

In Vivo and In Vitro Feasibility Studies of Intraocular Use of Seprafilm to Close Retinal Breaks in Bovine and Rabbit Eyes

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PURPOSE. Seprafilm, a sodium hyaluronate/carboxymethylcellulose absorbable barrier developed to prevent adhesions after abdominal surgery, adheres well to wet tissue. The authors studied the efficacy of this film for sealing retinal breaks in animals.

METHODS. In an in vitro study, a retinal detachment with a hole was created in bovine eyecups after the vitreous gel was removed. Seprafilm was placed over the retinal hole, and the strength of the retinal adhesion was measured by pulling the film. Permeability was tested by applying methylene blue to the film covering the retinal break. Seprafilm also was soaked in balanced salt solution (BSS) incubated at 37°C, and the pH of the BSS containing Seprafilm was measured as it melted. In an in vivo study, Seprafilm was powdered and mixed in BSS solution, and 0.1 mL was injected into the right vitreous cavity in study rabbits. The same amount of BSS was injected into the right vitreous cavity in control rabbits. Ophthalmologic examinations were performed. Bilateral electroretinograms were recorded simultaneously before and 6 weeks after injection. Both eyes were enucleated for histologic evaluation.

RESULTS. Seprafilm adhered well to the retina, was impermeable to methylene blue, and remained solid in BSS for 30 days before it dissolved, and its pH ranged from 7.2 to 8.0. No intraocular inflammatory reaction occurred after intravitreal injection of Seprafilm solution. There was no significant difference in amplitudes or implicit times of electroretinogram a-waves, b-waves, and oscillatory potentials before and after injection and between study and control groups. No significant retinal abnormality was detected by light microscopy in either group.

CONCLUSIONS. The film adhered well to the retina with no signs of ocular toxicities. Further study is warranted for possible means of patching retinal breaks. (*Invest Ophthalmol Vis Sci*. 2006;47:1142-1148) DOI:10.1167/iops.05-0931

Proliferative vitreoretinopathy (PVR), a major cause of surgical failure in retinal detachment, results from cellular proliferations that lead to membrane formation on the retina.

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Contraction of these membranes pulls the retina from the retinal pigment epithelium (RPE) and subsequently opens the break(s), resulting in total retinal detachment. Among the important cells that may be responsible for membrane formation are the RPE cells.¹ Covering the retinal break appears to be a logical approach to prevent the migration of the RPE cell into the vitreous cavity and, thus, to prevent PVR.²

The authors studied the efficacy of Seprafilm II Adhesion Barrier (Genzyme Corporation, Cambridge, MA), which was developed to help prevent adhesions after abdominal and pelvic surgery,^{3,4} for patching retinal breaks.

MATERIALS AND METHODS

Patch

Seprafilm II Adhesion Barrier is a bioresorbable transparent membrane composed of United States Pharmacopeia (USP)-modified anionic polysaccharides, sodium hyaluronate, and carboxymethylcellulose. USP glycerol was added for improved flexibility. Preclinical studies have demonstrated that this membrane is nontoxic, nonimmunogenic, and biocompatible for patients undergoing abdominal or pelvic surgery. Within 24 to 48 hours of placement, the membrane turns to a hydrophilic protective gel that remains in the peritoneal cavity for up to 7 days to reduce adhesion formation by acting as a physical barrier to separate adjacent traumatized serosal tissues during the critical early stages of wound repair. This membrane adheres strongly to moist tissues.^{5,6}

In Vitro Study

Strength of Adhesion. We first tested whether Seprafilm remains adherent to the retina in balanced salt solution (BSS). The anterior segment (cornea, iris, lens) of a bovine eye was excised, and the vitreous was removed to make an eyecup. A retinal detachment with a hole was created in the bovine eyecup. The hole was covered by Seprafilm, and the eyecup was filled with BSS (Fig. 1). The Seprafilm was pulled forcefully to measure the strength of the retinal adhesion. A thin cotton thread was glued to the center of a piece of Seprafilm 6 mm in diameter using cyanoacrylate. A piece of the bovine eye wall containing the retina, choroids, and sclera was fixed on a board using 27-gauge needles. The Seprafilm with the thread was placed on the retina, and the whole board, including the Seprafilm, was put into the BSS. One end of the thread was put through a pulley, and the other end of the thread was attached to a cup (Fig. 2). Distilled water was dropped into the cup until the Seprafilm lifted from the retina or the retina tore. Then the amount of distilled water was measured, with the amount in the cup indicating the adhesive force of the film—that is, the more water in the cup, the stronger the adhesive force. Measurements were performed six times. The same method was performed to test the strength of a piece of a copy paper and plastic wrap instead of Seprafilm to compare the strength of the retinal adhesion.

