Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by George B. Bartley, MD

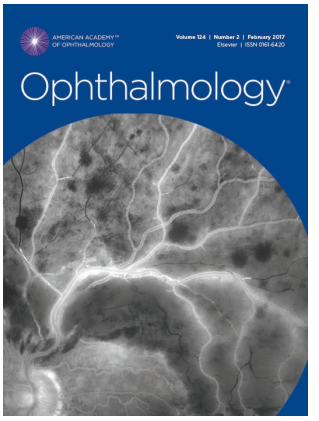
Perioperative Retinal Artery Occlusion: Risk Factors in Cardiac Surgery

February 2017

Calway et al. examined the incidence of and risk factors for perioperative retinal artery occlusion (RAO) in cardiac surgery. The authors found that the odds ratio (OR) for RAO was increased in the presence of cardiovascular risk factors including stroke, carotid stenosis, and hypercoagulability, as well as procedures in which the heart is opened, such as septal repair.

In this study, the authors reviewed hospital discharges in the U.S. National Inpatient Sample (NIS) to identify cardiac surgery. RAO in the perioperative period was ascertained by ICD-9-CM codes. Postulated risk factors were based on a literature review and included in multivariate logistic models.

An estimated 5,872,833 cardiac surgeries were performed in the United States from 1998 to 2013. The authors found that the overall rate of perioperative RAO incidence was 7.7 per 10,000 cardiac surgery procedures in this period. The conditions most strongly associated with RAO were giant cell arteritis (OR, 7.7), transient cerebral ischemia (OR, 7.67), carotid artery stenosis (OR, 7.52), embolic stroke (OR, 4.43), hypercoagulable state (OR, 2.9), diabetes mellitus (DM) with ophthalmic complications (OR, 1.89), and aortic insufficiency (OR, 1.85). Postoperative bleeding and surgeries in which the heart is opened (e.g., valve replacement or septal surgery) also increased the odds of RAO (range, 1.58-2.16).



Lower odds of RAO were associated with female gender, thrombocytopenia, acute coronary syndrome, atrial fibrillation, congestive heart failure, uncomplicated DM type 2, and smoking, although the reasons are unclear.

The authors noted that this retrospective review demonstrates associations, not cause and effect. Nevertheless, they suggested that their findings could help identify patients at higher risk of RAO and thus be useful in obtaining a proper informed consent and, potentially, in altering the surgical plan.

Late In-the-Bag IOL Dislocation: Lens Repositioning vs. Lens Exchange

February 2017

Kristianslund et al. carried out a prospective randomized parallel-group trial to compare the efficacy and safety of 2 surgical methods for managing late in-the-bag intraocular lens (IOL) dislocation: IOL repositioning by scleral suturing (i.e., repositioning) and IOL exchange with retropupillary fixation of an iris-claw IOL (i.e., exchange). They found that both methods yielded satisfactory—and not significantly different—best-corrected visual acuity (BCVA) at 6 months.

This study involved 104 patients (104 eyes) with IOL dislocation more than 6 months after implantation. Of these, 54 eyes were assigned to repositioning and 50 were assigned to exchange. All of the procedures were performed by the same surgeon between January 2013 and December 2015. Patients were assessed preoperatively and postoperatively; parameters included the following: presence/absence of pseudoexfoliation, corneal endothelial cell count, refraction and BCVA, and degree of IOL dislocation. In addition, the postoperative examination recorded complications.

The main outcome measure was BCVA at 6 months. There was no significant difference in BCVA between the 2 groups, both of which achieved a significant improvement after surgery. However, 21% and 26%, respectively, of patients in the repositioning and exchange groups experienced worse BCVA after the procedure.

The researchers found both operation methods to be generally safe, with a fairly low frequency of serious perioperative and postoperative complications. The 2 most common postoperative complications were IOP increase (25% overall), with 12 cases (28%) in the repositioning group and 9 cases (21%) in the exchange group; and

cystoid macular edema (8% overall), with 3 (7%) and 4 (10%) cases in the respective groups. Some complications varied between groups. The mean surgical time was longer for repositioning than for exchange. Furthermore, intraocular hemorrhage occurred only during repositioning, while iris injuries and the need for anterior vitrectomies occurred only during exchange; these differences were expected based on the specific surgical methods. Endothelial cell loss was significantly greater in the exchange group.

