

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Schlemm Canal Microstent in Patients With POAG and Cataract

January 2019

Samuelson et al. compared the safety and effectiveness of cataract surgery alone versus the Hydrus microstent (Ivantis) in conjunction with cataract surgery. They found that the combination was more effective at lowering intraocular pressure (IOP) by month 12 and month 24. Safety findings for the study groups were similar.

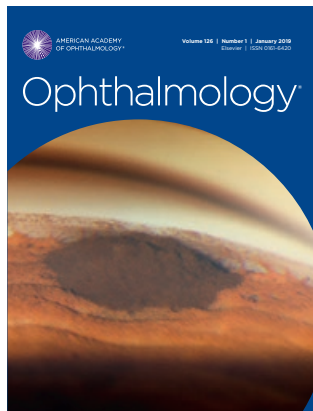
Enrollees of this single-masked trial had concomitant primary open-angle glaucoma (POAG), visually significant cataract, and washed-out modified diurnal IOP (MDIOP) ranging from 22 mm Hg to 34 mm Hg. After uncomplicated phacoemulsification, patients were assigned randomly (2:1) to receive either a single Hydrus microstent in the Schlemm canal or no stent. Comprehensive eye exams were performed at eight postoperative points, from the first day following surgery to month 24. Medication washout and MDIOP measurements were repeated at 12 and 24 months. The primary measure of

effectiveness was the proportion of subjects with a reduction of at least 20% in unmedicated MDIOP. The secondary measure was the change in mean MDIOP from baseline.

Use of topical medication for hypotension was tracked throughout follow-up. Safety measures included the frequency of surgical complications and the occurrence of adverse events.

After phacoemulsification, 369 eyes received the microstent and 187 did not. By month 24, unmedicated MDIOP had declined by $\geq 20\%$ in 77.3% of the stent-treated group and in 57.8% of the control group. The mean reduction in unmedicated MDIOP from baseline to 24 months was -7.6 mm Hg in the stent-treated group and -5.3 mm Hg in the control group. The mean number of medications declined from 1.7 at baseline to 0.3 by 24 months in the stent group and from 1.7 to 0.7 in the control group. (All p values $< .001$.) No serious ocular adverse events were associated with the microstent. Overall, safety findings were similar for the study groups. The microstent group had a higher rate of focal adhesions, and the control group had more IOP-related complications.

The authors recommend that long-term head-to-head studies be performed to better understand the efficacy and safety of microstent implantation and to compare this adjunct with other novel minimally invasive devices.



Low-Dose Atropine to Control Myopia Progression

January 2019

Low-concentration atropine is a new treatment for myopia progression, but its efficacy and optimal concentration are uncertain. In a large double-masked trial, Yam et al. compared efficacy and safety between eyedrops containing low amounts of atropine (0.05%, 0.025%, or 0.01%) and placebo eyedrops. They noted a concentration-dependent effect for the reduction of myopia progression. All doses were well tolerated and had no adverse effect on vision-related quality of life. The highest concentration (0.05%) proved the most effective for controlling spherical equivalent (SE) progression and axial length (AL) elongation in their one-year study.

This randomized placebo-controlled study included 438 children between the ages of 4 and 12 who had myopia of at least -1.0 D and astigmatism of -2.5 D or less. Patients were assigned randomly (1:1:1:1) to receive atropine eyedrops (0.05%, 0.025%, or 0.01%) or control drops, which contained sodium chloride. Drops were applied nightly for a full year. Accommodation amplitude, AL, best-corrected visual acuity, cycloplegic refraction, and pupil diameter were measured at five points (baseline, week 2, and months 4, 8, and 12). A visual function questionnaire was administered at the one-year visit. Main outcomes were changes in SE and AL. A generalized estimating equation was used to compare findings.