Permeability and Flexibility. To test the permeability of the film, four bovine eyecups were prepared, and the vitreous gel was removed from each cup. A full-thickness hole was created using an

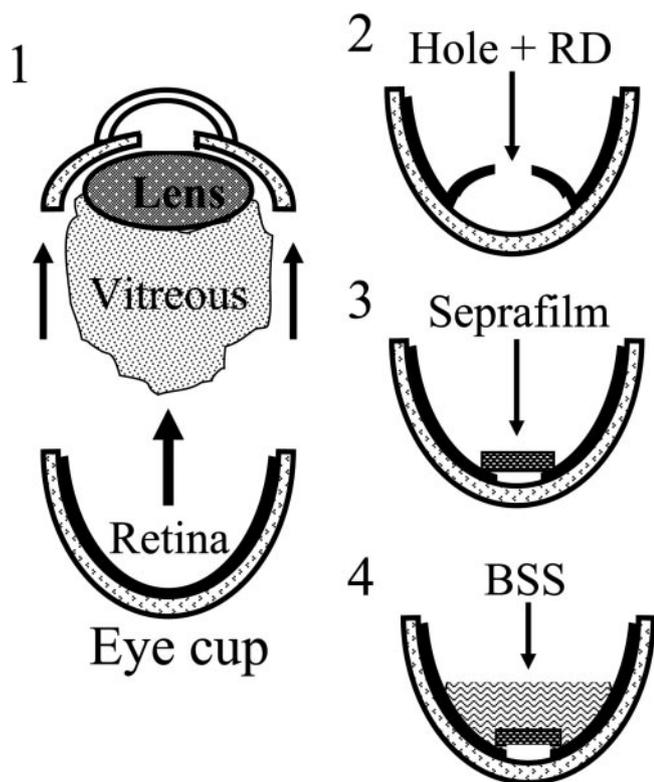


FIGURE 1. Diagram of the process for testing whether Seprafilm adheres to the retina in BSS. (1) Anterior segments (cornea, iris, lens) of a bovine eye are excised, and vitreous is removed to make an eye cup. (2) Retinal hole and retinal detachment are created. (3) Retina is reattached, and the hole is covered with Seprafilm in the air. (4) Eye cup is filled with BSS.

18-gauge needle at the bottom of each eye cup. In three of four eye cups, the holes were covered by Seprafilm; the other eye cup was used as a control, and the hole was not covered.

To test the flexibility of the material, four additional bovine eye cups with full-thickness holes were prepared. In three of four of the eye cups, the holes were covered by Seprafilm that had been folded once and then unfolded. For intraocular delivery, Seprafilm is folded first, passed through the small sclerotomy wound, and unfolded inside the eye to cover the retinal break. We tested whether this process of folding and unfolding the Seprafilm cracks the film. The other eye cup, without any covering, was used as a control.

All eight eye cups then were placed on white paper, and 0.3 mL methylene blue was diluted 10 times with BSS. Applying diluted methylene blue to the retinal surface covered by Seprafilm allowed us to observe whether the methylene blue penetrated the film to the paper after 1 hour.

Melting Time. To determine the time at which the film melted, six small (6×6 mm) pieces of Seprafilm and six glass tubes containing 8 mL BSS were prepared. The film was soaked in BSS and incubated at 37°C . The BSS was exchanged for fresh BSS every 24 hours, and the time to dissolution of the film was recorded.

pH. The pH of the Seprafilm in the BSS Plus (Alcon, Inc.) also was measured periodically. The pH of BSS Plus was approximately 7.4, and that of BSS was approximately 7.0. The BSS Plus was used for pH measurement because the pH of BSS Plus was closer to that of the human environment. Two samples each of three sizes of Seprafilm (6×6 , 12×12 , and 24×24 mm) and six glass tubes containing 8 mL BSS Plus (pH 7.2 ~ 8.2) were prepared. Each piece of Seprafilm was soaked in BSS Plus, and six glass tubes with 8 mL BSS Plus without Seprafilm served as controls. All glass tubes were incubated at 37°C .

