

News in Review

COMMENTARY AND PERSPECTIVE

Robot-Assisted RVO Clot Lysis

WITH ASSISTANCE FROM AN OPH-thalmic surgical robot, Belgian researchers have successfully injected a thrombolytic drug directly into a patient's occluded retinal vein, dissolving the clot and reversing the patient's sight impairment from macular edema.

Researchers from the Catholic University of Leuven and University Hospitals Leuven, in Leuven, Belgium, announced this first successful reversal of retinal vein occlusion (RVO) in a January press release.¹ The procedure, called retinal vein cannulation, was the first of 6 surgeries planned in a phase 1 clinical trial of robot-assisted treatment of RVO with the drug ocriplasmin, they said.

Synergy between surgeon and robot. The yet-unnamed robot, which took 7 years to create, looks like a smaller, refined version of the robot arms used in automotive factories. It is designed not to replace the surgeon's hand but rather to overcome the human hand's limitations when trying to insert a 30- μ m needle tip into a 100- μ m retinal vein, said Peter Stalmans, MD, PhD, the vitreoretinal surgeon on the research team.

"The principle of the robot is that it eliminates the tremor of your hands. To the surgeon it feels as if you are moving the instrument into a very thick gel. So you can make very gentle, slow motions with no sudden movements," Dr. Stalmans said.



"Then, when the needle is inserted into the vessel, you release the foot pedal and the robot will lock in place. So the surgeon can let go of the instrument and leave it there for several minutes while the ocriplasmin is being infused," he said.

Dr. Stalmans noted that the robot system's design for "co-manipulation" gives it a familiar feel. "The major difference from other surgical robots—for instance, the da Vinci—is that in this case there is co-manipulation with the robot," he said. "You are holding the instrument just as you would be doing in any type of ocular surgery. It is not operated with a joystick."

Initial patient results. Feasibility and safety are the primary endpoints of the ongoing study of RVO treatment, but the potential for clinical efficacy was apparent with the first patient, Dr. Stalmans said.

"The patient had only hand movements [vision] before the procedure, and to our surprise, after 2 weeks the patient had 0.16 visual acuity [20/125]. Before surgery, his macula was about 1,500 μ m thick, and the edema was completely gone after 2 weeks. That was

CO-MANIPULATION. *The surgeon's hand guides the instrument, which is simultaneously grasped and stabilized by the robotic arm.*

really, really a surprise to us," he said.

As of early March, 2 more patients had undergone retinal vein cannulation (results not available at time of press). No adverse events related to the procedure were recorded, Dr. Stalmans said.

What about arteries? Dr. Stalmans said that other ophthalmologists commonly ask him if robot-assisted retinal surgery might be used for treating central retinal artery occlusion. He doesn't consider that feasible, for 2 reasons. First, it would be difficult to treat an arterial occlusion quickly enough to protect the retina, he said.

Second, occluded arteries are too small. "In a vein occlusion the vessels swell, which makes it easier for us to do the cannulation. But in an artery occlusion, the vessels shrink. And using the current technology it's impossible in a shrunken artery to insert a needle. It is already very difficult in a vein, let alone in an artery," he said.

Possible applications. However, the

robot might be a good fit for other intraocular procedures, including targeted delivery of chemotherapy to tumors, treatment of arteriovenous malformations, and subretinal injections, such as for gene therapy, he said.

For now, the possibility of using the robot to treat RVO is exciting, he said. “The robotic device enables us to treat the cause of the thrombosis in the retina for the first time. I am, therefore, looking forward to what is next. If we succeed, we will literally be able to make blind people see again.”

—Linda Roach

1 Press release, Jan. 26, 2017. www.kuleuven.be/english/news/2017/surgical-eye-robot-performs-precision-injection-in-patient-with-retinal-vein-occlusion. [Also includes images and surgical video.]

Relevant financial disclosures—Dr. Stalmans: ThromboGenics: S.

OCULAR SURFACE BIOMARKERS

Metabolomics Links Dry Eye & Low Androgens

SAY HELLO TO THE POWER OF THE metabolome.

