ROBOT ASSISTS WITH INJECTIONS FOR RVO

A robot is the copilot as a surgeon injects a thrombolytic drug into tiny veins.

BY TIM DONALD, CONSULTING EDITOR

Retinal vein occlusions (RVOs) are relatively common retinal vascular disorders, often associated with vision loss. The prevalence of RVO has been estimated at 0.5% of the global population, affecting more than 16 million people worldwide. RVOs lead to a decrease in outflow from the retinal circulation and result in macular edema and an increase in intravenous pressure, leading to the development of retinal hemorrhages.[1]

The Branch Vein Occlusion Study Group found that visual acuity improved spontaneously in about one-third of branch RVOs (BRVOs).[2] Visual prognosis tends to be good in eyes with nonischemic central RVO (CRVO) but poor in those with ischemic CRVO.[3] Focal/grid laser can play a role in treatment of BRVO, but laser has shown little efficacy in CRVO, except in eyes with iris neovascularization, in which case panretinal photocoagulation is indicated.[1] In either condition, laser treatment does not affect the underlying occlusion.[1]

THE ROLE OF THERAPEUTICS IN RVO TREATMENT

In recent years, interest in pharmacotherapy for RVOs has grown. The efficacy and safety of several forms of corticosteroid therapy have been investigated in clinical trials. The SCORE study showed benefits with intravitreal triamcinolone acetonide injection in reducing macular edema in BRVO, but there was no visual benefit compared with standard care (grid photocoagulation) at 1 year.[4] In eyes with CRVO, the SCORE investigators saw a benefit at 1 year for intravitreal triamcinolone compared with observation.[5] The GENEVA trial demonstrated benefit with an intravitreal corticosteroid implant in reducing BRVO-associated macular edema.[6] However, intravitreal corticosteroid use can lead to ocular side effects including secondary glaucoma and cataract formation.[5]

Treatment of RVOs with anti-VEGF agents has been investigated in numerous clinical trials. A 2014 meta-analysis compiled data from six randomized controlled trials that included patients with CRVO, comparing outcomes at 6 months between sham injection and one of four anti-VEGF agents: ranibizumab (Lucentis, Genentech), aflibercept (Eylea, Regeneron), bevacizumab (Avastin, Genentech), or pegaptanib sodium (Macugen, Bausch + Lomb). The authors concluded that, compared with sham treatment, repeated injections of an anti-VEGF agent in eyes with macular edema secondary to CRVO improved visual outcomes at 6 months.[7]

A similar meta-analysis for treatment of BRVO with anti-VEGF agents in 2013 identified only two trials for inclusion.[8] The authors concluded that repeated treatment of nonischemic macular edema due to BRVO with ranibizumab can improve clinical and visual outcomes at 6 and 12 months. However, the use of rescue laser treatment in the larger of the two trials made it impossible to assess the effect of that therapy on the primary outcome measure.[8]

GETTING TO THE POINT

All of the therapeutic measures for RVO outlined above address only the secondary effect of the RVO—the macular edema that causes visual loss—not the underlying clot causing the occlusion. Now, for the first time, with the aid of an intraoperative robot, surgeons have successfully removed a clot from a vessel in a patient with CRVO.

Peter Stalmans, MD, PhD, of the University Hospitals Leuven and the University of Leuven (KU Leuven), Belgium, performed the first robot-assisted retinal vein cannulation (RVC) in a human patient with CRVO in January. With the aid of a robot arm, Dr. Stalmans injected a tiny volume of

AT A GLANCE

- Current treatment options for RVO address only the secondary effects of the RVO, not the underlying clot causing the occlusion.
- With the aid of an intraoperative robot, surgeons have for the first time successfully removed a clot from a vessel in a patient with CRVO.
- If the clot can be removed in the first 2 weeks after occlusion, full resolution of the disease may be achieved, rather than simply dealing with its secondary effects over a long period.
- In theory, both CRVO and BRVO could be treated using the robot, and the technology may also find applications outside of the eye some day.

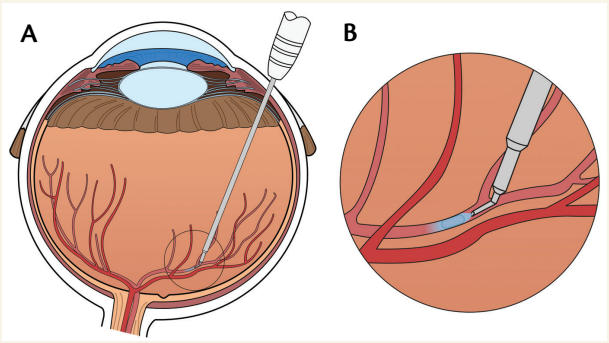

Figure 1. An ultrathin needle (A) was developed to handle injections into tiny retinal veins (B). Image courtesy of UZ Leuven.

ocriplasmin (Jetrea, ThromboGenics) into the occluded vein using a needle 0.03 mm in diameter.[9]

Since that first procedure, three more patients with CRVO have undergone the RVC procedure as part of a phase 1 clinical study, according to Dr. Stalmans. The first three patients were reviewed by a safety monitoring committee, which then approved further inclusion in the study. The study will eventually include a total of six patients, and four patients have been operated on as this issue is prepared for press.

In an interview with *Retina Today* in February, Dr. Stalmans said that, although the phase 1 trial is meant only to assess the feasibility of the procedure, the first patient did very well postoperatively.