The pH was measured by a pH meter 1, 3, 6, 12, 24, 36, 48, and 72 hours after Seprafilm was placed in the BSS Plus.

In Vivo Study

New Zealand Albino rabbits, each weighing 3.0 to 4.0 kg, were used. The study conformed to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Intravitreal Injection. All procedures were carried out with a sterile technique under a surgical microscope. Twelve rabbits were divided into two groups (six study rabbits and six control rabbits). The right pupil of each rabbit was dilated with 2.5% phenylephrine and 1% cyclopentolate eye drops. Rabbits were anesthetized by intramuscular ketamine hydrochloride (35 mg/kg), xylazine (5 mg/kg), and acepromazine (0.75 mg/kg). Topical anesthesia (0.5% proparacaine drops) was applied to the eyes. Seprafilm was minced into a powder and mixed in the BSS (200 mg/mL), and 0.1 mL of the solution was injected into the right vitreous cavity of each study animal. The needle was advanced under direct visualization toward the region of the optic disc as closely as possible to the retina. BSS 0.1 mL was injected into the vitreous cavity without Seprafilm in the right eyes of the control animals.

Clinical Examination. Slit lamp microscopy, funduscopy by indirect ophthalmoscopy, and fundus photography were performed with dilated pupils the day before injection and 1, 7, 14, 28, and 42 hours after surgery.

Electroretinograms. Under systemic and topical anesthesia and with the pupils dilated, electroretinograms (ERGs) were recorded 2 weeks before and 6 weeks after intravitreal injection of Seprafilm solution. A xenon flash (Grass Instruments, Quincy, MA) attached to a Ganzfeld screen (PS22; Grass Instruments) provided the stimulus for ERG. Maximal stimulus intensity in luminance was $75.4 \text{ cd} \cdot \text{s}/\text{m}^2$. This

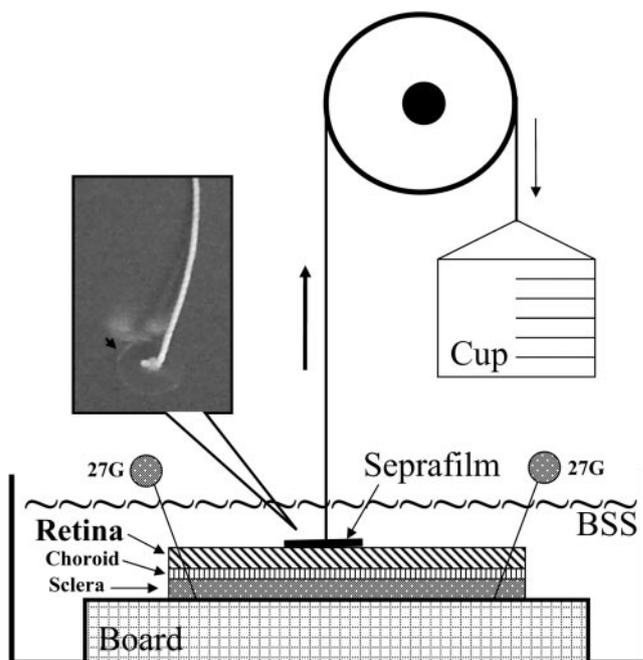


FIGURE 2. Diagram of the set-up to measure adhesive force of the Seprafilm to the retina. Section of the full-thickness wall of the eye, retina side up, is pinned with a 27-gauge needle to a board inside a container. A small piece of Seprafilm is placed on the wet retinal surface. (inset) A thread is fixed on the center of the Seprafilm (arrowhead) with cyanoacrylate. A lightweight cup is attached to the other end of the thread through a pulley. Water is dropped slowly into the cup until the cup falls.