At one year, mean SE had changed

by -0.27 D, -0.46 D, -0.59 D, and -0.81 D in the 0.05%, 0.025%, and 0.01% atropine groups and the placebo group, respectively. The corresponding mean increases in AL were 0.20 mm, 0.29 mm, 0.36 mm, and 0.41 mm. Accommodation amplitude was reduced by 1.98 D, 1.61 D, 0.26 D, and 0.32 D, respectively. The increases in pupil size under photopic and mesopic conditions (respectively) were 1.03 and 0.58 mm in the 0.05% atropine group, 0.76 and 0.43 mm in the 0.025% atropine group, 0.49 and 0.23 mm in the 0.01% atropine group, and 0.13 and 0.02 in the placebo group. (All p values $< .001$.) Visual acuity and vision-related quality of life were not impaired in any group.

More phases of the study are planned to assess the durability and longevity of these effects. After the second phase, the authors will report two-year efficacy and safety findings for the three concentrations of atropine. Subsequently, the researchers will assess the viability of discontinuing treatment once the myopia progression has been controlled, and atropine will be resumed in appropriate cases. (*Also see related commentary by Padmaja Sankaridurg, PhD, in the same issue.*)

DMEK Versus Ultrathin DSAEK for Corneal Endothelial Dysfunction

January 2019

Results of nonrandomized and observational studies have suggested that visual outcomes are similar for Descemet membrane endothelial keratoplasty (DMEK) and ultrathin Descemet stripping automated endothelial keratoplasty (UT-DSAEK). However, the study designs have hindered direct comparisons. To permit a more meaningful comparison of these procedures, Chamberlain et al. conducted a randomized controlled trial to evaluate visual outcomes and complication rates. They found that DMEK yielded superior visual acuity during the year following surgery, although complication rates

were similar for the two procedures.

Eligible participants had damaged or diseased endothelium (from Fuchs endothelial dystrophy or pseudophakic bullous keratopathy). Within two days prior to surgery, eyes were assigned randomly to receive DMEK or UT-DSAEK. Standardized surgical techniques were used. Patients were masked as to their intervention and received the same postoperative instructions. Moreover, the refractonist who assessed visual outcomes was unaware of each patient's procedure. The primary outcome was best spectacle-corrected visual acuity (BSCVA) at six months. Secondary outcomes were BSCVA at the three- and 12-month marks, intra- and postoperative complications, endothelial cell counts, and change in pachymetry.

Of the 216 patients with endothelial dysfunction who were screened, 38 (50 eyes) were enrolled. After the researchers corrected for baseline VA, DMEK was found to result in better visual outcomes. BSCVA was 1.5 lines better for the DMEK group at three months, 1.8 lines better at six months, and 1.4 lines better at 12 months. At six months, the average endothelial cell count was $1,963/\text{mm}^2$ in the DMEK group and $2,113/\text{mm}^2$ in the UT-DSAEK group. At 12 months, the average cell counts were $1,855/\text{mm}^2$ and $2,070/\text{mm}^2$, respectively.

Rates of intra- and postoperative complications were comparable for the study groups.

The authors noted that DMEK—when performed by experienced surgeons—appears to elicit better

visual outcomes and faster recovery than UT-DSAEK. They emphasized that larger multicenter trials may help to clarify the dissimilar outcomes. (*Also see related commentary by Marianne Price, PhD, in the same issue.*)

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachar, MD

Predictors of Postinjection Endophthalmitis

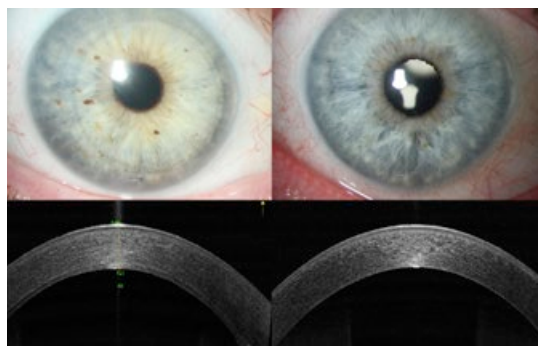
January 2019

Stem et al. set out to determine the incidence of endophthalmitis following anti-VEGF injections and to identify potential ways of lowering that risk. They found that the overall incidence of postinjection endophthalmitis was low—and that the use of lidocaine jelly or TetraVisc (tetracaine) may be associated with an increased risk.

