

Vitreous substitutes: challenges and directions

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Abstract

• **The natural vitreous body has a fine structure and complex functions. The imitation of the natural vitreous body by vitreous substitutes is a challenging work for both researchers and ophthalmologists. Gases, silicone oil, heavy silicone oil and hydrogels, particularly the former two vitreous substitutes are clinically widely used with certain complications. Those, however, are not real artificial vitreous due to lack of structure and function like the natural vitreous body. This article reviews the situations, challenges, and future directions in the development of vitreous substitutes, particularly the experimental and clinical use of a new artificial foldable capsular vitreous body.**

• **KEYWORDS:** vitreous substitute; artificial vitreous; foldable capsular vitreous body; silicone oil

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STRUCTURES AND FUNCTIONS OF THE VITREOUS BODY

The natural vitreous body is a transparent, gelatinous structure occupying four-fifths of the volume of the eye. Its thin membrane-like structure corresponds to the vitreous cortex, which extends from the ora serrata to the posterior pole^[1]. It is somewhat spherical but slightly flattened meridionally, and there is a cup-shaped depression in its anterior surface fitted with the posterior capsule of the lens. It consists of approximately 99% water by weight, collagen fibers (types II, V/XI, VI, and IX), hyaluronic acid, opticin, fibrillin, and hyaluronan, which can maintain a certain spatial relationship with dipolar water molecules, together

with 90% hyalocytes and 10% fibroblasts near the vitreous cortex^[1,2]. In adult humans, the vitreous body has an approximate weight of 4 g, a density of 1.0053-1.0089 g/cm³, a refractive index of 1.3345-1.3348, and a pH range of 7.0-7.4.

The physiological function of the vitreous body involves supporting adjacent posterior segment structures, providing an ocular refractive medium, transporting metabolites, such as oxygen, and acting as a cell barrier to inhibit cell migration from the retina to the vitreous cavity^[3]. With age,

the natural vitreous body gradually shrinks and collapses during the course of syneresis. This phenomenon may eventually lead to posterior vitreous detachment and can play a crucial role in the formation of retinal breaks, which result in rhegmatogenous retinal detachment and a various complications of vitreomacular traction syndrome^[4].

CURRENT VITREOUS SUBSTITUTES

The vitreous body cannot regenerate, so the vitreous cavity must be filled with suitable vitreous substitutes that keep the retina in place and prevent insertion of prosthesis after enucleation of the eye. Vitreous substitutes are one of the most interesting and challenging topics of research in ophthalmology^[2]. Although the several vitreous substitutes available include inert gas, silicone oil, heavy silicone oil, and hydrogels, to date, octafluoropropane (C3F8) and sulfur hexafluoride (SF6) are the most commonly used in clinics^[2]. These gases are spontaneously absorbed in 6 to 80d and then are replaced by aqueous humor most possibly complicated with lens opacification and high intraocular pressure (IOP)^[5]. Silicone oil is hydrophobic, viscous, transparent, and stable, with a specific gravity of 0.97 g/mL and a refractive index of 1.404. The viscosity of silicone oil is measured in centistokes, and it varies linearly in chain length and molecular weight. Varieties with 1000 and 5000 centistokes are commonly used in clinics. Their surface tension is approximately 40 mN/m. Introduced by Cibis *et al*^[6] in 1962, silicone oil has been the most important adjunct for internal tamponade in the treatment of complicated retinal or choroidal detachment for the past five decades. It is commonly applied to treat superior retinal detachment through buoyancy force and high interfacial tension, and it is the only substance currently accepted as a long-term vitreous substitute. Silicone oil is the preferred choice in complex retinal detachments, such as long-standing rhegmatogenous retinal detachment, traction retinal detachment, giant retinal tears, proliferative diabetic retinopathy, and severe endophthalmitis involving the posterior segment.

However, the use of silicone oil has not always been successful. An anatomic success rate of around 70% was reported, with complications that include cataract, keratopathy, anterior chamber oil emulsification, and glaucoma. Several reports demonstrated the migration of silicone oil droplets into the retina and the optic nerve. Others showed the widespread loss of myelinated optic nerve fibers caused by the oil's free-fluid characteristics within the eye^[7,8].

