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Decreased Corneal Sensation and Subbasal Nerve Density, and Thinned Corneal Epithelium as a Result of 360-Degree Laser Retinopexy

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Purpose: To assess the effects of 360-degree laser retinopexy on human corneal subbasal nerve plexus and to investigate correlations among corneal subbasal nerve plexus density, corneal epithelial thickness, and corneal sensitivity.

Design: Prospective, observational, nonrandomized study.

Participants: A total of 15 eyes of 15 patients who underwent pars plana vitrectomy (PPV) with 360-degree laser retinopexy for retinal detachment (RD) and 15 eyes of 15 patients who underwent PPV for macular hole (MH) without laser treatment.

Methods: Corneal sensation, corneal epithelial thickness, and corneal subbasal nerve plexus density were assessed before surgery and 6 months after surgery via in vivo confocal microscopy, anterior segment optical coherence tomography (AS-OCT), and Cochet−Bonnet esthesiometry (Luneau Ophthalmologie, Paris, France).

Main Outcome Measures: Corneal subbasal nerve plexus density, corneal epithelium thickness, and central corneal sensitivity.

Results: Compared with baselines values, the mean subbasal nerve density ($P < 0.001$), mean corneal epithelium thickness ($P = 0.006$), and mean corneal sensitivity ($P < 0.001$) in the RD group were significantly decreased 6 months after surgery by 74.3%, 4.7%, and 56.6%, respectively. Conversely, in the MH group there were no significant differences in the mean subbasal nerve density ($P = 0.34$), mean corneal epithelial thickness ($P = 0.19$), and mean corneal sensitivity ($P = 0.42$) between preoperative and 6-month postoperative values (0.7%, 0.4%, and 0.8%, respectively). The postoperative decrease in corneal subbasal nerve density after laser retinopexy was associated with a decrease in corneal epithelium thickness ($r^2 = 0.42$; $P = 0.006$) and a decrease in corneal sensitivity ($r^2 = 0.48$; $P = 0.004$). The postoperative decrease in corneal sensitivity poorly correlated with the decrease in corneal epithelial thickness ($r^2 = 0.24$; $P = 0.045$). Postoperative corneal nerve density decreased as total laser energy increased ($r^2 = 0.51$; $P = 0.002$).

Conclusions: Subbasal corneal nerve plexus density decreases after 360-degree laser retinopexy and is accompanied by epithelium thinning and decreased corneal sensation. Surgeons should eschew heavy confluent retinal laser treatment, and corneal sensitivity should be assessed postoperatively to determine whether significant anesthesia has occurred. In such instances, prophylactic measures may be warranted against the development of neurotrophic ulcers. *Ophthalmology 2015;122:2095-2102 © 2015 by the American Academy of Ophthalmology.*

Pars plana vitrectomy (PPV) has emerged as one of the leading approaches to the management of primary retinal detachment (RD) in recent years; however, recent reports indicate patients undergoing PPV combined with 360-degree laser retinopexy may develop neurotrophic corneal ulceration.[1,2] Reduction of corneal sensitivity also has been reported after RD repair using scleral buckle.[3] Because the sensory innervation of the cornea occurs through the long and short ciliary nerves that run mainly in the horizontal meridian through the choroidal and suprachoroidal spaces, compression or damage within these areas during *ab externo* or *ab interno* retinal reattachment procedures may affect corneal innervation. Ciliary nerve bundles branch profusely and enter the corneal stroma in a radial manner.[4,5] Nerve fibers thereafter run between epithelial cells and terminate as free nerve endings in the most superficial layers of the corneal epithelium.[4,5] Such nerve terminals serve to provide not only afferent sensory feedback but also essential peptides necessary for full epithelial cell growth and function. Denervation causes immediate loss of surface epithelial cell microvilli that serve to retain the mucous tear film layer, as well as a reduction in epithelial cell volume. With a lack of physical surface substrate to retain and maintain the mucous

Published by Elsevier Inc.

http://dx.doi.org/10.1016/j.ophtha.2015.06.010
ISSN 0161-6420/15

film layer on the cornea, tear film integrity is lost, with increased surface irritation ensuing.[5–7] Thus, ocular and systemic conditions associated with damage at any level of the trigeminal nerve, from the trigeminal nucleus to the corneal nerve endings, may lead to partial or complete corneal anesthesia with ensuing epithelial breakdown and neurotrophic keratitis.[8]

In vivo confocal microscopy has facilitated qualitative and quantitative in vivo analysis of subbasal corneal nerves.[9] Assessment of corneal epithelial thickness also has been facilitated by the development of anterior segment optical coherence tomography (AS-OCT).[10,11] We aimed at exploiting this potential to objectively evaluate the effect of PPV with 360-degree laser retinopexy on corneal sensory status and morphology.

The goal of this study was to investigate the effect of 360-degree laser retinopexy. For this purpose, corneal subbasal nerve density, corneal epithelium thickness, corneal sensitivity, and total laser energy delivered during surgery were assessed and correlations were noted.