The authors concluded that while both methods are acceptably safe, the specific complications vary between them. Thus, the surgeon should take these differences into consideration when selecting the most appropriate method for individual patients.

Dual Antagonism of PDGF and VEGF in Neovascular AMD in a Phase 2b Trial

February 2017

Jaffe et al. assessed the safety and efficacy of E10030 (Fovista), a platelet-derived growth factor (PDGF) antagonist administered in combination with anti-VEGF agent ranibizumab (Lucentis) in the treatment of neovascular age-related macular degeneration (nAMD). They found that the combination therapy demonstrated visual benefits compared with ranibizumab monotherapy.

This was a phase 2b multicenter superiority trial with a randomized prospective double-masked controlled design. The 449 participants with treatment-naive subfoveal nAMD were randomized 1:1:1 to the following intravitreal treatment groups: E10030 0.3 mg in combination with ranibizumab 0.5 mg; E10030 1.5 mg in combination with ranibizumab 0.5 mg; and sham in combination with ranibizumab 0.5 mg. Drugs were administered monthly in each of the groups for a total treatment duration of 24 weeks.

The main outcome measure was a prespecified primary endpoint of mean change in visual acuity (VA; measured in EDTRS letters) from baseline to 24 weeks. The E10030 (1.5 mg) combination therapy regimen demonstrated superiority in mean VA gain compared with anti-VEGF monotherapy (10.6 ETDRS letters at week 24 vs. 6.5 ETDRS letters, respectively; p = .019). All clinically relevant treatment endpoints of visual benefit (≥15 ETDRS letters gained, final VA 20/40 or better) and visual loss (≥1 ETDRS line loss, ≥2 ETDRS line loss, and final VA 20/125 or worse) favored the E10030 (1.5 mg) combination group. A dose-response relationship was evident at each measured time point beginning at 4 weeks. The researchers found no significant safety issues in any treatment group.

The researchers concluded that there was a 62% relative benefit from baseline in the E10030 (1.5 mg) combination therapy group compared with the anti-VEGF monotherapy group.

—Summaries by Marianne Doran

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Fornix-Based vs. Limbal-Based Conjunctival Trabeculectomy Flaps

February 2017

Opinions differ on surgical techniques for trabeculectomy and, in particular, whether the conjunctival incision should be made in the fornix or the limbus. In a Cochrane systematic review of randomized controlled trials (RCTs) involving adults with glaucoma, **Al-Haddad et al.** found similar efficacy for the 2 conjunctival flap locations.

Six RCTs (N = 361 patients) met the authors' inclusion criteria for comparing the benefits and complication rates of these methods. All trials had at least 12 months of follow-up, and 3 had at least 24 months. The main outcome measures were the proportion of failed trabeculectomies at 24 months and the mean intraocular pressure (IOP) at 24 months. Trabeculectomy failure was defined as the need for repeat surgery or uncontrolled IOP (>22 mm Hg) despite additional topical/systemic drugs.

None of the trials reported trabeculectomy failure at 24 months. Of the 3 studies that evaluated failure at 12 months, 1 reported a 2% rate of failure in the fornix-based group (1 of 50 eyes) and 6% in the limbal-based group (3 of 50 eyes). Another trial reported that 2 of 43 (4.6%) eyes in each group required reoperation during 3 years of follow-up. Of the 3 RCTs that included 24-month IOP data, no significant differences were found in mean postoperative IOP between the surgical groups.

With respect to complications, postoperative shallow anterior chamber was twice as common for limbal- versus fornix-based procedures. There were no other significant differences in complications between the 2 procedures.

The authors concluded that fornix-based and limbal-based flap incisions appear similar in terms of IOP control and bleb failure, but the risk of shallow anterior chamber was significantly greater after limbal-based surgery. However, the authors acknowledged that their low event rates and wide confidence intervals indicate a high degree of uncertainty about the findings.