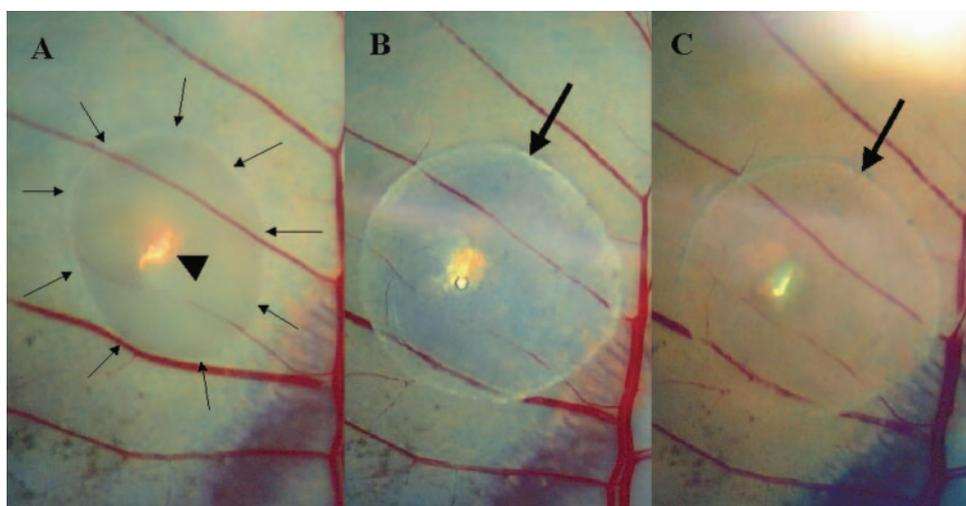


FIGURE 3. Photographs showing the Seprafilm covering the retinal break in the eyecup. (A) *Arrowhead* indicates retinal break; *small arrows* indicate retinal detachment. Seprafilm has not yet been applied. (B) The retinal break is covered with a round piece of Seprafilm (*arrow*). (C) Seprafilm remains attached to the retina in the BSS 2 hours after application.

maximal intensity was attenuated in 1.0-log unit steps by neutral density (ND) filters (ND, 4.0–1.0).

ERG responses were amplified by an evoked potential measurement system (Neuropack Sigma MEB5508; Nihon Kohden, Tokyo, Japan) with a bandpass filter (0.2–500 Hz for a-waves and b-waves; 50–500 Hz for oscillatory potentials). Two bipolar Burian-Allen-type contact lens electrodes were used to record ERG responses from both eyes simultaneously.

After 30 minutes of dark adaptation, the recording was started with the weakest stimulus using a 4.0-log unit ND filter; the stimulus was increased stepwise to ND 3.0 until no filter was used. No background light was used. At each light intensity, three responses were averaged for a- and b-waves. Photopic responses were recorded without an ND filter providing stimulus every second. The 10 responses were averaged. Amplitude and implicit time ratios were calculated between the right and left eyes. Two-tailed paired *t* test was used for statistical analysis to examine the relation before and after intravitreal injection. Paired *t* test was used for statistical analysis to examine the relation between study and control groups.

Histology. Rabbits were killed with an overdose of pentobarbital 6 weeks after injection, and the eyes were enucleated for histologic

study. After enucleation, all eyes were fixed in 2% paraformaldehyde and 2.5% glutaraldehyde solution, dehydrated with serial alcohols, and embedded in paraffin. Sections cut at 4 μ m were stained with hematoxylin and eosin and examined under a light microscope.

RESULTS

Adhesion of the Seprafilm to the retina was relatively strong in BSS; the film still adhered 2 hours after application (Fig. 3). When the strength of the adhesion was measured, it was observed that the retina had detached and tore with 1.5 to 2.5 mL of water in the eyecup, but the Seprafilm did not detach (Fig. 4). Paper and plastic detached from the retina in all cases as soon as they were put in the BSS and before any weight was applied.

Methylene blue did not go through the Seprafilm placed on the white paper in any eyecups except those in the control group (Fig. 5). The film did not crack; rather, it remained flexible despite folding.

Considering the water-soluble components of Seprafilm, the film might easily have washed away from the retinal surface.

