Vitreon, a new perfluorocarbon


Abstract
We evaluated a new liquid perfluorocarbon, perfluorophenanthrene (Vitreon). This material has proved to be non-toxic in vitrectomised rabbit eyes for up to six weeks. Present investigation under FDA guidelines establishes both the safety and efficacy of Vitreon in human eyes. We used Vitreon for intraoperative hydrokinetic retinal manipulation in 15 patients. In cases of proliferative vitreoretinopathy (6), rhegmatogenous retinal detachment (5), giant retinal tear (2), retinal dialysis (1), and tractional retinal detachment (1) the retina was successfully reattached. Postoperatively two patients developed proliferative vitreoretinopathy necessitating further surgery, and one patient developed hypotony. Follow-up showed 100% reattachment rate with a mean duration of 6-3 months. Postoperative visual acuity ranges from light perception to 20/30.

Although a denser-than-water vitreous substitute (fluorosilicone oil) was studied in 1962 in retinal detachment surgery, its importance in complex cases such as giant tears was recognised much later.1 The liquid fluorocarbons were initially introduced as oxygen carriers in medicine in 1966.2 Haidt et al used these substances for the first time as a vitreous substitute in 1982.3 Other investigators soon evaluated similar substances.4-16 Inherent in all perfluorocarbon liquids have been potential toxic effects on the retina within a short period of exposure.

In 1989 Nabih et al presented experimental evaluation of a new liquid fluorocarbon. The substance, perfluorophenanthrene (Vitreon), was found to be safe for up to six weeks in the vitrectomised eyes of New Zealand white rabbits if contact with the cornea was avoided.17 We used Vitreon as an intraoperative tool in the management of patients with complex retinal detachments in a limited phase I Food and Drug Administration (FDA) evaluation.

Patients and methods
Fifteen patients were recruited for this study, a phase I investigation under FDA guidelines. Informed consent was obtained under an investigational protocol approved by the institutional review board at the Louisiana State University in New Orleans. Of the 15 patients six presented with proliferative vitreoretinopathy (PVR) stages C2-D2, five with rhegmatogenous retinal detachment and peripheral tear; two with giant retinal tear; one with retinal dialysis; and one with tractional retinal detachment (Table 1). Nine patients (60%) were male and six (40%) female. The mean age was 48-5 years, range 28 to 79 years. Preoperative visual acuity ranged from 20/400 to light perception.

A standard 20-gauge three-port pars plana approach was used for vitrectomy. Once removal of the vitreous was completed, the decision to use Vitreon intraoperatively was made. The Vitreon was initially injected through a blunt 20 to 27 gauge needle over the optic disc. In the learning phase of the study it was discovered that a partial air-fluid exchange was necessary during the Vitreon injection process in order to tamponade the peripheral retina (Fig 1A, B, C). After a partial air-fluid exchange was performed, injection of Vitreon over the posterior pole was completed at a slow rate to allow displacement of the subretinal fluid anteriorly. In rhegmatogenous retinal detachments with peripheral breaks the subretinal fluid was forced from a posterior to an anterior direction out of the peripheral tear. The same procedure was used for giant retinal tears as well as with retinal dialyses with unfolding of the retinal flap. In complicated PVR cases, after membrane peeling a small amount of Vitreon was injected to determine if the retina would flatten at this point. If traction was still evident, more dissection from a posterior-to-anterior direction was attempted. The other option consisted in performing varying degrees of retinotomies or retinectomies. At this point partial air-fluid exchange was performed to tamponade the peripheral intact retina or the remaining retinal skirt in the case of a 360° retinectomy. The posterior vitreous cavity was then filled with Vitreon. Endolaser photo-coagulation was then performed under Vitreon at the end of the operation when the retina was completely flat. An air-Vitreon exchange was then performed in all cases, with subsequent partial air-fluid exchange in an attempt to remove all the remaining Vitreon (Fig 1D, E). At this point a decision was made either to maintain the air inside the eye with subsequent SF₆ (15-20%) or C₃F₈ (10-15%) injection or to inject silicone oil for a longer tamponading effect. In eight eyes (53%) intraocular gas was used; in six eyes (40%) silicone oil (12 500 centistokes was used; and in one eye (7%) fluorosilicone oil (300 cSt) was used. A no 20 silicone band was then placed at the equator, and cryopexy was done at the sclerotomy sites.

