

Vitreous Substitutes

As vitrectomy becomes a more attractive option for treatment of a number of retinal diseases, how do surgeons fill the space formerly occupied by the vitreous?

BY ARON SHAPIRO AND RYAN BOUCHARD

Retinal detachment is a significant cause of vision loss, with an incidence of approximately 12 per 100,000 individuals in the United States.¹ One common technique in retinal repair of conditions including retinal detachments is vitrectomy, wherein the vitreous is removed from the globe of the affected eye. Although this procedure has a high success rate, one aspect that is key to a positive outcome is the type of vitreous substitute used. Many materials have been proposed and tested, but the search for the ideal vitreous substitute continues. This column examines the function of the vitreous, provides a brief history of vitreous substitutes, and considers novel substitute options.

A BRIEFING ON THE VITREOUS

The vitreous humor is a clear, gelatinous substance that occupies the space between the lens and the retina.² Composed of 98% to 99% water by weight, the vitreous is a natural polymeric hydrogel with a molecular structure of collagen fibers and hyaluronic acid.^{3,4} As a gel, it has both solid and liquid qualities, with a higher viscosity in the posterior vitreous that gradually decreases towards the anterior segment.⁵ In addition to maintenance of normal orbit turgor, the vitreous functions to circulate metabolites and nutrients throughout the eye and provides hydrostatic pressure to hold the retina in place.⁶

As the eye ages, the vitreous undergoes a transformation from a gel-like substance to a fluid-like substance. Several vision-threatening occurrences such as macular holes, retinal tears, and retinal detachments may occur as a result of the liquefaction.^{6,7} It is believed that these phenomena are caused by the traction of the liquefying vitreous on the retina and retinal vessels during normal eye movements.

A vitrectomy is performed to remove vitreous for traction relief and to obtain access to the retina. It is a common ophthalmic surgical procedure recommended for a variety of indications. Because the vitreous humor cannot regenerate, the cavity must be filled with a substitute during and after surgery. Ideally, the substitute is

At a Glance

- The vitreous humor cannot regenerate; therefore, the cavity must be filled with a substitute material during and after vitrectomy.
- Natural polymers, although a reasonable choice for a vitreous substitute, are limited by low stability.
- Commonly used vitreous substitutes (eg, expansile gases, PFCLs, and silicone oil) can be used only temporarily and they come with significant drawbacks.
- The ideal vitreous substitute will be capable of being left in the eye for a long time and will demonstrate biocompatibility.

one that closely resembles the native vitreous in both structure and function.⁸

HISTORY OF VITREOUS SUBSTITUTES

Perhaps one of the earliest mentions of the use of vitreous substitutes was in 1911 when work carried out by Ohm utilized air injected into the vitreous cavity for retinal reattachment.⁹ In 1958, silicone oil was initially proposed as a vitreous substitute, but it was not employed until several years later.¹⁰ The use of longer-acting, expansile gases such as sulfur hexafluoride (SF₆) and perfluoropropane (C₃F₈) began in the early 1970s.¹¹ Surgeons in the 1980s and 1990s used perfluorocarbon liquids (PFCLs), which are denser than water, making them particularly useful as tamponades. Chang reported the use of PFCLs for the repair of significant retinal tears.¹² In the early 2000s, semifluorinated alkanes, used either as pure liquids or in conjunction with silicone oil, were explored as an option for vitreous substitute because of their intermediate specific gravity; they are lighter than PFCLs yet heavier than water.^{13,14}

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Although natural polymers such as hyaluronic acid (HA) and collagen seem reasonable choices for vitreous substitutes, they are limited by their low stability; both are rapidly degraded by endogenous hyaluronidases or collagenases, respectively. HA was investigated as a substitute as early as the 1960s because of its native presence in the vitreous humor, but by itself it does not provide a sufficient stabilizing effect on the retina. Despite these limitations, evaluations of natural, semi-synthetic, and synthetic polymers for vitreous substitutes have long been in the works.

WHAT'S NEXT?

Commonly used vitreous substitutes designed to produce an effective tamponade for detached retinas include expansile gases, PFCLs, and silicone oil. These can be used only as temporary substitutes, however, and they come with significant drawbacks. Patients with gas substitutes need to avoid high altitudes to prevent gas expansion¹⁴ and may also be required to maintain an awkward facedown position for several days to several weeks, which can hinder compliance and surgical success. PFCLs are routinely used only intraoperatively for complicated retinal detachments because of their toxicity over longer periods of time.¹⁴ Similarly, although silicone oil is a viable option for patients who are unable to maintain prolonged facedown positioning, it must be removed to prevent long-term complications.^{6,15} Although conventional silicone oil is not an effective long-term option, heavy silicone oils are being investigated in Europe. In fact, Densiron 68 (Fluoron) and Oxane HD (Bausch + Lomb), which are not approved in the United States, are currently used in Europe.

Polymeric hydrogels represent a new class of vitreous substitutes that have the potential to circumvent the limitations of available products. Hydrogels are hydrophilic polymers that form a gel network when cross-linked and swell to form a clear viscoelastic gel.¹⁴ One such vitreous substitute is an injectable, in situ-forming hydrogel (Vitargus, BioFirst) composed of

a combination of oxidated HA (oxi-HA) and adipic acid dihydrazide (ADH). Although HA is one of the major components of the vitreous humor, and as such is an ideal candidate, it has not been an effective long-term vitreous substitute. However, when oxidized by sodium periodate to create aldehyde functional groups, it can be cross-linked with ADH to form the oxi-HA/ADH hydrogel, ultimately improving retention time, limiting degradation, and enhancing viscosity. The oxi-HA/ADH in situ-forming hydrogel transforms from liquid to gel within 3 to 8 minutes at 37°C (98.6°F) and has shown a good safety profile to date.¹⁶

CONCLUSION

As evidenced by the history and lack of long-term solutions, finding the ideal material for a vitreous substitute is challenging. Although continued work is necessary, polymeric hydrogels appear to be a viable option and the next area of development for vitreous substitutes.

Ultimately, the future of vitreous substitutes will depend on developing a formulation that can be left in the eye for a long time while demonstrating biocompatibility. A future vitrectomy that does not come with the traditional doctor's order to remain face down will improve patients' postsurgical quality of life, compliance, and surgical success rates. ■

Ryan Bouchard is director of medical devices at Ora in Andover, Mass.

Aron Shapiro is vice president of retina at Ora in Andover, Mass.



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