As with the genomics and proteomics revolutions before it, the study of metabolite levels in the body—known as *metabolomics*—is promising to give ophthalmic researchers new molecular-level insights into the biological pathways behind some eye diseases.¹

Serum metabolites in dry eye disease (DED). One such example came early this year when a study of serum metabolites in a British population-based sample (n = 2,819) found an association between DED and decreased serum androgens.² Although

smaller studies by other groups have suggested a linkage, this is the first hypothesis-free screening study of hundreds of serum metabolites to find the association in a large population cohort, the authors reported.

“The study’s premise was to look for pathways involved in DED and to see if systemic metabolite alterations give us some clue about disease mechanisms in this common problem,” said coauthor Chris Hammond, FRCOphth, the Frost Professor of Ophthalmology at King’s College London. “The exciting discovery that androgen deficiency seems to be associated with DED, along with other work in this area, may lead scientists to developing hormone-based treatments for DED.”

Specifically, the group found a strongly significant metabolome-wide association between dry eye and lower levels of the metabolites androsterone

DIABETIC EYE DISEASE

Ranibizumab Reduces Worsening PDR

THE LATEST STUDY FROM THE DIABETIC RETINOPATHY Clinical Research Network (DRCR.net) supports the use of ranibizumab as an alternative to panretinal photocoagulation (PRP) to prevent worsening of proliferative diabetic retinopathy (PDR).¹

At 2 years, eyes treated with ranibizumab experienced fewer worsening events—defined as vitreous hemorrhage, retinal detachment, anterior segment neovascularization, or neovascular glaucoma—than those receiving PRP. The cumulative probability was 34% for ranibizumab compared with 42% for PRP. “Panretinal photocoagulation has been the gold standard for 40 years, but physicians now have a new option for treating patients,” said Lee Jampol, MD, chair of the DRCR.net.

Other factors affecting outcomes. The randomized clinical trial at 55 U.S. sites involved 394 eyes of 305 adults with PDR and no previous PRP; 191 eyes were assigned to ranibizumab and 203 to PRP. However, regardless of group assignment, the study protocol required all eyes with vision-impairing center-involved diabetic macular edema (DME) to receive ranibizumab at baseline.

Because this requirement was a potential confounder, the researchers also performed subgroup analysis of eyes without DME—and found that the difference in

treatment effect was more robust. In that subgroup, cumulative probability of worsening PDR was 45% with PRP and 31% with ranibizumab.

Regardless of treatment, severity of retinopathy at baseline was the most important factor. The risk of worsening in eyes with PDR classified as high-risk or worse was higher than in eyes with moderate or better PDR (64% vs. 23%, respectively).

Surprise finding. That the specific type of laser therapy makes a difference was unexpected, Dr. Jampol said. Pattern scan PRP was associated with higher risk of worsening than conventional single-spot laser—60% versus 39%, respectively. The finding may be a true effect, he said, or it might be due to chance or potential bias, as the choice of laser type was left to investigator discretion.

Clinical implications. Although the results support the use of ranibizumab, Dr. Jampol noted that “PRP is still the choice for many clinicians and patients, particularly if anti-VEGF treatment is unavailable or if there is a concern regarding patient compliance with follow-up visits.”

The researchers plan to follow these patients through 5 years. In the meantime, they emphasized: “Diligent follow-up of patients is required because more than one-third of eyes treated with either approach may experience a PDR-worsening event in this period.” —Miriam Karmel

1 Bressler SB et al. *Ophthalmology*. 2017;124(4):431-439.

Relevant financial disclosures—Dr. Jampol: None.

sulfate and epiandrosterone sulfate. Three other molecules involved in androgen metabolism were also lower in the subjects with DED but did not attain metabolome-wide statistical significance.

Considering other eye diseases.

There is interest in analyzing tear samples to identify metabolite profiles associated with ocular surface disease, Dr. Hammond said. In other eye diseases, metabolomics would present bigger challenges, he added.

“The difficulty is whether systemic metabolites—typically measured, as in our study, in serum—reflect intraocular diseases such as AMD or glaucoma,” he said. “But certainly, there is evidence of systemic inflammatory changes in AMD; and cataract, for example, has metabolic associations, so these may be possible.”