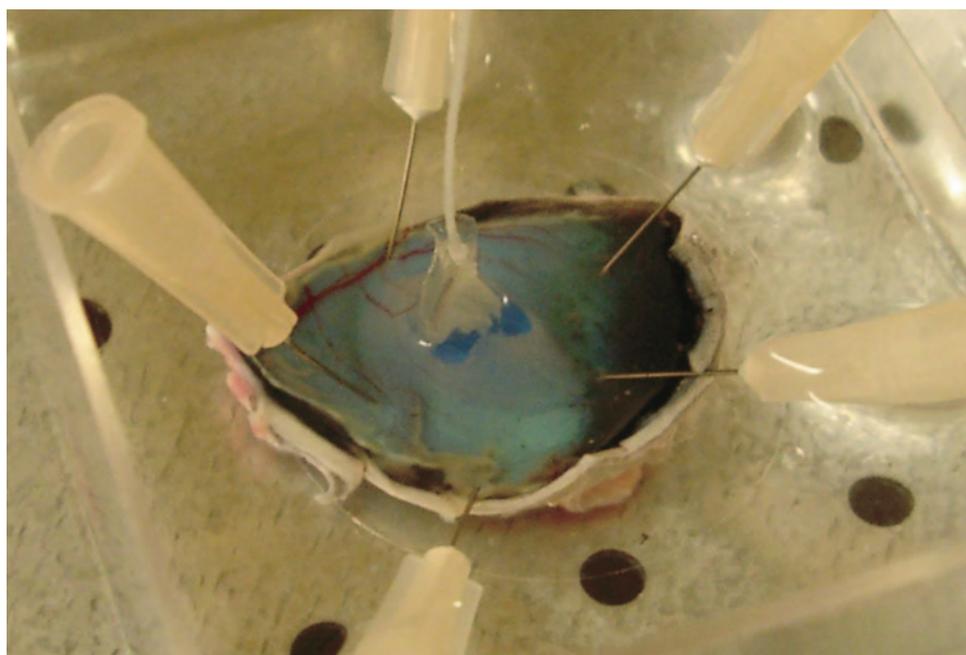


FIGURE 4. Photograph showing that the retina adhered to the Seprafilm is detached and torn but that the surrounding piece of Seprafilm remains on the retina, as in the experiment depicted in Figure 1.

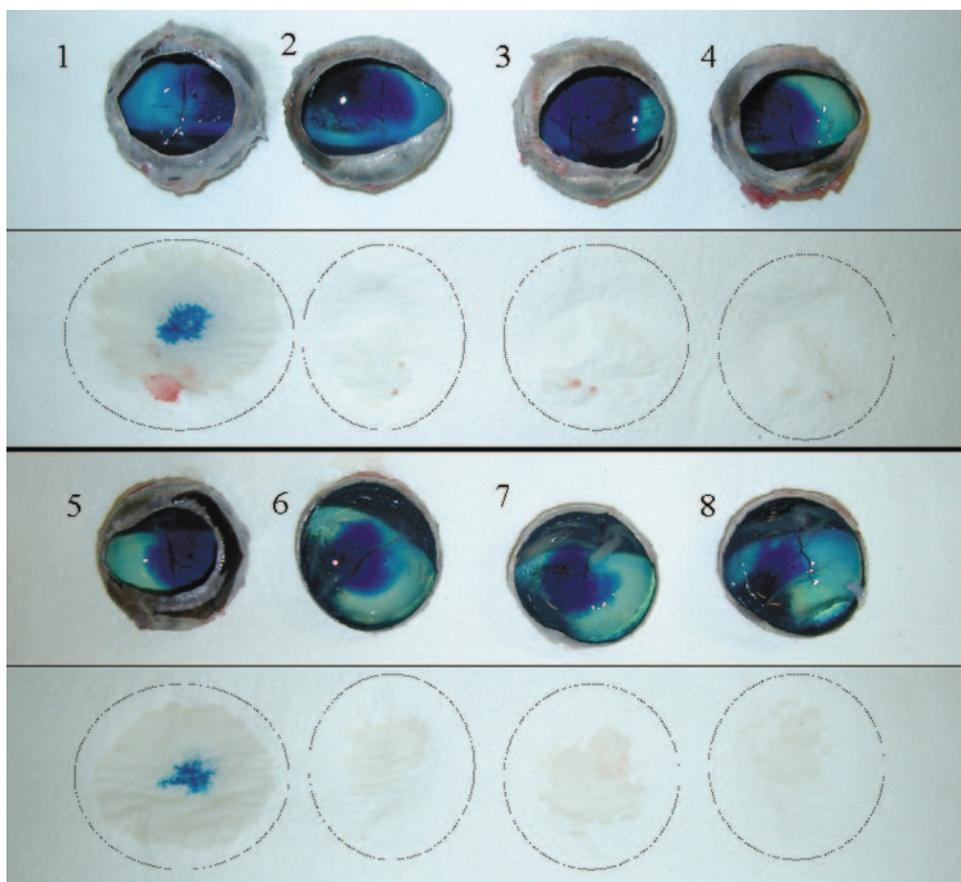


FIGURE 5. Photographs showing no permeability of Seprafilm to water. Two bovine eyecups were used as controls; the full-thickness retinal hole was not patched with Seprafilm. (1, 5) Seprafilm covers the hole. (2, 3, 4) Once folded and unfolded, Seprafilm is applied. (6, 7, 8) Methylene blue does not seep onto the underlying white paper. (2, 3, 4, 6, 7, 8). Underlying paper stained with methylene blue in two control eyes with no patching.

