

# Vitreous Substitutes

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## Abstract

*Vitreous humour is a gelatinous structure that not only maintains the intra ocular pressure but also plays an important role in nourishment of the eye. The search for an ideal vitreous substitute that is transparent, elastic and biocompatible like the vitreous itself is still on. Over a period of time, various compounds have been used such as balanced salt solution, air, gases, perfluorocarbons liquids and silicone oil. This review article looks at various conventional and investigational vitreous substitutes in detail.*

*Del J Ophthalmol 2012;23(1):9-13.*

**Key Words:** vitreous substitutes, gases, silicone oil, perfluorocarbon liquids, heavy silicone oil and polymeric vitreous substitutes.

**DOI :** <http://dx.doi.org/10.7869/djo.2012.34>

Vitreous humour is a gelatinous structure that fills the space between the lens and the retina.<sup>1</sup> Until recently functions of vitreous apart from its mechanical and optical presence, was not well understood. Now we know that vitreous, not only maintains the intra ocular pressure but also plays an important role in nourishment of the eye.<sup>2</sup> The ideal vitreous substitute should be transparent, elastic and biocompatible as is the vitreous itself. The use of intraocular vitreous substitute was first reported by Ohm in 1911, when he introduced air into the vitreous cavity to facilitate reattachment of the retina.<sup>3</sup> Over a period of time, various compounds have been used, and many of them play vital role in vitreo-retinal surgery.

*Vitreous substitutes can be divided into*

- 1) Conventional Vitreous substitutes
  - a) Gases – Air, SF<sub>6</sub>, C<sub>3</sub>F<sub>8</sub>
  - b) Liquids - Balanced salt solution, Perfluorocarbon liquids and Silicone oil.
- 2) Newer Vitreous substitutes
  - a) Semi Flourinated Alkanes
  - b) Silicone Oil/ Semi Flourinated Alkanes combinations
- 3) Experimental Vitreous substitutes
  - a) Polymers
    - Hydrogels
    - Smart hydrogels
    - Thermosetting gels

- b) Implants
- c) Cell culture

## Conventional Vitreous substitute

### Gases

#### Air

Mainly used intra operatively during fluid air exchange facilitating retinal reattachment. It is easily available and inexpensive but intraocular time is only 2-3 days, so cannot be used as long term tamponade.<sup>4</sup>

#### Expansile Gases

Both SF<sub>6</sub> and C<sub>3</sub>F<sub>8</sub> have been used commonly in pneumatic retinopexy and in non expansile concentrations for post operative endotamponade.<sup>5-7</sup> Gases have highest surface tension 70 dynes/cm<sup>2</sup> which allows them to maintain good tamponading effect.<sup>8</sup> Depending on the percentage of gas injected its intraocular stay ranges from 6-8 days.<sup>9</sup> It is eventually replaced by aqueous avoiding the need for another surgery. Although gases provide excellent results they can lead to cataract formation, corneal endothelial damage, raised IOP and central retinal artery occlusion.<sup>8,10,11</sup> Patients need to avoid change in altitude as it can lead to sudden gas expansion. Gases cannot be used for long-term tamponade in complicated cases as well as inferior tamponade in case of inferior breaks.<sup>6</sup>

### Liquids

#### Balanced Salt Solution

Balanced salt solution (BSS) is the most commonly used vitreous substitute, as irrigating solution to replace intraocular volume lost by vitreous removal intra operatively. It has also been used as vehicle to carry drugs for haemostasis, pupillary dilatation and anti-inflammatory effects.<sup>12</sup> Recently low molecular weight heparin and 5 -

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Fluorouracil have been added to infusion fluid to prevent post operative proliferative vitreoretinopathy.<sup>13</sup>

### **Perfluorocarbon liquid**

Perfluorocarbon liquid (PFCL) are fluorinated, synthetic, carbon - containing compounds that are clear, colorless, and odorless. PFCLs are immiscible and have a surface tension of approximately 14 to 16 dynes/cm<sup>2</sup> measured against air.<sup>14</sup> Perfluorocarbon liquids are also immiscible with silicone oil. PFCLs have capacity for transporting and releasing both O<sub>2</sub> and CO<sub>2</sub>.<sup>15</sup> Most remarkable property of the perfluorocarbon liquids is the specific gravity, which is higher than that of water. Typically the specific gravity range from 1.7 to 2.03. The intraoperative uses of perfluorocarbon liquids depend on their higher specific gravity, because it enables the fluid to settle posteriorly, opening folds in the retina while displacing subretinal fluid anteriorly through pre-existing retinal breaks. The direct toxicity of PFCLs and their tendency to induce inflammatory reactions limit use of PFCL as a long-term tamponade.<sup>16</sup> Commonly used PFCLs are perfluorodecalin (PFD), perfluorohexyloctane (F<sub>6</sub>H<sub>8</sub>), perfluoroperhydrophenanthrene and octafluoropropane.