Follow-up of the patients consisted in examin-
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IMPLANTATION

REMOVAL

Figure 1  Vitreon implantation (A and B) with partial air-fluid exchange during injection process (C). Vitreon removal (D and E) with multiple fluid washings.

The surgeons directed the use of Vitreon daily until stable, then weekly, bimonthly, and monthly for the first six months. Attention was directed to any excessive postoperative inflammation, cataract formation, intraocular pressure rise, membrane development, and retinal detachment. Any residual Vitreon noted in the eye postoperatively was removed by air-fluid or fluid-fluid exchange at the slit-lamp. Those eyes with silicone oil complications such as keratopathy, cataract formation, or emulsification were treated by immediate oil removal. Recurrent retinal detachments were repaired with another operation.

Results

Vitreon was effective in flattening the retinas in all 15 cases intraoperatively. In four cases intraoperatively, after removal of the Vitreon a retadetachment occurred progressing from the periphery to the posterior pole. By careful examination we found that part of the subretinal fluid was trapped in the peripheral portion of the retina beyond the retinal tear. This situation necessitated a partial air-fluid exchange to the level of the retinal tear followed by further intravitreal injection of Vitreon. The peripheral air bubble flattened the anterior retina while the Vitreon reattached the posterior retina. No other intraoperative complications related to the use of Vitreon were experienced.

Table 2 shows the postoperative results of the 15 patients. No patients had any unusual inflammatory or toxic reaction related to the use of Vitreon. One patient experienced a postoperative rise in intraocular pressure most likely related to the use of intraocular gas. Five patients had residual intraocular Vitreon bubbles, which were subsequently removed at the slit-lamp. Future cases then required multiple air-fluid exchange to ensure complete removal of the Vitreon. None of the patients with residual Vitreon showed an increased inflammatory reaction or keratopathy related to the Vitreon. One patient had a vitreous haemorrhage postoperatively secondary to an underlying bleeding diathesis. The blood cleared spontaneously over a six to eight week period.

Two patients experienced recurrent retinal detachments secondary to PVR. Both patients underwent successful surgery with membrane peeling and reattachment of the retina. Two patients in the series developed hypotony postoperatively with intraocular pressure of less than 5 mmHg, and another developed significant macular pucker. Overall, the retina was finally reattached in all the patients, with a mean follow-up duration of 6-3 months and a range of four to nine months. Postoperative visual acuities were better than or equal to the preoperative visual acuities in all cases except for patient five, who developed PVR necessitating another operation (Table 2).

Discussion

Perfluorophenanthrene (Vitreon) contains inherent physical properties necessary for a
Table 2  Postoperative results