Corneal Toxicity After Exposure to Aquarium Coral Palytoxin

February 2017

Farooq et al. conducted a multicenter retrospective analysis of 7 cases of corneal toxicity that occurred shortly after presumed exposure to palytoxin from zoanthid coral. Palytoxin is a non-proteinaceous compound that acts as a vasoconstrictor and inhibitor of sodium-potassium ATPase pumps. The authors found that the effects of corneal exposure to palytoxin vary from mild to severe and can be progressive.

At clinical presentation, all 7 patients (10 affected eyes) reported recent contact with zoanthid coral in aquarium water. Exposure to palytoxin was inferred from the patients' history; the toxin was not isolated from ocular samples. Corneal conditions ranged from superficial punctate epitheliopathy to bilateral corneal melt and eventual perforation. No patient had histologic evidence of ocular infection. A paracentral ring infiltrate developed in the cornea of 1 patient. Acute and chronic keratitis was observed near the ulcer of a patient

with corneal perforation; few inflammatory cells were found despite the presence of severe stromal keratolysis.

Mild corneal toxicities resolved after treatment with topical corticosteroids, lubrication, and antibiotic prophylaxis. More severe corneal cases required topical/oral steroids, topical/oral antibiotics, serum tears, and/or amniotic membrane. Two patients (3 eyes) experienced decreased vision and were fitted with contact lenses. Three other patients (4 eyes) underwent penetrating keratoplasty. Most patients had been unaware of their potential for palytoxin exposure.

Although many investigators have described systemic outcomes of palytoxin exposure, few have addressed the ocular effects. In this largest case series of the corneal effects of palytoxin, the authors concluded that a careful history, timely treatment, and frequent monitoring are crucial for patients who present with possible corneal exposure to this toxin. They also recommended that aquarists use protective goggles and gloves. Further, they noted that a national reporting system for this toxic exposure would be beneficial and that awareness of this danger should be heightened among eye care professionals, aquarium enthusiasts, and the general public.

CMV Retinitis After Initiation of Antiretroviral Therapy in Patients With AIDS

February 2017

Cytomegalovirus (CMV) retinitis is a common ocular opportunistic infection in patients with AIDS. **Jabs et al.** sought to determine the rates of new-onset and worsening CMV after patients with AIDS start combination antiretroviral therapy (cART). The likelihood of an immune reconstitution inflammatory syndrome (IRIS) also was explored. The authors found no increase in new-onset or worsening CMV in the initial months of therapy and noted that "immune recovery retinitis" (IRR), a previously proposed phenomenon, appears to be rare.

This observational study included participants in the Longitudinal Study of Ocular Complications of AIDS (LSOCA) who initiated cART after enrollment in LSOCA and whose $CD4^+$ T-cell count was <100 cells/μL when cART was initiated (106 without CMV retinitis, 52 with CMV retinitis). Of the 106 patients without CMV retinitis, 75 experienced immune recovery (defined as an increase in $CD4^+$ T-cell count to ≥100 cells/μL). Within 6 months of starting cART, CMV retinitis occurred in 1 of these patients and in 1 of the 31 patients who did not have immune recovery. Among patients with CMV retinitis at enrollment, the rates of retinitis progression and increasing border activity in the first 6 months of cART were 0.11 per person-year (PY) and 0.11 per PY, respectively, for those with immune recovery. For those without immune recovery, the respective rates were 0.67 per PY and 0.40 per PY.

Clinical assessments corroborated the expected overall reduction in retinitis and mortality associated with immune recovery. Event rates were consistently higher for patients who did not have immune recovery. Animal models of infectious retinitis suggest that vitritis and retinal vascular sheathing may be inflammatory responses to an antigen but that retinitis per se requires replicating organisms. Therefore, IRR would be unlikely to occur as an IRIS phenomenon.