### **Silicone Oil**

Silicone Oil (SO) was proposed as a vitreous substitute in 1958 but was first used for ocular surgery by Cibis in 1962.<sup>17</sup> SO are polymers of polydimethylsiloxane.<sup>18</sup> It is transparent, immiscible with water and has a refractive index of 1.4. The viscosity of silicone oil is expressed in centistokes. Most clinical trials have used 1000 and 5000 centistokes silicone oils.<sup>19</sup> Differences among the two determined by the length of the polymer, greater the length, greater the viscosity. SO is the only substance currently accepted for long-term vitreous replacement.<sup>18</sup> Recent studies suggest SO and C<sub>3</sub>F<sub>8</sub> are preferable for long-term tamponade in complicated detachments, and that SO may have advantages over C<sub>3</sub>F<sub>8</sub> in certain clinical situations such as hypotony.<sup>20</sup> It is preferable to use an SO tamponade if post-operative airplane or high elevation travel is planned, or with difficulties in post-operative positioning in children or adults with physical impairment, which makes it a more versatile replacement than air or gas. The time for the removal of SO is mostly around 3-6 months when the retina is attached and retinal traction is absent.<sup>21</sup> Anatomic outcomes and visual acuity remain stable from 6 to 24 months, which suggests a potential for longer term use.<sup>20</sup> Complications of SO are emulsification, corneal decompensation, band keratopathy, cataract and glaucoma.<sup>20</sup>

### **Newer Vitreous Substitutes**

#### **Semi Flourinated Alkanes**

PFCL offer higher specific gravity allowing it to settle posteriorly, opening folds in the retina while displacing

subretinal fluid anteriorly through pre-existing retinal breaks.<sup>22</sup> A long-term PFCL can set up quite high pressure on the choroid beneath the retina, so that the blood supply to the capillary system is impaired. The low specific gravity of Semi Flourinated Alkanes (SFA) (compared to PFCLs) is thought to produce less retinal damage.<sup>23</sup> SFAs are physically, chemically and physiologically inert, colorless and laser stable with densities reduced to between 1.1 and 1.7g/cm<sup>3</sup>. SFAs are soluble in PFCLs, hydrocarbons, and silicone oils and have a refractive index of 1.3.<sup>24</sup> SFAs' higher interface tension than silicone oil may bridge larger retinal breaks. They have been seen to be well tolerated in the eye upto 3 months, but main limitations are early emulsification and cataract formation.<sup>24,25</sup>

#### **Silicone Oil/ SFA combinations**

Till now, no single agent has fulfilled the criterion for an ideal vitreous substitute. Also, none of the available agents provide adequate inferior tamponade, hence by combining the SO and SFAs, the combination takes advantage of the high viscosity of SO and high specific gravity of the SFAs to produce a vitreous substitute with a good tamponade effect and lesser chance of emulsification.<sup>26</sup> SFA is soluble in SO but the solubility is dependent on the viscosity of SO and molecular weight of SFA. Higher the viscosity of SO and higher the molecular weight of SFA both make it less soluble in each other.<sup>24</sup> The combination of both produce either a homogenous clear solutions (heavy silicone oils) or separated solutions (double fills) depending on the ratio of the two liquids.

#### **Heavy Silicone Oil**

Heavy Silicone Oil (HSO) is heavier than water. It is a mixture of SO and a SFA producing a homogenous solution. Newer HSOs are viscous, stable and better tolerated, resulting in longer time tamponade and lesser emulsification.<sup>27</sup> Commonly used agents are Densiron 68, Oxane HD and HWS 46-3000. Recent studies have shown good anatomical and visual outcomes with no emulsification upto 3 months with these agents.<sup>28-30</sup> HSO works well as a long-term tamponade agent for complex retinal detachments involving inferior proliferative vitreoretinopathy.<sup>31</sup>

#### **Double Fill**

Double fill (DF) was originally thought to bring about simultaneous superior and inferior tamponade. Since both SFA and SO are hydrophobic it is possible to produce a single bubble with two layers, one layer providing upper support (SO) and the other providing inferior support (SFA).<sup>32</sup> However, DF may not provide enough superior support, as it produces an "eggshaped" bubble with pure F<sub>6</sub>H<sub>8</sub> inferiorly and a lighter solution of F<sub>6</sub>H<sub>8</sub> dissolved in silicone oil superiorly; the bubble as a whole behaves as a tamponade that is heavier than water.<sup>27</sup>

