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Patching retinal breaks with polyethylene glycol-based synthetic hydrogel sealant for retinal detachment in rabbits

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ABSTRACT

The purpose of this study was to evaluate absorbable polyethylene glycol (PEG)-based synthetic hydrogel as a sealant for retinal breaks in rhegmatogenous retinal detachment (RD). A three-port, 25-gauge vitrectomy was performed on nine Dutch pigmented rabbit eyes. Subsequently, RD was induced by creating a retinal break. The retina was then reattached by fluid-air exchange. In six of nine eyes (RD-PEG group), PEG sealant was applied to completely cover the retinal breaks, and then photopolymerized with light; thereafter, intravitreous air was replaced with balanced salt solution (BSS). In the remaining three eyes (RD group), PEG sealant was not applied, but the intravitreous air was replaced with BSS. Ophthalmological examinations and intraocular pressure measurements were conducted preoperatively, and at 1 and 7 days, and 1, 3, and 6 months postoperatively. Histological examinations of the eyes were performed after 6 postoperative months. At surgery, retinal reattachment with PEG sealant was achieved in all eyes in the RD-PEG group. Fundoscopic and optical coherence tomographic examinations revealed that the retina remained attached in all the eyes of the RD-PEG group throughout the 6-month observation period. Histological examination revealed no signs of damage in the retinal layers at the edges of the retinal breaks that were in contact with the sealant. In the RD group, the retinas detached in all eyes within 7 days postoperatively. The PEG sealant closed the retinal breaks and maintained retinal reattachment. Intraocular tamponade was not necessary.

1. Introduction

Rhegmatogenous retinal detachment (RD) is generally treated with scleral buckling, vitrectomy with vitreous tamponade by air, gas, or silicone oil, combined with cryotherapy, or laser photocoagulation in most cases (Schepens et al., 2000; Brinton and Wilkinson, 2009). However, failures do occur in some cases, but most are associated with proliferative vitreoretinopathy. Sealing retinal breaks with a material such as glue or film seems to be a logical approach for preventing vitreous fluid from flowing through the open retinal breaks into the subretinal space. Such a sealant would also obviate the need for gas or silicone oil tamponade, which are used to prevent fluid from re-entering the retinal breaks, and therefore may also obviate the need for face-down posturing for an extended period of time postoperatively.

Some adhesives, such as cyanoacrylate, fibrin glue, sodium hyaluronate/carboxymethylcellulose absorbable film, mussel protein, transforming growth factor β, and polysiloxanes, have been used to seal retinal breaks in the treatment of RD for many years (McCuen et al., 1986, 1987; Hida et al., 1988; Faulborn and Witschel, 1978; Hartnett and Hirose, 1998; Hotta et al., 1998; Sheta et al., 1990; Nasaduke and Peyman, 1986; Coleman et al., 1988; Smiddy et al., 1989; Liggett et al., 1990; Sueda et al., 2007); however, each has its own drawbacks, including potential ocular toxicity, difficulty in intraocular delivery, weak adhesive force, inflammatory response, and granulomatous tissue reaction. For these reasons, the use of glue has not yet become a standard procedure in the treatment of RD. A better material that is effective, non-toxic, and easy to use is urgently needed to seal retinal breaks.

We previously reported that an absorbable polyethylene glycol-based synthetic hydrogel (PEG sealant) adhered to the retina *in vitro*, was not toxic to the retina *in vivo*, and could be utilized in the treatment of rhegmatogenous RD (Hoshi et al., 2015). In the present study, we investigated if and how this PEG sealant is capable of patching retinal breaks in detached retinas in rabbits.

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2. Materials and methods

2.1. PEG sealant

The PEG sealant (FocalSeal; Genzyme Corporation, Cambridge, MA, USA) used in this study, which has been approved by the U.S. Food and Drug Administration (FDA) as a sealant to limit air leakage following pulmonary resection, is an absorbable PEG-based synthetic hydrogel that can be polymerized with visible illumination from a xenon arc lamp (450–500 nm, blue green) for 40–60 s to form a clear, flexible, and firmly adherent hydrogel that seals air and fluid leaks (Ranger et al., 1997; Macchiarini et al., 1999). This material is water soluble and absorbed by the body over a 1–6-month period, then eventually excreted (Ranger et al., 1997; White et al., 2000; Alleyene et al., 1998).

2.2. Experimental rhegmatogenous retinal detachment

Nine pigmented Dutch rabbits (weighing 2.0–3.0 kg; Kitayama Labes Ltd., Nagano, Japan) were used in our study. The nine rabbits were divided into two groups: one group included six rabbits that underwent retinal patching with the PEG sealant (RD-PEG group); the other group included three rabbits with RD, but the breaks were not patched (RD group). The study conformed to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. All procedures were performed on the left eye of each experimental animal using sterile techniques. The animals were anesthetized with intramuscular injections of ketamine hydrochloride (35 mg/kg) and xylazine (5 mg/kg). Topical anesthesia (0.4% oxybuprocaine hydrochloride drops) was also applied to the eyes. The pupils were dilated with topical 0.5% phenylephrine hydrochloride, 0.5% tropicamide, and 1% atropine.

