include the 6-month follow-up, lack of automated GCC segmentation in all cases, and absence of a non-peeling control group. Longer-term studies are needed to assess the durability of PhNR recovery and potential late effects of ILM peeling on Müller cell function.

Conclusions

PPV with ERM/ILM peeling restores VA and inner retinal function in macular pucker and FTMH. Inner retinal recovery, particularly PhNR improvement, is central to visual outcomes and should be integrated into prognostic models.

References

1. Frishman LJ. Origins of the photopic negative response (PhNR) of the full-field electroretinogram. Doc Ophthalmol. 2018;136(3):199-205.
2. Machida S. Clinical applications of the photopic negative response to optic nerve and retinal diseases. J Ophthalmol. 2012;2012:397178.
3. Frishman L, Sustar M, Kremers J, et al. ISCEV extended protocol for the photopic negative response (PhNR) of the full-field electroretinogram. Doc Ophthalmol. 2018;136(3):207-211.
4. Bringmann A, Unterlauft JD, Wiedemann P, et al. Müller cells and astrocytes in tractional macular disorders. Prog Retin Eye Res. 2022;86:100977.
5. Ueno S, Kondo M, Piao CH, et al. Selective amplitude reduction of the photopic negative response after macular hole surgery. Invest Ophthalmol Vis Sci. 2006;47(8):3545-3549.
6. Sustar M, Hawlina M, Brecelj J. Electroretinography in glaucoma: a review. Doc Ophthalmol. 2019;138(3):199-210.
7. Pierro L, Iuliano L, Gagliardi M, et al. Role of ganglion cell complex in visual recovery following surgical internal limiting membrane peeling. Graefes Arch Clin Exp Ophthalmol. 2015;253(1):37-45..