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Commentary

A consideration of the use of hyaluronic acid-based hydrogels in vitreous substitution

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Abstract

Vitreoretinal surgery involves the removal of the natural vitreous, which is essential for retinal adhesion, intraocular pressure (IOP) homeostasis, and optical transparency. Clinically utilized tamponades, including expansile gases, silicone oil (SO), and semi-fluorinated alkanes, necessitate face-down positioning. These tamponades frequently result in cataracts, glaucoma, or keratopathy, and invariably require a subsequent intervention for removal. As a major component of the vitreous humor, hyaluronic acid (HA) can be fabricated into injectable hydrogels with the characteristics of optical transparency, viscoelasticity, and enzyme-mediated biodegradability. These features render HA hydrogels one of the most promising candidates for vitreous substitutes. This commentary synthesizes recent polymer chemistry advances and emerging preclinical data, while critically examining early human experiences, to outline the current status and realistic trajectory of HA-based vitreous substitutes toward future clinical evaluation.

Introduction

The human vitreous is 98% water stabilized by a loose network of type-II collagen and 100-400 μg mL^{-1} high-molecular-weight hyaluronic acid (HA) (3-4 MDa). After vitrectomy its absence must be compensated by a material that preserves intra-ocular pressure (IOP) without swelling, transmits >90% visible light, resists saccadic shear (10-50 Pa), degrades within 3–6 months, and avoids secondary surgery [1]. When utilized as an intraocular tamponade, air is completely absorbed within a period of 5–7 days, resulting in a brief period of mechanical support for the retinal break. Conversely, the long-acting perfluorocarbon gases-most commonly sulfur hexafluoride (SF_6) and perfluoropropane (C_3F_8)-demonstrate a significantly longer duration of persistence [2]. Nevertheless, maintenance of the patient in the strict prone position is imperative. SO necessitates removal in ≥95% of cases and causes emulsification in 30–60%, whereas semi-fluorinated alkanes are limited by toxicity and cost. HA hydrogels promise to eliminate these sequelae by recapitulating the native gel while permitting 23G-27G injection and controlled biodegradation.

From Native HA to Covalent Networks

Native hyaluronic acid (HA) is cleared from the vitreous within 48 hours through hyaluronidase activity and free-radical depolymerization, necessitating covalent crosslinking for sustained residence [3]. Four chemistries currently dominate clinical and preclinical applications. Dynamic covalent oxime/Schiff base systems form rapidly under physiological conditions: HA-aldehyde reacts with HA-aminooxy to create oxime bonds at pH 7.4 within 30 seconds to 5 minutes without catalysts, enabling complete recovery after 95% strain within 10 seconds [4]. Similarly, oxidized HA (OHA) plus carboxymethyl chitosan (CMCTS) yields self-healing hydrazone gels injectable through 25-gauge needles [5]. Thiol-disulfide self-crosslinking utilizes cysteamine-grafted HA (SH-HA, 3-5% thiol substitution), which auto-oxidizes to disulfide networks in 2–10 minutes under ambient conditions; this approach prevents leaching of low-molecular-weight crosslinkers while allowing accelerated degradation via topical glutathione eye drops if removal is required [6]. Epoxide crosslinking with

1,4-butanediol diglycidyl ether (BDDE) represents the only system with established human dermal safety data; BDDE-HA (Healaflow®) achieves storage moduli of 50–150 Pa with 3-6 month half-lives, provided residual BDDE remains below 2 ppm, as concentrations ≥10 ppm induce caspase-3 activation in ARPE-19 cells [7]. Finally, hybrid interpenetrating networks reinforce HA with 1% silk fibroin or 2% thiolated gellan, doubling residence time while maintaining 98% water content and 95% transmittance [8,9], whereas reversible thermoresponsive PNIPAM-HA or Pluronic-HA conjugates gel at 34°C and have been employed for concomitant anti-VEGF delivery [10,11]. Due to publication bias, flawed study designs, technological advances, and ambiguous failure criteria, few failed cases have been reported in preclinical research on hydrogel-based artificial vitreous. However, not all crosslinking strategies can be successfully translated into clinically viable products. Selecting appropriate crosslinkers and optimizing crosslinking conditions remain key bottlenecks limiting clinical translation.

Physicochemical Benchmarking

Across published formulations (2019–2025) refractive index ranges 1.334–1.337 (vitreous 1.336), transmittance 90–98% (400-700 nm), water content 98–99%, density 1.005–1.025 g mL^{-1}, and G′ 10–200 Pa. All pass 27 G needles at 1000 s^{-1} shear without fragmentation [6,7,12]. However, these benchmarks are predominantly established in healthy animal eyes; their relevance to pathological human eyes with altered hyaluronidase activity, chronic inflammation, or abnormal IOP dynamics is speculative. The stated G′ range of 50–200 Pa is frequently cited as "optimal," yet clinical validation linking these values to retinal reattachment success or photoreceptor safety is absent.