## Experimental vitreous substitutes

### Polymers

Focus of recent vitreous substitute research has been on polymeric hydrogels. Hydrogels are hydrophilic polymers that form a gel network when crosslinked and are capable of absorbing several times their weight in water and swell.<sup>33</sup> The result is typically a clear viscoelastic gel that strongly resembles the natural vitreous humor. Hydrogels are more favorable vitreous substitutes because they are clear, tend to be biocompatible and can act as a viscoelastic dampener, much like the natural vitreous. Since hydrogels enable diffusion of ions or small particles, they are also currently used as drug delivery devices in the eye.<sup>34</sup> Their diffusion properties will allow oxygen, nutrients and growth factors to be either implanted in the hydrogel or to pass through from other parts of the eye. The main problem with preformed polymeric hydrogels as vitreous substitutes is that they shear thin upon injection into the eye and lose their elasticity and become more fluid like.<sup>35</sup>

In contrast to injecting a preformed hydrogel that would cause the gel to shear and lose elasticity, hydrogels are injected in aqueous form and then transformed into a gel in situ using a disulfide crosslinker that would retain structure and swell in the eye. Polyvinyl alcohol - methacrylate (PVA-MA) is one such hydrogel which is injected in aqueous form, containing a photoinitiator that can form a hydrogel in situ when irradiated with the proper wavelength of UV radiation.<sup>36</sup> Others like copolyacrylamide gel are first made soluble by reducing disulfide cross-linked bridges and then soluble gel can then be injected which undergoes gelation in situ upon exposure to oxidation by air.<sup>37</sup>

A relatively newer hydrogel, known as smart hydrogel, are stimuli-sensitive and can respond to a variety of signals including pH, temperature, light, pressure, electric fields, or chemicals.<sup>38</sup> These are ionic hydrogels that respond to environmental stimuli creating a closed feedback loops for drug delivery and other applications. Another experimental agent WTG-127 (Wakamoto Pharmaceutical, Tokyo, Japan) is a type of thermo-setting gel that can gelate at 36°C and retains transparency upon gelation.<sup>39</sup>

The main limitation of hydrogels is biocompatibility as it can trigger an immune reaction leading to inflammation and phagocyte mediated disappearance of the gel within weeks of injection.<sup>40</sup> Also, WTG-127 investigators noticed that the gel could drift under a retinal tear.<sup>39</sup> Hence due to early experimental nature of these materials and unknown complications associated with them, they are still at an early experimental stage, but do look promising.

### Implants

Implantable devices may be able to support the retina and control intraocular pressure without the need of a potentially reactive and biodegradable intravitreally injected solution. Foldable capsular vitreous bodies (FCVB)

injected with either saline or silicone oil showed good biocompatibility and retinal support in rabbit eyes over a 180-day implantation time. It is a thin, vitreous-shaped capsule made of a silicone rubber elastomer with a silicone tube valve system filled with a physiologically balanced solution or silicone oil.<sup>41</sup> The silicone rubber capsule has shown good biocompatibility and is easily implanted and removed experimentally in rabbit eyes. Over an 8-week treatment period, there was no corneal opacity, intraocular inflammation, or vitreal opacity but there was a high incidence of cataracts in the rabbit eyes, whether they were caused by the material of the FCVB or the lens structure of their eyes should be further evaluated.

### Cell Culture

Recently, hyalocyte cultures have developed, which produce hyaluronic acid and other vitreous components.<sup>42</sup> This could possibly lead to artificial generation of vitreous in vitro, which in turn would solve many problems with artificial substitutes. Vitreous synthesis could be stimulated by hyalocyte proliferation, which has been demonstrated with ascorbic acid in a dose-dependent manner by increasing collagen production and mRNA expression of cells in vitro.<sup>43</sup> Control of hyalocyte growth can be regulated by specific growth factors such as bFGF (stimulates) and TGF- $\beta$ 1 (inhibits).<sup>44</sup>

### Conclusion

Although various vitreous substitutes are available, there have been issues with the complications that come along with them. Intraocular gases have a risk of elevating intraocular pressure (IOP) and fast intraocular absorption. Conventional substitutes like silicone oil are widely used, but despite retinal attachment rate being 80%, it needs to be removed early because of complications like emulsification, secondary glaucoma and keratopathy. Heavy silicone oil looked promising because of its heavy gravity but unfortunately, it had the weaknesses of significant intraocular inflammatory reactions and caused more severe complications than conventional silicone oil. Polymers seem to be more biocompatible but they biodegrade quickly.