For this retrospective single-center study, the authors assessed all patients in their practice who received an intravitreal injection of an anti-VEGF drug between Jan. 1, 2014, and March 31, 2017. All told, 154,198 intravitreal injections were given during this time, and 58 cases of endophthalmitis occurred, for a rate of 1:2,659. Less than half of these cases (24; 41%) were culture-positive.

A number of risk factors were evaluated, including povidone-iodine (PVI) solution strength and the choice of anti-VEGF drug. No difference in endophthalmitis rates emerged among the anti-VEGF drugs (aflibercept, bevacizumab, and ranibizumab 0.3 mg and 0.5 mg). Moreover, the prophylactic use of 10% PVI neither reduced nor increased the risk of endophthalmitis relative to the use of a 5% PVI solution. In addition, no association emerged regarding several other potential risk factors, including lid speculum use, choice of injection site, or conjunctival displacement.

However, both 2% lidocaine jelly and 0.5% TetraVisc emerged as independent risk factors. As the authors noted, this finding has not previously been reported and merits further investigation. —Summary by Jean Shaw



COMPARISON. Clinical photographs and OCT images from patients who underwent UT-DSAEK (left) and DMEK (right).

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

What Degree of Visual Field Damage Causes Disability for Glaucoma Patients?

January 2019

Jammal et al. used latent class analysis (LCA) to classify patient-reported glaucoma outcomes and to quantify the amount of visual field damage that results in disability. They found that this model, which is rarely used in ophthalmology, is useful for both purposes, and they noted that early visual field loss in the better eye can cause substantial disability.

Participants in this cross-sectional study were required to have open angles on gonioscopy. The 263 enrollees completed the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25), after which an LCA model was applied to analyze the data. Patients were grouped into mutually exclusive classes according to questionnaire responses. Differences between the classes were documented, including standard automated perimetry mean deviations (SAP MD) and integrated binocular mean sensitivity values. The optimal number of classes was defined based on goodness-of-fit criteria, interpretability, and clinical utility.

The model containing two latent classes (disabled and nondisabled) had the best fit, demonstrating Lo-Mendell-Rubin test values superior to those of the one-class model and not significantly different from those of models with more classes. The two-class final LCA model had a high entropy value (0.965), denoting excellent distinction between the classes. Forty-eight patients (18%) were classified as disabled, and 215 (82%) were classified as nondisabled. The average SAP MD of the better eye was -5.98 dB in the disabled group and -2.51 dB in the nondisabled group ($p < .001$). Corresponding values for the worse eye were -13.36 dB and -6.05 dB ($p < .001$).

This study showed that damage of approximately -6 dB for SAP MD, denoting relatively early visual field

loss, may signal significant disability if present in the better eye. The research suggests that LCA may be a valuable tool to analyze patients' concerns about quality of life.

High-Dose Gene Therapy and BCVA in Choroideremia

January 2019

In a two-year clinical trial, Lam et al. looked at the safety and efficacy of high-dose gene therapy in patients with choroideremia. Their findings demonstrated that the treatment is safe and potentially effective and that best-corrected visual acuity (BCVA) may be an appropriate outcome measure for monitoring the progression of choroideremia.

The authors reported 24-month findings of their phase 2 clinical trial. Six men (32-72 years of age) with advanced choroideremia underwent subfoveal injection of adeno-associated virus 2 capsids that harbored a transcript encoding Rab escort protein 1 (i.e., AAV2-REP1; 1011 genome particles in 0.1 mL). The eye with worse visual acuity was treated, and the untreated fellow eye served as the control. Injection of vector was performed slowly, guided by microscope-integrated optical coherence tomography.

The primary outcome measure was change in BCVA from baseline. Secondary endpoints included changes in central visual field (by microperimetry), color vision, contrast sensitivity, and fundus autofluorescence. To assess safety, adverse events and immunologic parameters were recorded, including viral shedding and vector antibody responses.