Biological Performance

In vitro: extracts (1 mg mL^{-1}) maintain > 85% ARPE-19 and Müller-cell viability for 72 h; GFAP and CD68 remain at baseline for oxime and thiol gels, whereas BDDE-HA induces transient (<7 d) glial activation that normalizes by 14 days [13]. Notably, *in vitro* models cannot replicate the full complexity of the human ILM-vitreoretinal interface, including shear stress during eye movements and inflammatory cell migration. *In vivo*: rabbit and porcine vitrectomy models show successful retinal reattachment for 8–12 weeks without IOP spike or ERG amplitude loss; inflammation ≤ grade 2 resolves within a week [5,7,8,13]. These species display markedly different hyaluronidase profiles, retinal pigmentation, and cytokine responses relative to humans. Rabbit vitreous exhibits elevated baseline hyaluronidase activity, potentially overestimating degradation rates, whereas porcine eyes—though comparable in size—lack a true macula, limiting extrapolations for macular hole closure or submacular fluid resolution. Consequently, these models incompletely recapitulate human ocular physiology, particularly regarding long-term inflammatory responses, enzyme kinetics, and intraocular pressure homeostasis.

First-in-Man Experience

Healaflow® was used off-label in 12 eyes with complex inferior retinal detachment; anatomical success was 83% at 3 months without oil-related complications [7]. However, this evidence is severely limited: (i) the sample size is extremely small, (ii) no concurrent control group was included, (iii) follow-up is short for a chronic ophthalmic intervention, and (iv) off-label use introduces selection bias (only highly experienced surgeons and carefully selected patients). No long-term data on cataract progression, glaucoma incidence, or retinal toxicity beyond 12 weeks exist. These findings should be viewed as hypothesis-generating only, providing a basis for designing robust, controlled, prospective trials rather than supporting claims of imminent clinical adoption. Formal Phase I/II trials (NCT05982431) are now recruiting to establish maximum tolerated modulus (≤ 200 Pa) and crosslinker safety margin.

Remaining Challenges

Mechanical mismatch: G′<50 Pa may provide insufficient support for inferior retinal breaks, whereas G′>200 Pa risks photoreceptor stress and inner retinal compression. The optimal modulus for inferior breaks—where SO remains superior—has not been defined in humans. Substantial preclinical research is still required before HA hydrogels can be used as standalone tamponades for inferior ocular lesions. Hyaluronidase activity varies among species and pathologies; enzyme-cleavable peptide linkers or ROS-labile thioethers are being explored. But *in vivo* predictability remains a major translational hurdle. Degradation timelines of 3–6 months cannot be assumed uniform across patient populations, as variability may cause premature liquefaction or prolonged persistence. While transmittance >90% is widely reported, optical considerations—including light scattering, refractive-index mismatch at the gel-vitreous interface, and long-term clarity loss—remain underexplored. Moreover, long-term retinal safety beyond 3 months remains uncertain, particularly regarding subtle photoreceptor dysfunction or ganglion cell stress. Sterilization challenges persist, as γ-irradiation (25 kGy) reduces HA molecular weight by 30-40%, e-beam and aseptic filtration require GLP validation, scale-up is limited by medical-grade HA costs of US $40 k g^{-1}, and while recombinant microbial HA or gellan substitution may reduce costs by 60% [14], regulatory pathways for these alternatives remain nascent. Smart hydrogels coupling degradation to tissue healing via MMP-cleavable peptides hold promise but require validation in disease-relevant models. Dual-barrel syringes enabling on-demand mixing of HA-precursors with catalysts or photo-initiators could allow surgeon-controlled gelation kinetics. Patient-specific volumes derived from OCT biometry may minimize postoperative refractive shifts. Combination products releasing anti-VEGF or corticosteroids to prevent proliferative vitreoretinopathy are conceptually attractive, yet drug release kinetics and long-term stability in the eye remain poorly characterized.

Conclusions

Hyaluronic acid hydrogels have evolved from viscoelastic solutions to modular, injectable, self-gelling biomaterials that can mimic the properties of the native vitreous humor over a limited timeframe. While current evidence is primarily derived from animal models and small, uncontrolled human case series, hyaluronic acid hydrogels represent a promising research platform. A cautiously optimistic approach coupled with continued preclinical investigations is warranted.

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