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex (Years)</th>
<th>Nature Rd</th>
<th>Preop. vis. acuity</th>
<th>Intraop. complications</th>
<th>Postop. complications</th>
<th>Follow-up (months)</th>
<th>Postop. vis. acuity</th>
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<tbody>
<tr>
<td>1</td>
<td>50 M</td>
<td>Rhegmatogenous</td>
<td>CF</td>
<td>0</td>
<td>Residual Vitreon</td>
<td>5</td>
<td>20/60</td>
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<td>2</td>
<td>32 M</td>
<td>RD with dialysis</td>
<td>CF</td>
<td>0</td>
<td>Exotropia</td>
<td>9</td>
<td>20/30</td>
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<tr>
<td>3</td>
<td>68 F</td>
<td>Rhegmatogenous</td>
<td>20/400</td>
<td>Relegation due to redetachment</td>
<td>Rhegmatogenous haemorrhage; residual Vitreon; Increased IOP</td>
<td>8</td>
<td>20/200</td>
</tr>
<tr>
<td>4</td>
<td>39 F</td>
<td>Tractional with vitreous haemorrhage</td>
<td>HM</td>
<td>0</td>
<td>PVR with redetachment, reoperation</td>
<td>8</td>
<td>LP</td>
</tr>
<tr>
<td>5</td>
<td>48 M</td>
<td>Rhegmatogenous with choroidal detachment</td>
<td>HM</td>
<td>Choroidal detachment; relegation due to redetachment</td>
<td>PVR with redetachment, reoperation with Vitreon</td>
<td>7</td>
<td>HM</td>
</tr>
<tr>
<td>6</td>
<td>64 F</td>
<td>Rhegmatogenous</td>
<td>LP</td>
<td>0</td>
<td>PVR with redetachment, reoperation with Vitreon</td>
<td>5</td>
<td>20/70</td>
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<tr>
<td>7</td>
<td>58 F</td>
<td>PVR D1 and Macular hole</td>
<td>CF</td>
<td>0</td>
<td>Hypotony</td>
<td>7</td>
<td>CF</td>
</tr>
<tr>
<td>8</td>
<td>79 F</td>
<td>PVR DI</td>
<td>CF</td>
<td>0</td>
<td>Vitreon</td>
<td>4</td>
<td>CF</td>
</tr>
<tr>
<td>9</td>
<td>33 M</td>
<td>Rhegmatogenous with choroidal detachment</td>
<td>LP</td>
<td>Relegation of fluorosilicone due to redetachment</td>
<td>PVR</td>
<td>5</td>
<td>20/100</td>
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<tr>
<td>10</td>
<td>28 M</td>
<td>Giant tear</td>
<td>HM</td>
<td>0</td>
<td>Cataract</td>
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<tr>
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<td>PVR G1</td>
<td>LP</td>
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<td>6</td>
<td>CF</td>
</tr>
<tr>
<td>13</td>
<td>49 M</td>
<td>PVR D1</td>
<td>LP</td>
<td>0</td>
<td>Residual Vitreon</td>
<td>5</td>
<td>CF</td>
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<tr>
<td>14</td>
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<td>CF</td>
<td>0</td>
<td>Macular pucker</td>
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<td>CF</td>
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<tr>
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<td>35 F</td>
<td>PVR G1</td>
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desirable denser-than-water temporary vitreous substitute. It has a specific gravity of 2.03, a viscosity of 8.03 cSt, and a boiling point of 215°C. It is immiscible with water, optically clear, and easily injected and removed through a small (20–27 gauge) needle. Past experimental studies with this substance have demonstrated no toxicity to culture-grown retinoblastoma cells. Vitreon was not toxic to the vitrectomised rabbit eyes when left in place for six weeks. No acute toxic or inflammatory reactions were noted during the operation or in the immediate post-operative period. In rabbit eyes fragmentation of the Vitreon into small globules in the vitreous cavity was noted at six weeks, which is later in onset than for previously studied liquid fluorocarbons. Postoperative electroretinographic recordings revealed no pathological changes in eyes tested. Light and electron microscopy of rabbit eyes at the end of follow-up showed retention of normal retinal architecture with no evidence of retinal toxicity. Corneal toxicity was noted, however, on injection of Vitreon into the anterior chamber of rabbit eyes as evidenced by corneal oedema.

In the present study we used Vitreon to facilitate rettachment of the retina in a variety of complex vitreoretinal disorders. None of the eyes showed any adverse or toxic effects directly related to its use, either intraoperatively or postoperatively. Even the eyes with inadvertent small amounts of Vitreon in the anterior chamber postoperatively failed to show any corneal toxic effects.