"We were very pleased to learn that it was easily possible to do RVC in humans," he said. "A surprise was that, when we saw the patient back 2 weeks later, the tremendous retinal edema that he had preoperatively was completely gone, and his visual acuity improved from counting fingers at close distance to 0.16 [Snellen decimal] in just those 2 weeks' time, which is remarkable. We have not noted any adverse effects from the procedure in the patients operated so far."

A LONG ROAD

Although these first surgeries represent only the beginning of clinical application for the KU Leuven eye surgery robot, they also mark the culmination of years of collaboration on the project between the university's surgeons and its department of mechanical engineering. Dr. Stalmans said engineers from the university's robotics department came to him 7 or 8 years ago asking about possible uses for robots in ocular surgery.

"At first," he said, "I told them that I did not think it was needed because we can do membrane peeling and other procedures with great control and precision. Then they asked me, 'Is there something that you cannot do now that you would like to do,' and I said yes, something like RVC."

Dr. Stalmans noted that the idea of RVC is not new. There are publications touching on the idea dating back 15 to 20 years.[10-12]

Figure 2. A robot arm steadies Dr. Stalmans' hand while he injects ocriplasmin into the occluded vein of a human patient with CRVO. Photo courtesy of UZ Leuven.

"The main conclusions of these publications were that it is technically not possible to do RVC because (A) there was no needle small enough to inject into a vessel that is 100 µm in size, and (B) it is too difficult to keep the needle still enough for a long time in the vessel. The surgeon, with bare hands, cannot hold the needle still for several minutes for injection," Dr. Stalmans said.

The surgeons and the engineers talked about possibilities. Prototypes were built and tested, not only of the robot, but also of the ultrathin needle needed to inject a thrombolytic agent into a tiny retinal vein. Testing progressed from mock-up eyes to cadaveric porcine eyes to anesthetized living pigs.[13]

Finally, last year, "we were confident that we could do it in humans," Dr. Stalmans said. "We were experienced enough, and we had the proper tool to do it—the robot—and the proper needle to do it (Figure 1). So we sought approval from the university ethics committee to do a phase 1 trial, in which the outcome of the trial would be not the visual acuity results, but the feasibility. Can we do the cannulation? Can

we infuse the liquid? And that is where we are now, in the middle of that phase 1 trial."

ROBOT COPILOT

In the procedure as conceived and designed by the Leuven engineers and clinicians, the surgeon performs the RVC in tandem with the robot. The eye surgeon and the robot co-manipulate the instrument. The surgeon guides the needle, and the robot stabilizes the movements and eliminates any vibration (Figure 2). Once the needle is in place in the vein, the robot is locked, and the needle and eye are automatically stabilized. Then the injection of ocriplasmin can proceed in a controlled and safe manner.

"You just hold the instrument, just as you would hold any vitreoretinal instrument such as forceps," Dr. Stalmans explained. "The difference is that, while you are moving it, the robot arm is also holding it and eliminating any vibrations. But it feels quite familiar. So I think there will be a fast learning curve for others using this device."

"The Leuven device differs from other surgical robots, such as the da Vinci minimally invasive surgery system (Intuitive Surgical), in that no joystick is used," added engineer Andy Gijbels, who was involved in developing the robot for RVC. "In using a system like the da Vinci, the surgeon sits remotely and controls the action using the joystick."

"We tried this," Dr. Stalmans said. "We have a joystick for this robot. Then we compared that with a system where the surgeon holds the instrument together with the robot. We found in testing that, for both experienced and nonexperienced operators, it was more precise to use this co-manipulation approach, and it feels more familiar."

WHERE TO NOW?

With assessment of the feasibility well under way in the phase 1 study, Dr. Stalmans and graduate student Koen Willekens recently presented early findings on RVC at a local retina meeting.[14] Assuming all goes well, a phase 2 study will further assess safety and efficacy. Beyond treatment for CRVO, what lies ahead for this technology? Dr. Stalmans said the future is wide open.

"In theory, both CRVO and BRVO could be treated using the robot," he said. "In this pilot study we opted to go for CRVO because the visual acuity is much worse in these patients, and we found it ethically more reasonable to do these very poorly seeing eyes first."

Further, Dr. Stalmans said, "In theory, any surgery in the eye in which precision manipulation and fixation of an instrument is necessary could be done using this technology. Another use may be to perform high-precision subretinal injections. Gene therapy and stem cell therapies are becoming much more popular, and one of the requirements of these types of therapies is that you have to dose exactly. So for these applications the robot may also be of use."

The technology may also find applications outside of the eye. "Right now, the range of motion that we have with this robot is made for the eye: about 3 cm," he said. "If we built a similar robot, but bigger, it could be used for brain surgery," a field in which precision and steady hands are also vital.

Regarding the potential cost of robot-assisted surgery for RVO, Dr. Stalmans said the expense may not be as great as one might expect. "Right now, the standard of care for RVO patients is to give anti-VEGF injections, which deals only with the secondary effect of the occlusion, the macular edema," he noted. "It has been calculated that this therapy costs society about $32,000 per eye.[15] If we can remove the clot, we believe, in the first 2 weeks after occlusion, we may achieve full resolution of the disease, rather than simply dealing with its secondary effects over a long period. So perhaps robot surgery will not be cheap, but RVO treatment is currently quite costly to society as well."

The Department of Mechanical Engineering at KU Leuven is in the process of creating a spinoff company, Mynutia (www.mynutia.com), with the aim of commercializing this promising technology. ■

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