However, the Seprafilm remained solid in BSS for 30 days, after which time it dissolved completely.

The pH of the BSS Plus in which the Seprafilm was placed was from 7.2 to 8.0 at all time points. It was neutral for intraocular use.

No inflammatory reaction was observed in the eyes in which Seprafilm solution was injected during the 6-week follow-up. Slit lamp and indirect ophthalmoscopy examinations showed normal corneas, aqueous, crystalline lenses, and retinas at all time points. Seprafilm solution injected into the vitreous cavity became invisible 5 days after injection. Thereafter, the vitreous was clear.

ERGs recorded before and after injection showed the typical components of an ERG: a slowly rising b-wave without an a-wave at lower stimulus intensities and an a-wave followed by a rapidly rising b-wave at the higher stimulus intensities. Oscillatory potentials were recorded with higher stimulus intensities. Figure 6 shows the ERGs from both eyes recorded 6 weeks after injection of Seprafilm solution. In the amplitude ratio of the a-wave in ND1, slight increases were seen for study and control groups after injection (Fig. 7). There was no significant difference in the amplitude ratios or implicit time ratios of the a-waves, b-waves, and oscillatory potentials of the ERG at any stimulus intensity level before and after injection and between study and control groups.

Histologic examination with a light microscope did not reveal any abnormality or inflammation in either group at the end of the study.

DISCUSSION

Closing all the retinal breaks is an essential part of treating retinal detachments. The scleral buckling, cryopneumopexy,

and vitrectomy used to treat retinal detachment all attempt to bring the entire edge of the retinal break into contact with the RPE and to create adhesion between the sensory retina and the RPE. Most retinal detachments can be resolved by one of these surgical procedures. However, occasionally the breaks are brought into contact with the RPE with complete retinal reattachment at the time of surgery, but the retina later detaches when PVR develops. One such case is that of retinal detachment with giant retinal tears, considered significant factors in the development of PVR.⁷ In the presence of a giant tear, the surgeon may reattach the retina completely and apply laser treatment around the tear. However, a relatively large area of the RPE remains exposed to the vitreous because edge-to-edge closure of the tear is not usually accomplished. The exposure of a large area of RPE can give the RPE cells a chance to migrate to the vitreous and initiate the cascade of events leading to the development of PVR. In fact, no procedure used today to reattach the retina closes the retinal break; all current procedures simply put the edge of the retinal tear in contact with the RPE. Unless edge-to-edge closure of the retinal tear is accomplished, the break remains open to the vitreous cavity. Attempts have been made to ablate the RPE by laser or to scrape the exposed RPE cells mechanically to treat giant retinal tears while relieving vitreous traction with vitrectomy or a scleral buckle with some success.⁸ However, if it is not performed gently, ablating the RPE can cause hemorrhage and intraocular inflammation.⁸ A better method would be to cover or patch the breaks.² Retinal detachments may occur in rare diseases, such as from breaks in choroidal coloboma or optic nerve coloboma. Conventional treatment may not work because of the lack of underlying pigment in patients with choroidal coloboma or an unusual location of the break in patients with optic nerve coloboma. The ideal treatment would be to plug