FCVBs injected with either saline or silicone oil showed good biocompatibility and retinal support but incidence of cataracts was unresolved hence the influence of FCVB on the human lens should be further evaluated. The long-term biocompatibility of these materials needs to be investigated, and to this day there is still a lack of suitable materials to replace the vitreous body.

## References

1. Sebag J, Balazs EA. Morphology and ultrastructure of human vitreous fibers. *Invest Ophthalmol Vis Sci* 1989; 30:1867-71.
2. Sebag J. Imaging vitreous. *Eye* 2002;16:429-39.
3. Peyman GA, Ericson ES, May DR. A review of substances and techniques of vitreous replacement. *Surv Ophthalmol* 1972; 17:41-51.
4. Marcus DM, D'Amico DJ, Mukai S. Pneumatic retinopexy versus scleral buckling for repair of primary rhegmatogenous retinal detachment. *Int Ophthalmol Clin* 1994; 34:97-108.
5. Chan CK, Lin SG, Nuthi AS, Salib DM. Pneumatic retinopexy for the repair of retinal detachments: a comprehensive review (1986-2007). *Surv Ophthalmol* 2008; 53:443-78.
6. Chang TS, Pelzek CD, Nguyen RL, Purohit SS, Scott GR, Hay D. Inverted pneumatic retinopexy: a method of treating retinal detachments associated with inferior retinal breaks. *Ophthalmology* 2003; 110:589-94.
7. Mansour AM. Inverted pneumatic retinopexy. *Ophthalmology* 2004; 111(7):1435.
8. Kim RW, Bauman C. Anterior segment complications related to vitreous substitutes. *Ophthalmol Clin North Am* 2004; 17:569-76.
9. Thompson JT. The absorption of mixtures of air and perfluoropropane after pars plana vitrectomy. *Arch Ophthalmol* 1992; 110:1594-7.
10. Lee DA, Wilson MR, Yoshizumi MO, et al. The ocular effects of gases when injected into the anterior chamber of rabbit eyes. *Arch Ophthalmol* 1991; 109:571-5.
11. Wilkinson C, Rice T. Instrumentation, materials, and treatment alternatives, in Craven L (ed) *Michels Retinal Detachment*. St. Louis, MO, Mosby, ed 2 1996, pp 391-461.
12. de Bustros S, Glaser BM, Johnson MA. Thrombin infusion for the control of intraocular bleeding during vitreous surgery. *Arch Ophthalmol* 1985; 103:837-9.
13. Asaria RH, Kon CH, Bunce C, Charteris DG, Wong D, Khaw PT, Aylward GW. Adjuvant 5-fluorouracil and heparin prevents proliferative vitreoretinopathy: Results from a randomized, double-blind, controlled clinical trial. *Ophthalmology* 2001; 108:1179-83.
14. Chang S. Low viscosity liquid fluorochemicals in vitreous surgery. *Am J Ophthalmol* 1987; 103:38-43.
15. Peyman GA, Schulman JA, Sullivan B. Perfluorocarbon liquids in ophthalmology. *Surv Ophthalmol* 1995; 39:375-95.
16. Orzalesi N, Migliavacca L, Bottoni F, et al. Experimental short-term tolerance to perfluorodecalin in the rabbit eye: a histopathological study. *Curr Eye Res* 1998; 17:828-35.
17. Cibis PA, Becker B, Okun E, Canaan S. The use of liquid silicone in retinal detachment surgery. *Arch Ophthalmol* 1962; 68:590-9.
18. Kreiner CF. Chemical and physical aspects of clinically applied silicones. *Dev Ophthalmol* 1987; 14:11-9.
19. Foster WJ. Vitreous substitutes. *Expert Rev Ophthalmol* 2008; 3:211-8.
20. Azen SP, Scott IU, Flynn HW Jr, et al. Silicone oil in the repair of complex retinal detachments. A prospective observational multicenter study. *Ophthalmology* 1998; 105:1587-97.
21. Pastor JC. Proliferative vitreoretinopathy: an overview. *Surv Ophthalmol* 1998; 43:3-18.
22. Ferenc Kuhn, Dante J. Pieramici. *Ocular Trauma: Principles and Practice*. Page 434
23. Matteucci A, Formisano G, Paradisi S, et al. Biocompatibility assessment of liquid artificial vitreous replacements: relevance of in vitro studies. *Surv Ophthalmol* 2007; 52:289-99.
24. Meinert H, Roy T. Semifluorinated alkanes - A new class of compounds with outstanding properties for use in ophthalmology. *Eur J Ophthalmol* 2000; 10:189-97.
25. Kirshhof B, Wong D, Van Meurs J, et al. Use of perfluorohexyloctane as a long-term internal tamponade agent in complicated retinal detachment surgery. *Am J Ophthalmol* 2002; 133:95-101.
26. Wetterqvist C, Wong D, Williams R, et al. Tamponade efficiency of perfluorohexyloctane and silicone oil solutions in a model eye chamber. *Br J Ophthalmol* 2004; 88:692-6.
27. Heimann H, Stappeler T, Wong D. Heavy tamponade 1: a review of indications, use, and complications. *Eye* 2008; 22:1342-59.
28. Rizzo S, Genovesi-Ebert F, Belting C, et al. A pilot study on the use of silicone oil-RMN3 as heavier-than-water endotamponade agent. *Graefes Arch Clin Exp Ophthalmol* 2005; 243:1153-7.
29. Rizzo S, Genovesi-Ebert F, Vento A, et al. A new heavy silicone oil (HWS 46-3000) used as a prolonged internal tamponade agent in complicated vitreoretinal surgery: a pilot study. *Retina* 2007; 27:613-20.
30. Sandner D, Engelmann K. First experiences with highdensity silicone oil (densiron) as an intraocular tamponade in complex retinal detachment. *Graefes Arch Clin Exp Ophthalmol* 2006; 244:609-19.
31. Lim BL, Vote B. Densiron intraocular tamponade: a case series. *Clin Experiment Ophthalmol* 2008; 36:261-4.
32. Herbert E, Stappeler T, Wetterqvist C, et al. Tamponade properties of double-filling with perfluorohexyloctane and silicone oil in a model eye chamber. *Graefes Arch Clin Exp Ophthalmol* 2004; 242:250-4.
33. Kopecek J. Polymer chemistry: swell gels. *Nature* 2002; 417:388-91.
34. Maruoka S, Matsuura T, Kawasaki K, et al. Biocompatibility of polyvinylalcohol gel as a vitreous substitute. *Curr Eye Res* 2006; 31:599-606.
35. Swindle KE, Hamilton PD, Ravi N. In situ formation of hydrogels as vitreous substitutes: viscoelastic comparison to porcine vitreous. *J Biomed Mater Res A* 2008; 87:656-65.
36. Cavalieri F, Miano F, D'Antona P, et al. Study of gelling behavior of poly-methacrylate for potential utilizations in tissue replacement and drug delivery. *Biomacromolecules* 2004; 5:2439-46.
37. Swindle-Reilly KE, Shah M, Hamilton PD, et al. Rabbit study of an in situ forming hydrogel vitreous substitute.