In conclusion, the rate of new or worsening CMV retinitis in the first 3 to 6 months of cART is no higher for persons with AIDS who experience immune recovery than for those who do not. These findings are consistent with the known benefits of immune recovery and the 3- to 6-month lag in recovery of specific immunity to CMV after initiation of cART.

—Summaries by Lynda Seminara

JAMA Ophthalmology

Selected by Neil M. Bressler, MD

Postoperative Symptoms and Satisfaction With LASIK Surgery

January 2017

Eydelman et al. reviewed surveys from the 2 PROWL (Patient-Reported Outcomes With LASIK) observational studies to determine patient satisfaction and document the frequency of patients' ocular symptoms. They found that patients were more likely to report adverse symptoms on self-administered questionnaires than directly to their health care providers.

Participants in the PROWL-1 (active-duty U.S. Navy personnel) and PROWL-2 (civilians) studies underwent LASIK (N = 534) for myopia, hyperopia, and/or astigmatism. They completed a web-based questionnaire both preoperatively and postoperatively. Ocular symptoms evaluated were dry eye, double images, glare, halos, and starbursts. Clinical assessments included visual acuity, refractive error, slit-lamp evaluations, and posterior segment eye exams. Visual symptoms and dissatisfaction with vision were common preoperatively.

Although most participants were satisfied with their results, the rates of postoperative dissatisfaction with vision ranged from 1% to 4%, and dissatisfaction with the surgery ranged from 1% to 2%. The overall prevalence of symptoms decreased postoperatively, but many patients reported new symptoms within 3 months (43% of PROWL-1 participants; 46% of PROWL-2 participants). The proportion of participants in PROWL-1 with normal Ocular Surface Disease Index (OSDI) scores was 55% at baseline, 66% at 3 months, and 73% at 6 months. The percentage of participants in PROWL-2 with normal OSDI scores was 44% at baseline and 65% at 3 months (no assessment was done at 6 months). Among all study participants with normal baseline scores, approximately 28% had symptoms of mild, moderate, or severe dry eye 3 months after surgery.

This study is one of a few noting the occurrence of new visual symptoms after LASIK surgery. Previous research has shown that patients are reluctant to report negative effects to their health care professionals and that the administration of questionnaires in a private setting, with assurance that the health care provider would not be privy to responses, leads to increased unbiased reporting of such effects.

The authors concluded that typical methods of reporting symptoms after LASIK surgery may lead to underestimating true incidence rates by a factor of 2 to 4. Thus, they recommend making the validated PROWL questionnaire publicly available as a tool for the ophthalmic community.

Association Between Myopia and UVB, Vitamin D Levels, or Genetics of Vitamin D Metabolism

January 2017

Spending time outdoors is known to protect against myopia, but it is not clear whether the primary reason is light intensity, ultraviolet radiation, serum vitamin D concentrations, or other factors. **Williams et al.** conducted a secondary analysis of the European Eye Study and found that of the factors above, only ultraviolet B (UVB) radiation exposure, particularly during adolescence and early adulthood, was associated with a reduced odds ratio (OR) for myopia.

Their study cohort (N = 3,168) was selected from a cross-sectional, population-based random sample of individuals 65 years of age and older; 371 participants had myopia, defined as a mean spherical equivalent of –0.75 D or worse. All participants received an eye exam, including refraction; provided a blood sample; and completed a comprehensive questionnaire on demographics, education, and other lifestyle factors. Of particular interest was the amount of time spent outdoors during daylight hours from age 14 years onward.

Vitamin D serum concentrations were measured using spectrometry and were adjusted by season. Data on vitamin D pathway single nucleotide polymorphisms (SNPs) were available for approximately one-third of the study population. Logistic regression was used to estimate ORs for myopia and UVB exposure, serum vitamin D concentrations, and vitamin D SNPs.

An increase in UVB exposure in the age groups of 14-19 and 20-29 years was associated with reduced odds for myopia. In keeping with earlier studies, the OR for myopia was significantly higher for the most-educated subset of participants. There was no evidence of a direct link between myopia and serum vitamin D concentrations or the genes involved in vitamin D metabolism. Unexpectedly, very high concentrations of plasma lutein appeared to correlate with reduced odds of myopia, a finding that warrants further investigation.

