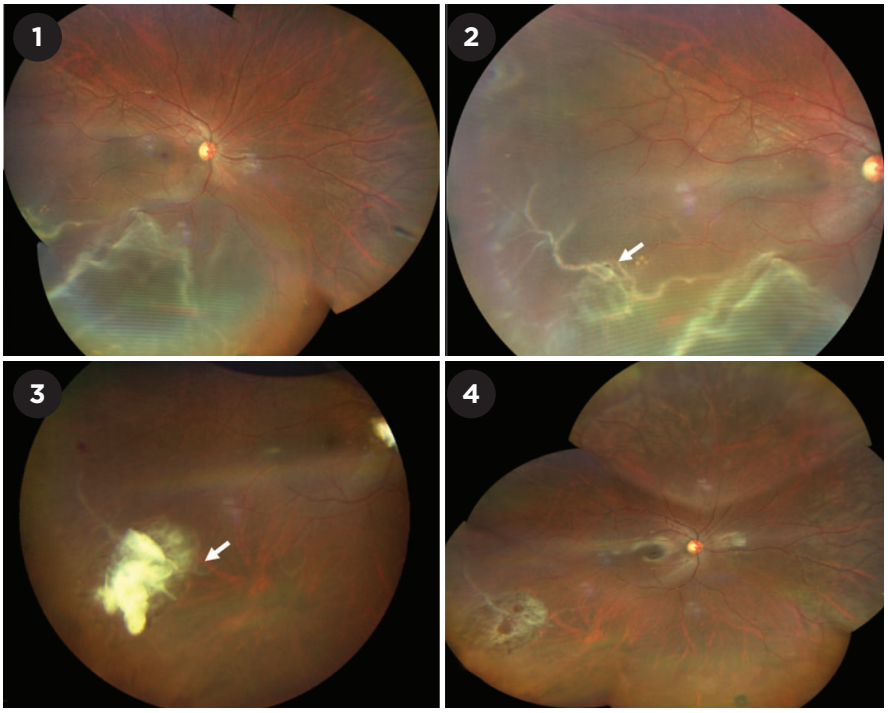
New Approaches to Securing Retinal Breaks During Surgery

Surgically treating rhegmatogenous retinal detachments (RRDs) often requires use of a tamponade agent such as silicone oil or gas to cover retinal breaks, preventing fluid from entering the subretinal space. Although they are needed only until the laser permanently seals the breaks, these agents come with their own set of disadvantages, said Mudit Tyagi, MD, at LV Prasad Eye Institute in Hyderabad, India.

For example, with gas, patients usually must maintain face-down postoperative positioning and restrict air travel until the gas bubble disappears. And with silicone oil, removal of the oil requires one more surgery for the patient. In addition, these tamponades cause blurry vision and raise the risk of increased IOP, corneal changes, and cataract formation.

"The way patients recover after this surgery hasn't really changed since the '70s," said Tomasz P. Stryjewski, MD, at Tallman Eye Associates in the greater Boston area. "After surgery, patients rarely complain about their eyes, but many have said that the week after vitrectomy was the worst of their life."

Challenges like these inspired Dr. Tyagi and Dr. Stryjewski each to explore alternatives for sealing the retinal breaks that cause detached retinas. Although neither of their approaches is quite ready for prime time, the prospects show promise.



FUNDUS IMAGES. *(1) A temporal break. (2) Arrow pointing to break. Fibrin glue was applied over the break after completion of vitrectomy and endolaser around the break. No silicone oil or gas was used, and no postoperative positioning was required. (3) At postoperative day 1 with a fibrin coagulum covering the break (arrow). (4) At one week, the coagulum has completely resorbed, leaving behind an attached retina with surrounding laser marks.*

Fibrin Glue-Assisted Retinopexy

The two main ingredients of fibrin glue are purified thrombin and fibrinogen, said Dr. Tyagi, who is testing its use as a substitute for silicone oil and gas tamponades after a vitrectomy in cases of RRD.

GuARD study. At the LV Prasad Eye Institute in Hyderabad, Dr. Tyagi initially conducted a study using fibrin glue-assisted retinopexy in five patients with RRD. Reattachment occurred in all cases and was maintained at follow-ups ranging from three to eight months.[1] A later study with 25 patients showed a 76% reattachment rate, all of which were maintained at the six-month mark.[2] In both studies, the median BCVA improved from 20/100 preopera-

Courtesy Mudit Tyagi, MD

BY ANNIE STUART, CONTRIBUTING WRITER, INTERVIEWING **MATTHEW R. STARR, MD, TOMASZ P. STRYJEWSKI, MD,** AND **MUDIT TYAGI, MD.**

tively to 20/80 at one week and 20/50 at one month after surgery.