- Invest Ophthalmol Vis Sci* 2009; 50:4840-6.
38. Chaterji S, Kwon IK, Park K. Smart polymeric gels: redefining the limits of biomedical devices. *Prog Polym Sci* 2007; 32:1083-122.
  39. Katagiri Y, Iwasaki T, Ishikawa T, et al. Application of thermo-setting gel as artificial vitreous. *Jpn J Ophthalmol* 2005; 49:491-6.
  40. Vijayasekaran S, Chirila TV, Hong Y, et al. Poly(1-vinyl-2-pyrrolidinone) hydrogels as vitreous substitutes: histopathological evaluation in the animal eye. *J Biomater Sci PolymEd* 1996; 7:685-96.
  41. Gao Q, Mou S, Ge J, et al. A new strategy to replace the natural vitreous by a novel capsular artificial vitreous body with pressure-control valve. *Eye* 2008; 22:461-8.
  42. Nishitsuka K, Kashiwagi Y, Tojo N, et al. Hyaluronan production regulation from porcine hyalocyte cell line by cytokines. *Exp Eye Res* 2007; 85:539-45.
  43. Sommer F, Kobuch K, Brandl F, et al. Ascorbic acid modulates proliferation and extracellular matrix accumulation of hyalocytes. *Tissue Eng* 2007; 13:1281-9.
  44. Sommer F, Pollinger K, Brandl F, et al. Hyalocyte proliferation and ecm accumulation modulated by BFGF and TGF-beta1. *Graefes Arch Clin Exp Ophthalmol* 2008; 246(9):1275-84.



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