The authors concluded that exposure to UVB radiation between 14 and 29 years of age is associated with the greatest protection against myopia.

Incidence and Causes of Acquired Third-Nerve Palsy: Population-Based Study

January 2017

There are many causes of third-nerve palsy, including life-threatening aneurysms. **Fang et al.** used a population-based approach to determine the etiologies and presenting characteristics of third-nerve palsies and found a higher incidence of presumed microvascular third-nerve palsies and a lower incidence of aneurysmal compression than observed in non–population-based studies.

Using data from the Rochester Epidemiology Project, the authors identified all cases of acquired third-nerve palsy diagnosed in Olmsted, Minn., from 1978 through 2014. Medical records were reviewed to confirm the diagnosis and to record etiology and presenting signs. Incidence rates were adjusted to the age and gender distribution of the 2010 white population of the United States.

There were 145 newly diagnosed cases of acquired third-nerve palsy. The age- and gender-adjusted annual incidence was 4.0 per 100,000 (95% CI, 3.3-4.7 per 100,000). The annual incidence was greater for patients aged >60 years than for younger patients (12.5 vs. 1.7 per 100,000; difference, 10.8 per 100,000; 95% CI, 4.7-16.9; $p < .001$). The most common etiologies were presumed microvascular causes (42%), trauma (12%), compression from neoplasm (11%), post-neurosurgery sequelae (10%), and compression from aneurysm (6%).

Pupil involvement was present in 43% of the study patients, including 16 with compressive palsy (64%) and 10 with microvascular palsy (16%). Although the likelihood of pupil involvement was greater for compressive lesions, pupil involvement did not exclude a microvascular origin, and the lack of it did not rule out a compressive cause. Ptosis was present in 86% of patients; its incidence was similar for the various causes. Pain occurred in 69% and varied substantially by cause.

In conclusion, this study suggests that the incidence of presumed microvascular third-nerve palsy is higher, while the incidence of aneurysmal compression is lower, than in previous reports. Because microvascular and compressive origins cannot be differentiated by clinical characteristics alone, neuroimaging is recommended for all cases of acquired third-nerve palsy that lack an obvious known cause.

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Blunt- vs. Sharp-Needle Anesthetic Injection in Upper Blepharoplasty

JAMA Facial Plastic Surgery
Published online Nov. 23, 2016

Although sharp needles are commonly used to administer anesthesia in upper blepharoplasty, **Yu et al.** evaluated the potential benefits of using blunt-needle injection instead. They found that use of blunt needles to administer local anesthesia for this procedure was less likely to cause hemorrhage and to require interventional pain procedures than use of sharp needles.

In a randomized clinical trial in an academic medical setting in China, 44 patients, aged 18-56 years, underwent bilateral upper blepharoplasty. Patients received local anesthesia injections (lidocaine 2%; 27-gauge needle) with a blunt needle in 1 eyelid and a sharp needle in the other eyelid (the specific injection technique for each was randomly assigned). Patients self-evaluated the pain for each injection on a visual analog scale (VAS) ranging from 0 to 10 (lower score indicating less pain).

In addition, after injection and skin incision, the eyelids of each patient were photographed, and the images were evaluated for bruising and hematoma by plastic surgeons who were masked as to the type of injection.

The patients' mean (SD) VAS scores were 5.48 (1.59) and 4.64 (1.67) for sharp and blunt needles, respectively (p = .002). The evaluation of photographs revealed bruising and/or hematoma in 11 eyelids (25%) treated with sharp needles compared with 0 eyelids treated with blunt needles.

The researchers stated that blunt needles are easier to use and less likely than sharp ones to cause inadvertent penetration of arteries or adjacent vital structures. Thus, blunt needles can reduce complications, including bleeding, bruising, blood vessel impalement, and subsequent intravascular injection and hemorrhage.