Methods

Patients

This prospective observational nonrandomized comparative study was performed at the Quinze-Vingts National Ophthalmology Hospital in Paris, France. Thirty eyes of 30 patients (14 men and 16 women) who underwent PPV between November 2012 and February 2014 were included on the basis of inclusion and exclusion criteria. All patients were treated and followed according to protocols approved by the French Regulatory Agency. Informed consent was obtained before surgery according to the Declaration of Helsinki, and the study was approved by the Ethics Committee of the French Society of Ophthalmology (Institutional Review Board 00008855).

Fifteen eyes underwent PPV combined with 360-degree laser retinopexy and C2F6 gas tamponade for RD, and 15 eyes underwent PPV and SF6 gas tamponade for macular hole as a control group for laser treatment.

Inclusion criteria were the following: first PPV for RD or macular hole repair. Exclusion criteria were previous ocular trauma or surgery, giant retinal tears, retinal dialysis, proliferative vitreoretinopathy (grade C or higher), ocular or systemic disease that could affect the cornea, and diabetes and other causes of neuropathy. Subjects with a history of cataract surgery were excluded, an intraocular procedure known to cause reduction in corneal sensitivity and innervation.[12]

Data Collection

The following patient information was collected: age, gender, systemic disease, previous ocular surgery, and associated eye diseases. Postoperatively, a complete ocular examination was performed at 1 and 7 days, 2, 4, 6, 8, and 10 weeks, and every month for a minimum of 6 months. All patients were followed for at least 6 months after surgery.

The following were recorded at each visit: findings on slit-lamp examination, best spectacle-corrected visual acuity using a conventional Snellen chart, tonometry, and funduscopic examination. Corneal sensation was assessed with a Cochet–Bonnet esthesiometer (Luneau Ophthalmologie, Paris, France), corneal epithelial thickness was measured by Fourier-domain AS-OCT (RTVue-100, Optovue Inc., Fremont, CA), and laser scanning in vivo confocal microscopy images of the corneal subbasal plexus were obtained with the Heidelberg Retina Tomograph II with Rostock Corneal Module (Heidelberg Engineering GmBH, Heidelberg, Germany). The latter 3 measurements were recorded only preoperatively and at the 6-month postoperative visit.

Corneal sensation was assessed with a Cochet–Bonnet esthesiometer in the central and peripheral (4 quadrants) zones of the cornea. The monofilament diameter was 0.08 mm. The filament length was sequentially reduced in 5-mm steps starting from 60 mm. A positive answer was considered as a positive result. The longest filament length resulting in a positive response was recorded as the corneal sensitivity threshold. The average sensitivity value of all 5 areas was used for statistical analysis.[13] All measurements were performed in a masked manner by the same investigator.

Optical Coherence Tomography

A Fourier-domain OCT system with a corneal adaptor module (RTVue-100 AS-OCT, Optovue Inc., Fremont, CA) was used in this study. Data output included total corneal and epithelial thickness maps corresponding to a 6.0-mm diameter area. Optical coherence tomography imaging was always performed by the same investigator and obtained before clinical examination to avoid potential artifacts due to instillation of eye drops. The OCT settings used were L-Cam lens and 8 radial meridional B-scans per acquisition consisting of 1024 A-scans each with a 5-μm axial resolution. These 8 radial meridional scans were used by the system software to produce 3-dimensional thickness maps by interpolation. Two consecutive individual acquisitions were obtained in each case to ensure data validity. The average epithelial thickness value across the 6-mm diameter sample area was used for statistical analysis.

Confocal Microscopy

A cornea-specific in vivo laser scanning confocal microscope was used (Heidelberg Retina Tomograph II with Rostock Corneal Module, Heidelberg Engineering GmBH). After topical anesthesia with 1% tetracaine eyedrops (Novartis Laboratories Inc., East Hanover, NJ) and instillation of high-viscosity eye gel (carbomer 3.0 mg/g; Thilogel; Alcon Laboratories, Inc., Fort Worth, TX), patients were asked to fixate using an external fixation target. The microscope lens then was brought into contact with the corneal tissue via a disposable sterile polymethyl methacrylate cup with high-viscosity gel. Images of all corneal layers were taken across the whole cornea by the same investigator. Acquired images consisted of 384×384 pixels over a 400×400 μm field of view. The manufacturer quotes transverse resolution and optical section thickness as 2 and 4 μm, respectively. The subbasal nerve plexus images were defined as the first clear images of the nerves anterior to Bowman's layer, at the level of the basal epithelial cell layer. All selected images were de-identified and randomized by an examiner (L.H.). Quantitative analysis was subsequently performed by a single masked examiner (N.B.) using Neuron J software (National Institutes of Health, Bethesda, MD) for subbasal nerve density.[14] The full 400×400 μm frame of each image of subbasal nerve plexus was used for analysis. Subbasal nerve density was calculated by measuring the total length of nerves per image.[15]

Surgical Technique

Twenty-three gauge PPV was performed with the Constellation Vision System (Alcon Laboratories). None of the operated eyes underwent simultaneous scleral buckle surgery or limbal peritomy. Preoperatively, the pupil was dilated with 0.5% topical