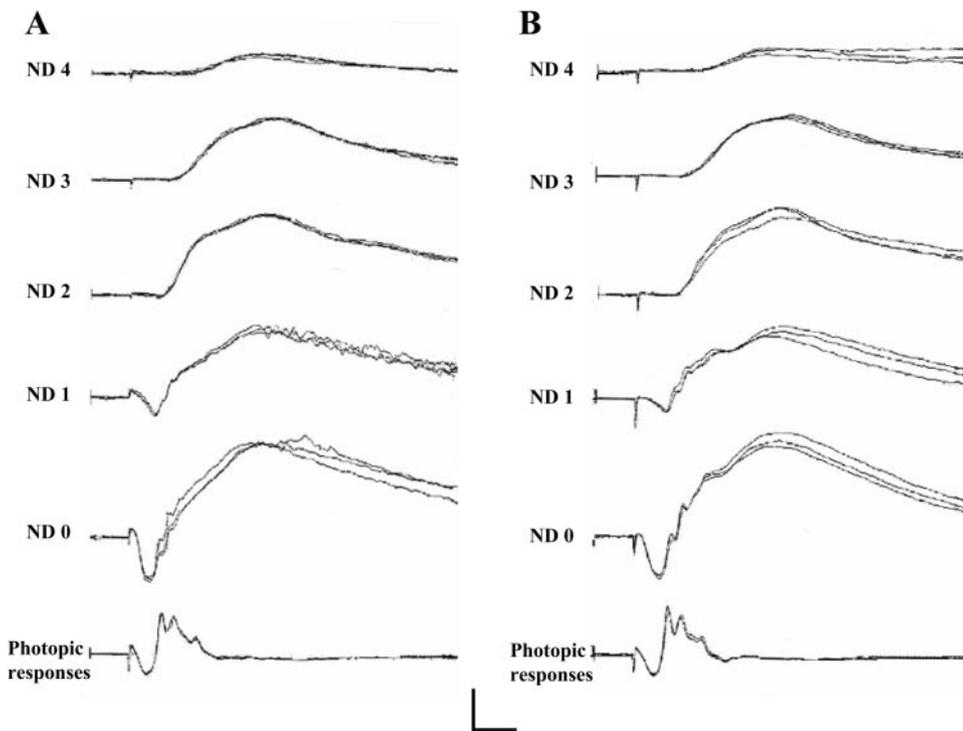


FIGURE 6. ERGs recorded from (A) right eye and (B) left eye simultaneously 6 weeks after injection of Seprafilm solution into the right eye. Three responses were superimposed. Numbers to the left of the ERGs (ND4-ND0) represent the log unit neutral density filters used to reduce the full-intensity stimulus. At 0 or no filter, luminance was 75.4 cd · s/m². Bar, 100 μV and 20 ms.

the retinal hole with tissue adhesive; this has been done successfully using cyanoacrylate.⁹⁻¹³

Cyanoacrylate, a glue that has been evaluated by a number of investigators,^{2,14-21} is already used to treat human eyes.⁹⁻¹³ N-butyl-2-cyanoacrylate has been used in retinal detachments from giant tears caused by perforating injury,⁹ complicated retinal detachments from PVR associated with inferior retinal breaks or retinotomy,¹⁰ retinal detachment associated with

retinal breaks within a choroidal coloboma,^{11,13} recurrent holes in the macula,^{11,12} and breaks after dissection of the preretinal membrane during open-sky vitrectomy in retinopathy of prematurity.¹¹ However, the use of cyanoacrylate has serious drawbacks. Rapid polymerization makes application and delivery extremely difficult. This problem appeared to have been solved by mixing cyanoacrylate with iophendylate used as a contrast agent for myelography; this technique is