The researchers noted that, to their knowledge, this is the first prospective side-by-side comparison study of the 2 types of needles in upper blepharoplasty. They concluded that use of blunt needles presents fewer complications, allows for a more accurate surgical procedure, and enables faster patient recovery.

Ocular Toxicity of Mitogen-Activated Protein Kinase Inhibitors

JAMA Oncology
Published online Nov. 17, 2016

In a clinical research letter, **Purbrick et al.** reported that investigators at the Oxford Eye Hospital and Oxford Experimental Cancer Centre collaborated to study the ocular effects of 3 experimental mitogen-activated protein kinase inhibitors (MEKIs). These drugs are currently in clinical development as treatment for disorders such as advanced cutaneous melanoma. Overall, 18% of patients developed ocular adverse events, the most common of which was central serous chorioretinopathy (CSC) or CSC-like changes.

The investigators reviewed the clinical records of 40 patients enrolled in clinical trials of 3 different MEKIs, including 11, 19, and 10 patients in MEKI trials A, B, and C, respectively. The parameters examined included baseline visual acuity (VA); ophthalmic and general medical history; ophthalmic imaging data, including macular optical coherence tomography (OCT); and evidence of ocular toxic effects.

Overall, 7 of 40 patients (18%) developed adverse ocular effects. In trial A, 3 of the 11 patients (27%) developed bilateral CSC, which was multifocal in 1 case. In trial B, 2 of the 19 patients (11%) developed ocular adverse effects; 1 patient had a left central retinal vein occlusion, and 1 patient had bilateral, multifocal CSC-like changes. In trial C, 2 of 10 patients (20%) developed problems: 1 had bilateral, multifocal CSC-like changes, and 1 had a severe increase in intraocular pressure.

The authors noted that the role of MEKIs in these complications could not be fully assessed, in part because of malignancy-related hypercoagulability in some of the patients and/or concurrent use of other drugs. However, they recommended that patients receiving MEKI therapy should be monitored prospectively by means of appropriate validated techniques and have a baseline ophthalmic examination before starting treatment, including VA and IOP measurements, dilated fundus examination, fundus photography, and macular OCT. Further studies may help determine which patients are at particular risk of ocular toxic effects.

Durability of the Rituximab Response in Myasthenia Gravis

JAMA Neurology
2017;74(1):60-66

Although the benefits of B-cell–targeted therapy with rituximab have been observed in myasthenia gravis (MG), the duration of these effects after treatment is unclear. Thus, **Robeson et al.** set out to evaluate the durability of response to rituximab in the treatment of refractory acetylcholine receptor autoantibody–positive (AChR$^+$) generalized MG. They found that 56% of patients who had achieved disease control relapsed at a mean of 36 months of follow-up, while 44% remained relapse free at a mean follow-up of 47 months after the last rituximab treatment.

This retrospective case series included 16 patients with AChR$^+$ MG who were treated at an MG clinic from Jan. 1, 2007, to Dec. 31, 2015. The patients received rituximab and were followed for 18 to 84 months after treatment. The main outcome measures included long-term clinical response, durability of response and/or relapse rate, AChR autoantibody levels, adverse effects, and inflammatory markers.

All patients achieved complete stable remission, pharmacologic remission, or minimal manifestations, as defined by Myasthenia Gravis Foundation of America criteria. The improvement was observed in parallel with complete withdrawal or reduction of other immunotherapies. With regard to AChR antibodies, a 33% decrease was seen after cycle 1 of rituximab, 20% after cycle 2 (compared with cycle 1), and 17% after cycle 3 (compared with cycle 2).

Nine patients (56%) experienced a relapse during a mean follow-up of 36 months (range, 24-47 months). Seven patients (44%) remained relapse free at a mean follow-up of 47 months (range, 18-81 months) since their last rituximab treatment.

The authors concluded that rituximab therapy appears to be an effective option in patients with refractory AChR$^+$ MG, who were observed to have had a durable response after treatment. Identification of markers of disease relapse and sustained remission are critical next steps in the development of pathophysiology-relevant, evidence-based practice parameters for rituximab in the treatment of MG.

—Summaries by Marianne Doran