Heavy silicone oil (HSO), which is a solution of perfluorohexyloctane and silicone oil prepared as an internal tamponade, has recently been used in retinal detachment surgery. However, it causes complications, such as emulsification and inflammatory reactions^[9]. The preliminary results of a recent multicentric randomized trial failed to demonstrate the real superiority of HSO in comparison with standard silicone oil in eyes with proliferative vitreoretinopathy of the lower retina^[10].

Hydrogels and smart hydrogels seem the best candidates as long-term vitreous substitutes because they show excellent transparency and good biocompatibility. They can act as viscoelastic shock-absorbing materials, thereby closely mimicking the behavior of natural vitreous body. Because hydrogels are networks of polymer chains that contain 99.9% water, they are hydrophilic and not flowable. Recently, several cross-linked polymeric hydrogels have been proposed, such as poly (vinyl alcohol) (PVA), poly (1-vinyl-2-pyrrolidone), poly (acrylamide) (PAA), and poly (ethylene glycol) (PEG)^[2,11-13]. They showed excellent biocompatibility, are biodegradable, and mimic closely the physico-mechanical properties of natural vitreous body^[2]. However, many issues, such as retinal toxicity, increased IOP, and the formation of opacities still need to be addressed. Fragmentation and changes in viscoelastic properties and resiliency after injection through a small-gauge needle have also been found in some types of hydrogels. Smart hydrogels are a relatively new class of stimuli-sensitive hydrogels. They possess the common properties of conventional hydrogels, and they can respond to a variety of signals, including PH, temperature, light, pressure, electric fields, and chemicals^[14]. Generally, smart hydrogels appear promising, but research on their use is still at an early experimental stage, and their effects of long-term toxicity are unknown^[5].

CHALLENGES TOWARDS VITREOUS SUBSTITUTES

In order to mimic perfectly the natural vitreous body, current research on vitreous substitutes aims to develop ideal materials that are nontoxic and inert and transparent, with good water and oxygen permeability, high compatibility, and good elasticity^[15-20]. The materials must be hydrophilic and capable of forming a gel within the vitreous cavity.

Therefore, although research over the past 50y has sought to replace the natural vitreous body of the eye, an ideal and permanent vitreous substitute has yet to be found^[15]. When the natural vitreous body is speculated from its normal position, it contacts very tender tissues, such as the retina, ciliary body, and lens. Therefore, the vitreous substitute must have specific eye-related compatibility. Speculated from normal functions of the natural vitreous body, the vitreous substitute must have a transparent and vitreous-closed refractive index in order to see clearly, transport metabolites, such as oxygen, and act as a cell barrier to inhibit cell migration. The vitreous substitute should also be injectable such that it easily passes through small incisions. More importantly, bio-reactions between vitreous substitutes and the eye should be seriously considered and evaluated after the vitreous substitute is injected into the vitreous cavity. Even though silicone oil is inert *in vitro*, subsequent bio-degradation is inevitable. In fact, current injected vitreous substitutes, such as silicone oil, heavy oil, and hydrogels, cannot form solid structures, and they are biodegraded by ocular humor over time. In addition, they cannot transport metabolites, such as oxygen.

NEW CONCEPT OF ARTIFICIAL VITREOUS

Silicone oil, heavy oil, and hydrogels are called vitreous substitutes instead of artificial vitreous. Similar to the artificial lens, they are solid in shape and have a refractive function. Our new concept of artificial vitreous includes these qualities. Inspired by the structure of the natural vitreous body, we postulate a novel foldable capsular vitreous body (FCVB) to restore the shape and function of the natural vitreous body^[21]. FCVB is a globally innovative product developed by the State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University and jointly produced by Guangzhou Vesber Biotechnology Co., Ltd. FCVB can be regarded as an artificial vitreous and consists of a thin vitreous-shaped capsule, a drain tube, and a valve. After foldable implantation into the eye, an injectable medium, such as a balanced salt solution (BSS), silicone oil, or hydrogels, is then injected into the capsule which inflated to support the retina. The capsular material of FCVB is silicone rubber. The capsule was fabricated *via* a computer simulation of the human and rabbit vitreous cavities. The control of the IOP is achieved with adjusting the amount of injected medium through the tube-valve system^[21]. Too much will lead to anterior segment ischemia and neovascularization. After the medium was injected into the capsule through the tube-valve system, the valve was subsequently fixed onto the sclera surface similar to the glaucoma valve (Figure 1). In our experiments with animal models, FCVB was found to mimic closely the morphology of the natural vitreous body and to restore its physiological functions, including