Dr. Tyagi recently presented his long-term findings in 30 cases at the American Society of Retina Specialists (ASRS) meeting in New York City.[3] Using revised inclusion criteria of early retinal detachments, with two or three localized breaks and PVR not more than grade B, the success rate now is more than 90%, he said. "That would be on par with our current techniques [of scleral buckling and vitrectomy]," said Matthew R. Starr, MD, at the Mayo Clinic in Rochester, Minnesota.

In 2020, Chinese researchers reported similar results in 26 patients: the retina attached in all 26 patients, and BCVA was significantly improved. However, two patients developed an epiretinal membrane and three experienced increased IOP the first week after surgery—which lowered to a normal range after use of timolol.[4]

Patient selection. This technique works well for most early, simple, uncomplicated retinal detachments, said Dr. Tyagi. "Two to three breaks localized within two to three quadrants are the ones that are easily amenable, and we have even used it for inferior retinal detachments."

Dr. Tyagi, however, would not recommend using this technique for patients with extensive proliferative vitreoretinopathy (PVR) or with large breaks. "If a break is too large—more than three disc diameters—this may lead to subretinal migration of the fibrin," he said. Multiple breaks in multiple quadrants are also a bit difficult because the fibrin glue coagulums can coalesce into a single coagulum and then the breaks are not covered adequately, he said.

The procedure. Dr. Tyagi describes the technique as fairly straightforward, without a big learning curve. After the first three steps—vitrectomy, fluid-air exchange, and laser photocoagulation—the surgeon puts a single drop of fibrin glue over the break, instead of using oil or gas. "We occasionally add a small amount of air at the end of surgery, which goes away within one to two days," he said.

The glue technique. One challenge of sealing retinal breaks with fibrin glue has been that, when mixed, the two components that constitute the glue solidify very rapidly, said Dr. Stryjewski. Dr. Starr agreed, describing fibrin glue as runny before being mixed and immovable afterward.

Dr. Stryjewski pointed out that Dr. Tyagi and colleagues seem to have overcome this challenge for far peripheral breaks by first injecting the liquid fibrinogen onto the posterior pole, followed by thrombin to polymerize the gel. Then, the solid gel-clot can be mobilized with forceps to the site of the far-peripheral break.

Recovery. Patients thus far have experienced minimal or no adverse effects, including no lasting inflammation, said Dr. Tyagi. In his ASRS presentation, he said that three patients had minimal anterior chamber inflammation on the first postoperative day, which was successfully managed using a slightly higher frequency of topical steroids. Two patients had CME that resolved within a month with nepafenac drops.[3] More importantly, patients did not require any postoperative positioning, and visual recovery occurred within five to seven days, with the glue spontaneously getting resorbed within eight to 14 days, he said.

Prospects for widespread use. Fibrin glue has been used extensively in a variety of ocular surgeries, including in vitreoretinal surgery.[5] But without FDA approval, it is an off-label use in the United States. In fact, the package carries warnings about intraocular use, said Dr. Starr, who has used fibrin glue for conjunctival closure and membrane grafts on the surface of the eye but rarely inside the eye. "That said, I have used it successfully for patients with diabetic retinopathy and hemorrhages by placing it on the posterior pole to prevent postoperative bleeding." In addition, fibrin glue has been used for closing macular holes and for optic disc pit maculopathy and optic disc

Other Past and Present Attempts

"When we started on this work, it seemed as though no one was really talking about novel methods of tamponade," said Dr. Stryjewski. "Now there are a number of alternatives to seal retinal breaks. I think that's really encouraging because something is likely to come out of these global efforts."

Here's a sample of what's been tried.

Seprafilm adhesion barrier. Researchers reported on this technique in four patients about five years ago, said Dr. Tyagi. The challenge, he said, is with the delivery of Seprafilm inside the eye, as well as repositioning and stabilizing it over the break.

Animal studies. A number of preclinical research efforts are underway, with most focused on permanent hydrogels, said Dr. Stryjewski. "Unfortunately, we have some bad history with permanent hydrogels." Dr. Starr agreed. "Surgeons are worried about what hydrogels will do over time," he said, pointing to the example of the MIRAgel hydrogel scleral buckle, which produced serious complications many years after implantation.

Cyanoacrylate glue. A synthetic sealant, cyanoacrylate glue has been used mainly for corneal perforation surgeries.[1] "But it's been shown to be toxic to the retina," said Dr. Tyagi.

Healaflow. Another product approved for use outside the eye is called Healaflow, a very large molecular weight, cross-linked hyaluronic acid molecule meant to be used following trabeculectomy surgery, said Dr. Stryjewski. "Its label carries a warning regarding intraocular use, but some doctors in China[2] have applied it over retinal breaks with some success," he said.

1 Park HC et al. *Expert Rev Ophthalmol.* 2014;6(6):631-655.
2 Ren XJ et al. *Retina.* 2020;40(10):1900-1908.

pit-associated macular detachments, said Dr. Tyagi.