An experienced vitreoretinal surgeon (F.O.) performed a 3-port, 25-gauge vitrectomy in each study animal. Each rabbit underwent the following procedures. The conjunctiva was prepared using 5% povidone-iodine solution. A conjunctival peritomy was performed at the corneoscleral limbus for 120°, clockwise from the 10 to 2 o'clock positions. Three-port, 25-gauge sclerotomies were performed 1 mm from the corneoscleral limbus by trocar insertion (Alcon Laboratories, Inc., Fort Worth, TX); one port was used for the infusion cannula, while the other two ports were used for the vitreous cutter and endoilluminator optical fiber. Subtotal vitrectomy was performed using the Constellation Vision System (Alcon Laboratories, Inc.) under a surgical microscope with a fundus wide-angle viewing system (Resight; Carl Zeiss Meditec AG, Jena, Germany). The lens was not removed. Posterior vitreous detachment was created and core vitrectomy was performed, utilizing triamcinolone acetonide in the vitreous to enhance visibility of the cortical vitreous gel. After subtotal vitrectomy, a retinal break, approximately one half to 1 disc diameter (DD) in size, was made 2 DD inferior to the optic disc with an extrusion needle. A balanced salt solution was gently infused under the retina through the retinal break to create a localized retinal detachment which was approximately 3–5 DD in size (Fig. 1A). Fluid-air exchange was performed to reattach the retina. Then, in the RD-PEG group, PEG sealant was applied with a 27-gauge needle through a trocar cannula to completely cover the retinal break (Fig. 1B), then was polymerized by a 60 s application of intraocular xenon light (420–700-nm wavelength) from the Advanced Xenon Illuminator of the Constellation Vision System (Fig. 1C). The air in the vitreous was replaced with balanced salt solution (Fig. 1D). The RD group underwent the same procedures as the RD-PEG group, except PEG sealant application and application of intraocular xenon light. All scleral ports and conjunctival wounds were closed with 8-0 vicryl sutures (Coated VICRYL® [polyglactin 910]; Ethicon Inc., Sommerville, NJ), and 25 mg gentamicin and 2 mg betamethasone were injected subconjunctivally. Antibiotic ointment was applied to the eyes at the end of surgery. Following surgery, 0.1% betamethasone and 1.5% levofloxacin were applied to the eyes three times a day for 7 days.

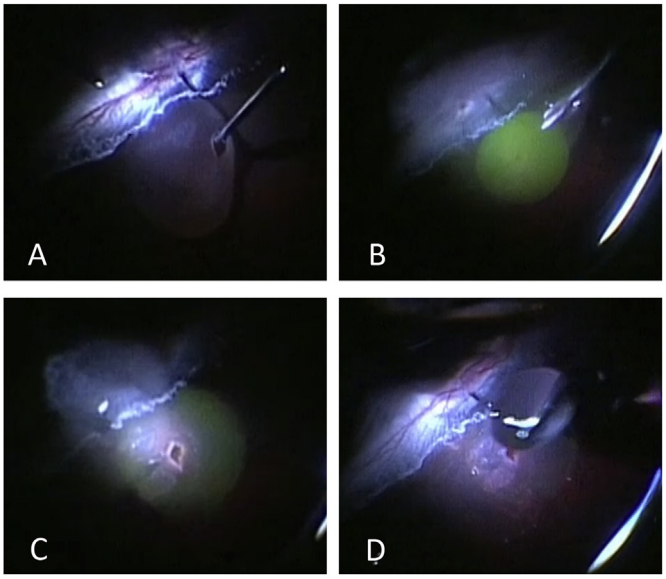

Fig. 1. Fundus images during vitrectomy for an eye of the RD-PEG group. (A) A created retinal break and detachment. (B) The retinal break covered by hydrogel. (C) Hydrogel polymerized with Xenon light. (D) Fundus of the eye filled with BSS.
RD-PEG: retinal detachment-polyethylene glycol, BSS: balanced salt solution.

2.3. Ophthalmologic examinations

Slit lamp microscopy and fundoscopy by indirect ophthalmoscopy were performed with the pupil dilated preoperatively, and 1 and 7 days, and 1, 3, and 6 months postoperatively. Optical coherence tomography (OCT) was used to evaluate the state of the retinal breaks in the study group at 7 days, and at 1, 3, and 6 months after surgery. Intraocular pressure was measured using a rebound tonometer (Icare® Pro; Icare Finland Oy, Helsinki, Finland) preoperatively, and during each postoperative examination. The time course of changes in intraocular pressure of the eyes in the RD-PEG group was assessed by repeated-measures analysis of variance (ANOVA).

2.4. Histology and immunohistochemistry

Rabbits were euthanized with an overdose of pentobarbital 6 months after surgery, and their eyes were enucleated, dissected, and placed in a fixative (Superfix KY-500, Kurabo, Japan) for 1 day. The specimens were washed with a 0.1 M phosphate buffer (PB) solution, and then washed again using the same solution with increasing concentrations of sucrose (10–20%). The specimens were cryosectioned through the dorsal-ventral/superior-inferior axis of the eye, with a section thickness of 20 μm, and every 10th slide was stained with hematoxylin and eosin before examination under a light microscope.

For immunohistochemical analysis, sections were washed three times at room temperature with 0.1 M sodium-phosphate-buffered saline (PBS; pH 7.2), and incubated in PBS with 0.5% Triton X-100 with 5% normal donkey serum. The sections were then incubated overnight at +4 °C with primary antibodies (diluted in PBS with 0.4% Triton X-100 and 2% normal donkey serum) against the following antigens: goat ionized calcium binding adaptor protein 1 (Iba-1; Ab5076, Abcam, Cambridge, UK) diluted 1:200, and mouse glial fibrillary acidic protein (GFAP; Sigma-Aldrich, St. Louis, MO) diluted 1:500. The slides were rinsed with PBS before being incubated with fluorescein isothiocyanate (FITC)-conjugated secondary antibodies (donkey anti-goat IgG [H + L], diluted 1:200, and goat anti-mouse IgG [H + L], diluted 1:500; Invitrogen, Carlsbad, CA) for 2 h together with 4′-6-diamidino-2-phenylindole (DAPI) stain. The slides were rinsed with PBS, and mounted

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