The baseline mean BCVA was 65.3 ± 8.8 letters in treated eyes and 77.0 ± 4.2 letters in untreated eyes. Two years after therapy, the changes from baseline ranged from -1 to $+10$ letters in treated eyes and -2 to $+4$ letters in untreated eyes. No eye had a substantial change in microperimetry findings, color vision, or contrast sensitivity; all eyes (treated and control) had progressive shrinkage in areas of fundus autofluorescence. No serious adverse events were noted, and the immunologic profiles were favor-

able. In two patients, an atrophic retinal hole developed in a nonfunctioning macular area.

This slow-injection technique of high-dose gene therapy appears to be safe and may permit maintenance, or even improvement, of BCVA in patients with choroideremia. The fact that no untreated study eye had significant improvement in BCVA suggests that BCVA is a suitable primary outcome measure for future choroideremia trials. The authors acknowledged that larger studies are needed to confirm the promising results. (Also see page 26.)

—Summaries by Lynda Seminara

JAMA Ophthalmology

Selected and reviewed by Neil M. Bressler, MD, and Deputy Editors

Cadmium Exposure Increases Risk of Contrast Sensitivity Impairment

December 2018

Paulsen et al. set out to determine the incidence of and factors associated with deficits in contrast sensitivity (CS). They found that CS impairment was linked to smoking and blood levels of cadmium, but not to lead levels.

For this study, the authors included patients from the Beaver Dam Offspring Study who had normal CS in both eyes at baseline. Participants were between the ages of 21 and 84, and baseline data were gathered from June 2005 through early August 2008. Two follow-up exams occurred subsequently at five-year intervals. CS testing was assessed with Pelli-Robson letter sensitivity charts. Incident impairment was defined as a log CS score <1.55 in either eye at a follow-up exam. Levels of cadmium and lead were measured in whole blood by using inductively coupled plasma mass spectrometry. Associations between baseline characteristics and CS impairment were evaluated using Cox proportional hazard models and were expressed as hazard ratios (HR) and 95% confidence intervals (CI).

The mean age of participants ($N = 1,983$) was 48 years; 52% were female. The 10-year cumulative incidence of CS impairment was 24.8% (95% CI, 22.9-

26.8) and was similar for men (24.6%) and women (24.9%). It was highest (66.3%) in the oldest participants (65-84 years). Factors linked to greater risk of CS impairment were cadmium level in the highest quintile (HR, 1.35; 95% CI, 1.02-1.78), older age (HR, 1.36; 95% CI, 1.25-1.47), and plaque sites (four to six sites: HR, 2.75; 95% CI, 1.26-6.05; one to three sites: HR, 1.43; 95% CI, 1.07-1.92). Other contributors were impaired visual acuity (HR, 3.61; 95% CI, 1.61-8.10), cataract (HR, 1.99; 95% CI, 1.21-3.28), and larger waist circumference (HR, 1.06; 95% CI, 1.01-1.11). Factors denoting lower risk were male sex (HR, 0.77; 95% CI, 0.60-0.98) and any alcohol consumption in the last year (HR, 0.61; 95% CI, 0.43-0.88). When cadmium exposure was replaced with smoking status in these models, the findings were similar. Lead level did not affect risk.

Many of the identified risk factors are modifiable, which may imply that changes in lifestyle could reduce the risk of CS impairment. Weight loss and efforts to improve vascular health also may be beneficial. (*Also see related commentary by Xiang Li, PhD, in the same issue.*)

Use of Deep Learning to Estimate Five-Year Risk of Advanced AMD

December 2018

Burlina et al. applied deep learning (DL) to fundus images from the Age-Related Eye Disease Study (AREDS) to automatically assess the severity of age-related macular degeneration (AMD) and estimate the five-year risk of progression to advanced-stage AMD. They found that the DL model's performance was comparable to that of humans when the AREDS 4-step severity scale was used. Promising results were achieved with the AREDS 9-step severity scale (which normally requires highly trained graders) as well as for estimating five-year risk of progression.