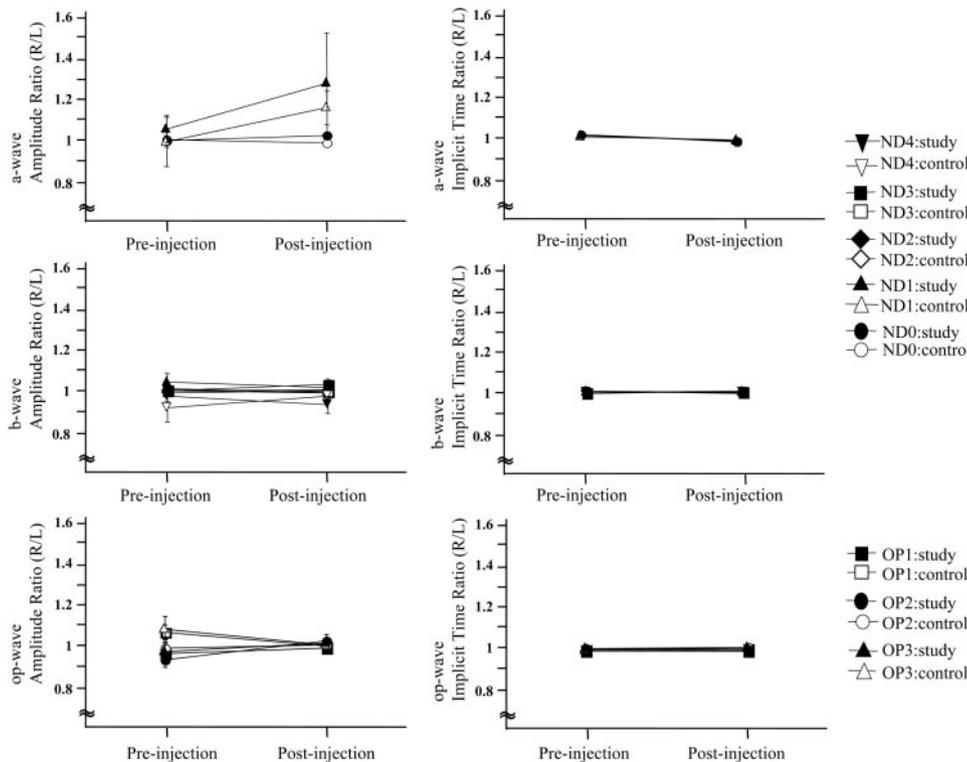


FIGURE 7. Amplitude ratio and implicit time ratio between right and left eyes of a-wave, b-wave, and oscillatory potentials at all stimulus intensity levels before and after injection in study and control groups. OP indicates oscillatory potential.

rarely used today, and the agent is not readily available. Furthermore, cyanoacrylate forms a hard mass rather than a thin sheet of membrane, making it difficult to cover a large retinal tear.

Fibrin glue^{2,9,22-25} appears to be nontoxic to retinal glia in tissue culture. It is usually refined from bovine blood or from human autologous serum. Although it is less likely to cause a foreign body reaction, doubts exist as to the adhesive qualities of fibrin in the posterior segment.²²⁻²⁴ Coleman et al.²⁵ treated giant retinal tears by applying fibrin glue to the edges of the breaks after vitrectomy; however, none of the giant tears remained flat after surgery because fibrin glues are effective for only 4 to 6 days.

Other adhesives^{9,26,27} evaluated for retinopexy are mussel protein, transforming growth factor-beta (TGF- β), and polysiloxanes. Mussel protein adhesive (Cell-Tak; Becton Dickinson, Bedford, MA) caused an inflammatory response.²⁶ Although breaks were sealed with TGF- β , cryotherapy and internal tamponade are still necessary. TGF- β seems to have the same disadvantage as fibrin glue, namely, temporary adhesion.²⁷ The polysiloxane adhesive is advantageous in that it can be delivered in an aqueous environment, but it causes a localized granulomatous tissue reaction.⁹ The search for a better adhesive continues because of limitations of the previously described adhesives. Some are toxic to the retina, others lack adequate adhesive strength. Alternative synthetic retinal glues, such as hydrogels, are now being tested. Margalit et al.²² tested the suitability of some biologic adhesives for ophthalmic use in a study of three polyethylene glycol hydrogels, commercial fibrin sealant, autologous fibrin sealant, mussel adhesive, and three photocurable glues and showed that mussel protein adhesive caused retinal damage, especially to the retinal ganglion cell layer, and that fibrin glue and photocurable glue had lower strength of adhesion to the retina. Hydrogels proved to be superior for intraocular use in terms of consistency, adhesiveness, stability, impermeability, and safety, though they and other liquid gels are disadvantageous in that the application area is limited to the posterior pole. When applied to the side of the fundus, the liquid descends as the result of gravity from the area of application. Moreover, when liquid glue is applied to a retinal hole or break, the glue tends to slip under the retina, partially because of the difficulty of mixing the two components of the glue—one gel and the other liquid—before delivery of the mixture to the retinal break. Therefore, a method of mixing the two components of the glue effectively and a method of intraocular delivery right after mixing must be developed.

Seprafilm is water soluble and will not permanently patch retinal breaks. The membrane eventually dissolves in the vitreous fluid. The behavior of the RPE cells covered by Seprafilm is important; it is unknown whether RPE cells stay viable under the patch and migrate to the vitreous and proliferate once the patch is dissolved. The concern is that when the Seprafilm dissolves, the RPE cells may start to become active. Further study of these factors is needed. Seprafilm appeared to effectively patch the retinal break in our in vivo experiment. It did not migrate to the subretinal space, and it was not toxic to the eye.

An effective intraocular delivery system must be developed. We tried to insert a small piece of Seprafilm through the vitrectomy opening in the air-filled animal eye with vitreous forceps, one of which carried the light pipe. However, the surgical maneuver to cover the retinal break inside the eye was technically difficult. We are now developing a system whereby minced Seprafilm is sprayed against the retinal break.

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