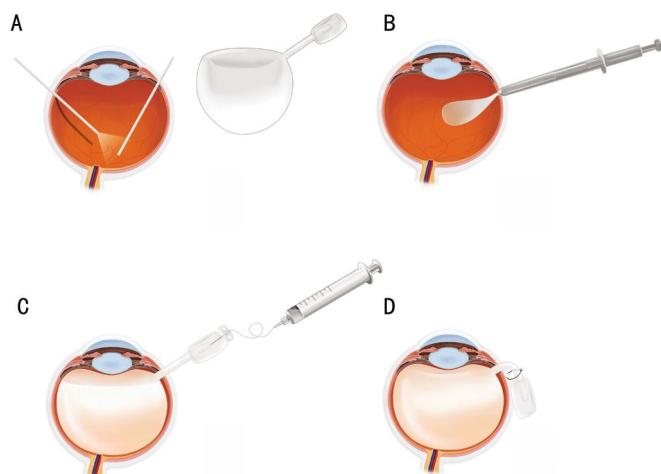


Figure 1 Implantation of the FCVB into the vitreous cavity A: Pars plana vitrectomy and fluid air exchange; B: The capsule was folded and implanted into the vitreous cavity; C: Silicone oil was injected into the capsule through a silicone tube-valve system to support the retina; D: The valve was subsequently fixed onto the sclera surface.

360-degree full-filled support, refraction, and cellular physical barriers, without obvious oxygen changes. In contrast, the silicone-oil control group showed obvious partial-filled support for the retina [22-27]. Reports by the State Food and Drug Administration in China showed that the FCVB has good mechanical, optical, and biocompatibility properties [28]. Its optical characteristics indicate that FCVB has high light transmission and laser irradiation stability.

We have conducted a pilot study on the treatment of severe retinal detachment at Zhongshan Ophthalmic Center of China. A standard three-port pars plana vitrectomy was performed, and FCVB was triple folded and sent into the vitreous cavity of three eyes; then silicone oil was injected into the capsule to support the retina. The treated eyes were examined using Goldmann applanation tonometry, fundus photography, optical coherence tomography, noncontact specular microscopy, and ultrasound biomicroscopy during a 12mo follow-up appointment. The results showed good flexibility, safety, and efficacy of FCVB in severe retinal detachment which helped avoid complications induced by silicone oil, such as silicone oil emulsification and migration within the eye, during a 12mo implantation period^[29-32]. Based on this result, a much bigger multi-center clinical trial of 122 cases in nine hospitals was conducted in China to ascertain the safety and efficacy of FCVB as an artificial vitreous. The observation periods ranged from 2.5 to 5y and the preliminary results are encouraging. No silicone emulsification was found in these patients at one-year follow-up period. The long-term effects are still under observation.

FCVB prevents silicone oil emulsification in the eye, is a long-term intraocular tamponade, and obviates the need for

ocular prosthesis implantation in some severely damaged eyes. However, because it requires a relatively bigger incision and fails to reconstruct completely the oxygen transportation function of the natural vitreous body, FCVB is recommended as an intermediate product for use between silicone oil and ocular prosthesis. Nonetheless, it shows obvious advantages compared to ocular prosthesis. FCVB is patented in 21 countries including China, the United States, Russia, Australia, and Japan. In 2012, FCVB was rated one of four advances in retinal detachment surgery worldwide^[33]. In 2013, it was rated one of the ten advances in ocular injury in China.

In addition, due to the tiny apertures in the capsule of FCVB, it can slowly release various drugs, such as dexamethasone sodium phosphate, protein kinase C α , levofloxacin, and so on. Therefore, FCVB can also be used as an intravitreal and episcleral drug delivery system^[34-40].

DIRECTIONS IN VITREOUS SUBSTITUTES

With the exceptions of silicone oil and heavy silicone oil, FCVB is the only artificial vitreous presently undergoing clinical trial. Although the problems of silicone oil emulsification and migration have been solved, and the vitreous cavity is fully filled by FCVB, many tough issues, such as maintaining the function of oxygen and metabolism transportation, need to be resolved. Therefore, much research remains to be done. Future research on vitreous substitute and artificial vitreous should focus on the following topics: solid structure and fully filling, uneasy to biodegradation by aqueous humor in the preceding 6mo, reconstructing the function of oxygen transportation and the metabolism to mimic the natural vitreous body, as well as the previously mentioned refraction, injectability, and biocompatibility.

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