Modifications in the injection and removal techniques were made as experience was gained during the progression of the study. A few of the earlier patients were noted postoperatively to have small amounts of Vitreon remaining intraocularly. As a result all subsequent cases underwent multiple air-fluid exchanges in order to achieve complete removal of the Vitreon. Also during the injection a unique problem was confronted early in the series. In patients with rhegmatogenous retinal detachments with peripheral tears or holes Vitreon was used to 'steamroll' the subretinal fluid from the posterior pole out through the anterior retinal tear. This was achieved simply by injecting the Vitreon over the optic disc and observing the flattening effect as the Vitreon level rose. However, on removal of the Vitreon redetachment occurred in some cases as the liquid fluorocarbon level decreased. In these cases subretinal fluid was pushed by Vitreon pressure in the periphery past the retinal tear, not escaping through the defect. On removal of the Vitreon the subretinal fluid simply shifted back to its posterior gravity-dependent position. To avoid this complication in subsequent cases we performed a limited air-fluid exchange prior to filling the vitreous cavity with the Vitreon, causing the air bubble to tamponade the retina anterior to the tear. Vitreon injection over the optic disc was continued, slowly displacing the subretinal fluid out through the peripheral break, but not allowing it to go anterior to this point. Once the retina was flat, a perfluoropropane and/or cryotherapy was applied, and the air-fluid exchange was completed with resultant complete reattachment of the retina.

The diversity of preoperative diagnoses in our series demonstrates the potential utility of Vitreon in vitreoretinal surgery. Five patients presented with rhegmatogenous retinal detachments with peripheral breaks. Vitreon was used as described above, thus avoiding a posterior retinotomy for internal drainage of subretinal fluid. This step bypassed the potential complications associated with posterior retinotomies, such as bleeding and reproliferation from the site of the retinotomy.

Many different techniques have been proposed for management of giant retinal tears; liquid fluorocarbons are the most recent method to be investigated. Two patients in our study presented with giant retinal tears. Vitreon injection after vitrectomy greatly simplified the repair of these difficult cases. Injection was begun over the optic disc. Further injection resulted in the unfolding of the retina, hydrodynamically tamponading the retina back against the retinal pigment epithelium with the patient in a supine
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The substance was a poor long-term vitreous substitute because of the dispersion, foam cell response, and photoreceptor toxicity if the retina was exposed to it for longer than two weeks. Chang et al. subsequently reported on the use of perfluorotributylamine and perfluorodecalin intraoperatively in four patients with good intraocular tolerance. In the management of traumatic retinal detachments Chang reported the intraoperative use of three liquid perfluorocarbons (perfluorotributylamine, perfluorodecalin, and perfluorocarbons) in 14 patients. Of 11 eyes, with at least six months' follow-up, eight (73%) had the retina anatomically reattached. Giant retinal tears have also been successfully treated by intraoperative liquid fluorocarbons.

In all previous studies of liquid fluorocarbons the intraocular tolerance of them has been shown to be very poor when left in the eye postoperatively. The properties of the ideal denser-than-water vitreous substitute must also include an inert nature providing ample ocular tolerance. Investigation of Vitreon has proceeded in a step-wise fashion. The first investigation established good ocular tolerance in rabbit eyes for up to six weeks. The next phase of study is presented here, with the establishment of good ocular tolerance in human eyes intraoperatively. The next step in the order of progression will be to leave the Vitreon in human eyes postoperatively until the formation of a firm chorioretinal scar. Thus Vitreon would provide a short-term tamponading effect that is occasionally desirable in complicated cases. We are now evaluating this phase of the study.

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The Vitreon was donated by Vitrophage Inc, Downer's Grove, IL, USA.

The other disadvantage is found when comparing the viscosity of the two substances. The viscosity of fluorosilicone oil ranges from 300 to 10,000 cSt, thus greatly hampering both the injection and removal of this substance. Vitreon, with a viscosity of 8-03 cSt, is injected and removed from the eye as easily as balanced salt solution. This factor is important during intraoperative removal of the vitreous substitutes. Vitreon removal is accomplished easily by passive flow through a flute needle. The fluorosilicone oil, however, must be removed with an extraction needle at high suction, which can be dangerous under air because of rapid swings of intraocular pressure when air is aspirated.

Previous studies of liquid fluorocarbons have been performed by various investigators. Miyamoto et al. looked at two separate perfluoroether liquids, Freon E15 and Fomblin-H Fluorinated Fluid, finding both substances to be unsuitable vitreous substitutes owing to poor ocular tolerance of them. More recently Chang and associates studied perfluorotributylamine (C12F27N) in rabbit eyes and observed good intraoperative tolerance, but poor postoperative tolerance when left in the eye. They concluded