Remaining concerns. Although Dr. Tyagi describes fibrin glue as an agent that has proved to be nontoxic to the retina, both Dr. Stryjewski and Dr. Starr expressed concerns about potential inflammatory responses. "We will need to see more success rate and safety data," said Dr. Starr, "but if the material is nontoxic and disappears completely, it shouldn't cause a lot of very late postoperative complications." Typically, fibrin glue does dissolve, he added, although there are reports of epiretinal membrane formation following its use.[4] However, this may be related to the surgery itself and not the fibrin glue, he said.

A Novel Biodegradable Hydrogel

As residents, Dr. Stryjewski and Tony Stefater, MD, PhD, asked themselves whether there might be a way to seal retinal holes without use of gas or oil to eliminate the burdens associated with postoperative recovery after vitrectomy. Seven years ago, they took on the challenge of developing a practical and stable agent by cofounding a start-up called Pykus Therapeutics; the company's hydrogel retinal sealant, PYK-1105, is now in early feasibility clinical trials.

Defining criteria. "Our goal was to give patients clear vision right after surgery by creating a material that would be biodegradable and safe inside the eye," said Dr. Stryjewski. They also sought to maintain the current steps of surgery except for the last one: injection of a sealant, rather than oil or gas. Finally, they wanted a material that would feel familiar to surgeons and be easy to use.

Pilot trial. Following years of preclinical work, they recently conducted a pilot trial to demonstrate proof of concept. "Seven patients were enrolled," said Dr. Stryjewski. "In three patients, we filled the entire posterior segment with the product, but then modified the technique in four additional patients, applying the product only to the site of the pathological breaks." In preclinical studies in rabbits and miniature pigs, there were no issues with IOP when the entire posterior cavity was filled with the product; however, in the initial three patients when it was filled, IOP challenges occurred at the time of gel breakdown, explained Dr. Stryjewski. But, he noted, there was no significant cataract progression.

Surgeons in the trial reported that the product was easy to apply when used focally. "Vision recovery occurred within days of surgery, which really surprised us," said Dr. Stryjewski.

Patient selection. "We're still learning," said Dr. Stryjewski, "but we think most detachments or retinal breaks should qualify for this technique." This includes patients with breaks in multiple quadrants or inferior tears, he said.

The procedure. With PYK-1105, the surgeon repairs the retina in the standard way, sealing the retinal breaks with laser. "Then, instead of injecting gas or oil, PYK-1105 is applied to the site of the retinal breaks using a custom applicator, and PYK-1105 then forms a barrier sealant on the retinal surface," said Dr. Stryjewski, explaining that the product comes as two components, which are mixed and activated like a fibrin glue. "At the time of application, it has a viscosity that is similar to Healon, which ophthalmologists are familiar with," he said. "It appears to be easily placed, forms a tight bond, and doesn't move around."

Recovery. The patients experience better vision the day after surgery, said Dr. Stryjewski, and the gel biodegrades and leaves the eye after several weeks. Given that retinal detachment repairs mostly fail due to a combination of PVR and poor patient adherence to face-down recovery, Dr. Stryjewski is optimistic that PYK-1105 will not only improve patients' quality of life, but also perhaps decrease the rate of PVR by providing a continuous seal against the retinal pigment epithelium, thus preventing migration of PVR constituents onto the retinal surface.

In addition, he is hopeful that the sealant may allow for smoother reattachment of the macula, permitting improved photoreceptor alignment and perhaps better vision. This hypothesis is based on a post hoc analysis of photoreceptor integrity among PIVOT study participants.[6] (PIVOT found that patients who underwent pneumatic retinopexy had better vision than those who underwent vitrectomy with face-down positioning.)

Prospects for widespread use. "We will need to compare our tamponade head-to-head to standard of care [i.e., gas] in a randomized clinical trial," said Dr. Stryjewski. "We want to offer patients a superior recovery experience after vitrectomy." That is often easier said than done, said Dr. Starr, given that no two patients have the same pathology.

More Data Needed

In some patients, these products may work well, said Dr. Starr, but safety data will be key. Certainly, many patients would prefer the quicker visual recovery, as well as the ability to travel and avoid face-down positioning. "But unless results are superior, I don't know if I would make the switch immediately," he said. "I think it would take a while to be fully adopted."

1 Tyagi M, Basu S. *Indian J Ophthalmol.* 2019;67:677-680.
2 Tyagi M, Pappuru R. *Invest Ophthalmol Vis Sci.* 2020;61(7):3707.
3 Tyagi M. Fibrin glue–assisted retinopexy for rhegmatogenous retinal detachments: GuARD study; long-term outcomes of a new surgical technique with no silicone oil or gas tamponade. Presented at ASRS; July 15, 2022: New York, N.Y.
4 Wang Q et al. *Retina.* 2020;40:718-724.
5 Lopezcarasa-Hernandez G et al. *Int J Retina Vitreous.* 2021;7:33.
6 Muni RH et al. *JAMA Ophthalmol.* 2021;139(6):620-627.

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