For their study, the authors gathered information from the AREDS dataset to develop deep convolutional neural networks that were trained to provide detailed automated AMD grading. Algorithm performance was compared

with results from a human grader and against a criterion standard (gradings from a fundus photograph reading center). Three methods for estimating five-year risk were developed: hard, soft, and regressed. Main outcomes were weighted κ scores and mean unsigned errors for estimating five-year probability of progression to advanced AMD. The study included 67,401 color fundus images from a total of 4,613 patients.

Analysis showed a weighted κ score of 0.77 for the 4-step scale and 0.74 for the 9-step scale. The overall mean estimation error for 5-year risk ranged from 3.5% to 5.3%. The error was smaller for lower-risk classes. Of the three methods, hard prediction performed best for all classes except those in which the soft prediction outperformed all and in which the regressed prediction outperformed all.

The authors noted the large imbalances among some of the severity classes: For instance, for the 9-step scale, 24,411 images were classified as step 1, and 1,160 images were classified as step 3. Nonetheless, they said, DL has the potential to assist physicians with detailed risk assessment and evaluation of disease progression during treatment. (*Also see related commentary by Harpal S. Sandhu, MD, FRCSC, Ayman El-Baz, PhD, and Johanna M. Seddon, MD, ScM, in the same issue.*)

Is It Time to Narrow the Criteria for ROP Screening?

December 2018

Current guidelines for detecting retinopathy of prematurity (ROP) in the United States include a wide range of birth weights and gestational ages and thus may entail unnecessary evaluation of infants who are at low risk for ROP. Quinn et al. examined data from the Postnatal Growth and ROP (G-ROP) study to discern the incidence, timing of onset, and early course of ROP. Of those who received serial ROP exams, 43.1% developed ROP, and 12.5% developed severe ROP. Nearly all of those affected by severe ROP weighed less than 1,251 g at birth.

This study was conducted at 29 hospitals in North America (from 2006-

2011) and included 7,483 infants. Mean birth weight was 1,099 g. The most severe ROP in either eye was classified as none, mild, type 2, or type 1, according to criteria of the Early Treatment for ROP Study. Other documented data were postmenstrual age at ROP onset, stage of ROP, and treatment given.

ROP occurred in 3,224 infants (43.1%), with type 1 disease developing in 459 (6.1%) and type 2 disease in 472 (6.3%). Roughly 98% of those with type 1 or 2 ROP had a birth weight <1,251 g. Of the babies born at ≤ 24 weeks' gestation, severe ROP developed in 49.5%. Of those born after 30 weeks who weighed >1,501 g at birth, only four (0.75%) had severe ROP. Treatment was given to 514 infants (6.9%), in one or both eyes. Zone I disease was present in 147 infants (2%). Only about half the eyes (49.4%) had vascularization into zone III by 37 weeks' postmenstrual age.

Unlike other large studies, this research included all infants who were eligible for ROP screening. Although ROP was present in more than 40% of "at-risk" premature infants, most cases did not require treatment. The lower-risk profile noted for larger babies supports efforts to improve the specificity of risk assessment and raise the possibility of a revision of the criteria that warrant examination for ROP. (*Also see related commentary by Amy K. Hutchinson, MD, in the same issue.*)

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Favorable Vision Effects of Retinal Gene Therapy for Choroideremia

Nature Medicine
2018;24:1507-1512

Choroideremia is a chronic X-linked retinal degeneration that leads to blindness because of deficiency in the Rab escort protein 1 (REP1). Xue et al. designed an adeno-associated viral vector to express REP1 and then evaluated it in a gene therapy trial during which it was injected into patients with choroideremia. Compared with control

eyes, and despite complications in two patients, the treated eyes had substantial improvement in visual acuity (VA; 4.5-letter gain vs. 1.5-letter loss). Moreover, the treatment was well tolerated.

The two-year study was conducted at Oxford Eye Hospital and included 14 patients. All participants were male (age range, 25-73 years) and had confirmed null mutations of the *CHM* gene. Each patient received a single subretinal injection of a virus containing the missing gene. The injection was administered to one eye of each patient; the untreated fellow eye served as the control. The primary endpoint was vision change from baseline to two years in treated versus untreated eyes.