—Linda Roach

1 Tan SZ et al. *Eye (Lond)*. 2016;30(6):773-783.

2 Vehof J et al. *Ophthalmology*. 2017;124(4):505-511.

Relevant financial disclosures—Dr. Hammond: None.

STRABISMUS TX IN KIDS

Botox Is Effective Option for a Rare Esotropia

ONABOTULINUMTOXIN A (BOTOX), used for decades in the treatment of adult strabismus, may now have a role in the treatment of children with a rare form of esotropia. Researchers at Boston Children’s Hospital have found that Botox injection was not inferior to surgery in children with acute-onset comitant esotropia.¹

“Furthermore, the cost of treatment with botulinum toxin was significantly lower, and patients spent less time in the hospital,” said David G. Hunter, MD, PhD, ophthalmologist-in-chief at Boston Children’s Hospital.

Study details. The retrospective nonrandomized comparative clinical study involved 49 children who had undergone esotropia treatment at

Boston Children’s Hospital from 2000 to 2014. Of those, 16 had been treated with botulinum toxin, and 33 had undergone strabismus surgery.

Although the study was not randomized, the decision for treatment was the random result of which doctor happened to see the patient at presentation. Prior to 2009, all patients underwent strabismus surgery, after which several surgeons began using Botox exclusively, Dr. Hunter said. “Ours is probably the best data clinicians will have to make a treatment decision.”

Results. There were no significant differences between the 2 groups in terms of success rate, angle of deviation, or stereoacuity at 6 or 18 months. Among the findings:

- At 18 months, the success rate of the initial treatment was 67% in the injection group, and 58% in the surgery group.
- Duration of anesthesia was 71 minutes in the surgery group versus 5 minutes in the injection group. And time spent in the postanesthesia care unit was 93 minutes after surgery versus 37 minutes postinjection.
- Treatment cost was approximately \$1,909 (69%) less with injection.
- At 6 months, failure occurred in 3 of 16 children in the injection group and 13 of 33 in the surgery group.

No serious complications. Each group had unique complications, the researchers said, but this did not favor one treatment over the other.

Half the children in the chemodenervation group experienced transient postoperative ptosis, and 56% experienced transient exotropia, complications that do not occur following surgery. After resolution—about 6 weeks for ptosis and 8 weeks for exotropia—none of the children developed new or worsening amblyopia. In the surgical group, complications included conjunctival injection and scarring.



BEFORE & AFTER. Top, 10-year-old girl with acute, comitant, 50-prism diopter esotropia prior to injection of 5 units of Botox into both medial rectus muscles; her diplopia resolved in 4 days. Bottom, 4 months after treatment, she is orthophoric, with 25 seconds of stereopsis; today, 18 months post-injection, her alignment remains stable.

Clinical implications. Dr. Hunter cautioned against extrapolating the results to all forms of esotropia. Acute-onset comitant esotropia is notable for the high degree of binocular function that most patients have before developing the rare condition, he said. “The botulinum toxin can be thought of as a way of resetting the alignment of the 2 eyes, allowing the brain to rediscover binocular vision and regain a hold on normal alignment.”

Prior to the study, Dr. Hunter had confidence offering Botox as a first-line treatment, though he told parents that retreatment might be necessary. “Now I am able to offer botulinum toxin without having to offer that caveat, anticipating that a single injection will correct the problem in most cases, with really no reason to choose surgery,” he said.

“But regardless of which treatment option one selects, there is always a chance that more treatment will be needed, and I don’t believe either choice can minimize that chance.”

—Miriam Karmel

1 Wan MJ et al. *Am J Ophthalmol*. 2017;176(4):33-39.

FDA disclosure: Botox is FDA approved for treatment of adults and children over age 12. The use in children under age 12 is considered off label.

Relevant financial disclosures—Dr. Hunter: REBIScan; C,O,P.

See the financial disclosure key, page 10. For full disclosures, including category descriptions, view this News in Review at aao.org/eyenet.