Initially, 12 patients were enrolled. However, complications in two patients (related to vector administration) led to a 24-month delay and a protocol change to improve the surgical technique and immune-suppression regimen. The ethics committee approved an extension of the trial, including recruitment of two additional patients, so that 12 patients would receive the per-protocol therapy and follow-up, as originally planned.

The gain in vision was at least 1 line in six treated eyes and at least 3 lines in three treated eyes. In general, the VA gains and recovery occurred within six months of the treatment. Small gains in VA were noted for eyes with end-stage choroideremia, which otherwise would have declined rapidly. Longer follow-up, up to five years for some patients (mean, 3.6 years), confirmed that the improvements had been maintained.

The findings suggest that a single treatment with a single gene may be sufficient to prevent blindness and, perhaps, ultimately cure other debilitating genetic conditions. (*Also see page 25.*)

Myo-Inositol Lacked Efficacy and Safety in a Multicenter Trial

JAMA

2018;320(16):1649-1658

In studies of preterm infants with respiratory distress, *myo*-inositol appeared to reduce the severity of retinopathy of prematurity (ROP) and the frequency

of ROP, death, and intraventricular hemorrhage. However, its efficacy and safety had not been tested in large trials until a recent multicenter study by Phelps et al. In their large population of infants, *myo*-inositol did not reduce the risk of death or type 1 ROP relative to placebo, suggesting that it is not a viable treatment for this age group. The study was terminated early because the mortality rate was significantly higher in the *myo*-inositol arm.

This randomized trial included 638 infants (gestational age [GA] <28 weeks) who were enrolled from 18 U.S. neonatal intensive care centers in 2014 and 2015. (The planned enrollment was 1,760 participants, which would have been sufficient to detect an absolute reduction in death or type 1 ROP of 7% with 90% power.)

Participants received either *myo*-inositol 40 mg/kg (n = 321) or placebo (n = 321) for up to 10 weeks. Administration was every 12 hours, intravenously and then enterally (when feeding). The main outcomes were type 1 ROP or death before the determination of an unfavorable ROP status. The designated favorable outcome was survival without type 1 ROP. The final month of follow-up was February 2016.

In the study population (mean GA, 26 weeks; 50% male), 92% had a documented outcome. Death or type 1 ROP occurred more frequently in the *myo*-inositol group (29% vs. 21%; adjusted relative risk, 1.41; p = .01). Before 55 weeks' postmenstrual age, death (any cause) had occurred in 18% of the *myo*-inositol group and 11% of the placebo group (adjusted relative risk, 1.66; p = .007). The most common serious adverse events with active treatment versus placebo, respectively, were systemic infection (16% vs. 11%), respiratory distress (15% vs. 13%), intraventricular hemorrhage (10% vs. 9%), poor perfusion or hypotension (7% vs. 4%), and necrotizing enterocolitis (6% vs. 4%).

Although these findings do not support the efficacy or safety of *myo*-inositol in premature infants, the trial's early termination does not allow for definitive conclusions.

—Summaries by Lynda Seminara

Coming in the next

EyeNet®

Feature

Cataract Spotlight

Managing nerve-racking complications in 18 hair-raising cases.

Clinical Update

Glaucoma Now that Cypass has been withdrawn from the market, what should your management plan be?

Oculoplastics Treatment of thyroid eye disease is taking a new turn toward medical management. An update.

Pearls

Mixing and Matching IOLs

How blended vision can improve patients' quality of life.

Savvy Coder

CPT 2019 Get up to date with this quick summary of code changes.

Practice Perfect

MIPS 2019, Part 2 What's new with quality, cost, and improvement activities.

Blink

Take a guess at the next issue's mystery image.

For Your Convenience

These stories also will be available online at aao.org/eyenet.

FOR ADVERTISING INFORMATION

Mark Mrvica or Kelly Miller
M. J. Mrvica Associates Inc.
856-768-9360
mjmrvica@mrvica.com