Photo Cross-linkable Biodendrimers as Ophthalmic Adhesives for Central Lacerations and Penetrating Keratoplasties

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Purpose. Biodendrimer-based hydrogel adhesives were derived from biocompatible building blocks and poly(ethylene glycol) of 3,400, 10,000 and 20,000 g/mole. The leaking pressures were determined for these adhesives when used to seal 4.1-mm central lacerations and penetrating keratoplasties (PKPs) in enucleated porcine eyes.

Methods. Three biodendrimers, $([G1]\text{-}PGLSA\text{-}MA)_2\text{-}PEG_{3,400}$, $([G1]\text{-}PGLSA\text{-}MA)_2\text{-}PEG_{10,000}$, and $([G1]\text{-}PGLSA\text{-}MA)_2\text{-}PEG_{20,000}$, at a range of weight percents were each photo cross-linked in the presence of a photo-initiator to form a hydrated network. These biodendrimer-based adhesives were applied directly to a 4.1-mm linear central laceration. In a PKP, the corneal button was initially secured with 8 or 16 sutures and then sealed with the adhesive.

Results. For the 4.1-mm central lacerations, the $([G1]\text{-}PGLSA\text{-}MA)_2\text{-}PEG_{3,400}$ at 20% and 40% wt/vol, the $([G1]\text{-}PGLSA\text{-}MA)_2\text{-}PEG_{10,000}$ at 10 and 20% wt/vol, and the $([G1]\text{-}PGLSA\text{-}MA)_2\text{-}PEG_{20,000}$ at 20% wt/vol held to leaking pressures above 200 mm Hg. In the autograft with 16 sutures, the 20% wt/vol of the $([G1]\text{-}PGLSA\text{-}MA)_2\text{-}PEG_{3,400}$, $([G1]\text{-}PGLSA\text{-}MA)_2\text{-}PEG_{10,000}$, and $([G1]\text{-}PGLSA\text{-}MA)_2\text{-}PEG_{20,000}$ held to a pressure at or above 100 mm Hg. In the autograft with eight sutures, the $([G1]\text{-}PGLSA\text{-}MA)_2\text{-}PEG_{10,000}$ and $([G1]\text{-}PGLSA\text{-}MA)_2\text{-}PEG_{20,000}$ formulations at 20% wt/vol held to leaking pressures of 85 ± 22 and 80 ± 30 mm Hg, respectively.

Conclusions. The 10% wt/vol $([G1]\text{-}PGLSA\text{-}MA)_2\text{-}PEG_{10,000}$ formulation withheld leaking pressures above 200 mm Hg when used to secure a 4.1 mm central laceration. The 20% wt/vol $([G1]\text{-}PGLSA\text{-}MA)_2\text{-}PEG_{10,000}$ and $([G1]\text{-}PGLSA\text{-}MA)_2\text{-}PEG_{20,000}$ formulations, with 8 or 16 sutures, secured the PKP well above normal IOP. Biodendrimer-based adhesives are of potential use for repairing corneal wounds. (*Invest Ophthalmol Vis Sci.* 2007;48:2037–2042) DOI:10.1167/iovs.06-0957

Ocular tissue repair using a sutureless strategy has the potential to promote healing, reduce trauma, and restore structural integrity and function to the native tissue. Consequently, there has been significant interest in evaluating new adhesives for the repair of corneal wounds. Each year, more than 1 million individuals in the United States seek treatment for the repair of corneal wounds.[1] In addition, there are another >2 million surgical procedures that could potentially benefit from use of an adhesive (e.g., penetrating keratoplasties, cataracts, LASIK flaps, vitrectomies, etc.).[2]

Today, most ocular wounds are repaired using sutures. The use of sutures to repair ocular wounds has several drawbacks. First, the act of suturing inflicts additional damage to the tissue. Second, sutures can act as a nidus for infection as well as inflammation, vascularization, and foreign-body sensation.[3] Third, suturing of the cornea can yield uneven healing resulting in a regular and/or irregular astigmatism.[4] Fourth, sutures can become loose or broken, Fifth, depending on the material, the use of sutures usually requires postoperative removal at a future time. Finally, suturing necessitates an acquired technical skill that can vary from surgeon to surgeon, influencing the clinical outcome.

Sealants for ophthalmic use are being evaluated as alternatives to sutures for improving the clinical outcome and reducing postoperative complications. The first sealants tested in the 1960s were super glues (or cyanoacrylates), as described by Webster et al.[5] for repairing corneal perforations. Cyanoacrylate adhesives have been an effective therapeutic option in certain ophthalmic settings, such as sealing small corneal perforations (1 mm) and preemptive treatment of progressive corneal thinning disorders.[5–11] However, the limitations of this system include difficult application techniques, limited effectiveness, discomfort, toxicity, and lack of biodegradation.[9,12–19] Complications with cyanoacrylates have also been reported and include cataract formation, corneal infiltration, granulomatous keratitis, glaucoma, and even retinal toxicity.[15–18]

Fibrin-based sealants have also been evaluated for repair of ocular wounds. Fibrin sealants were originally developed for vascular applications but have been used off label for ophthalmic applications.[20–22] This hemostat meets many of the requirements for a tissue adhesive, but the disadvantages of this autologous system include lengthy preparation time, high cost, and inherent risk of viral transmission.[22] Recently, a chondroitin sulfate aldehyde adhesive has been reported for sealing 3-mm corneal incisions.[23] This two-component adhesive is composed of an oxidized chondroitin sulfate (CS) and polyvinyl alcohol covinyl amine (PVA-A) polymer. This adhesive forms as a result of the reaction between the amine of PVA-A and the aldehyde of CS forming a reversible Schiff-base linkage.

Our laboratory is developing and evaluating hydrogel adhesives that are polymerized in situ for the repair of various ocular wounds. In 2002, we reported two new adhesives for the repair of full-thickness corneal lacerations based on hyaluronic acid and glycerol-succinic acid-poly(ethylene glycol) dendrimers, respectively.[24–27] Of the two adhesive formulations, the dendritic polymer system provides a greater opportunity to control and optimize chemical, physical, and mechanical properties. Dendrimers are single-molecular-weight macromolecules that consist of a core, branching segments, and a multitude of functional end groups.[28–31] Because of their

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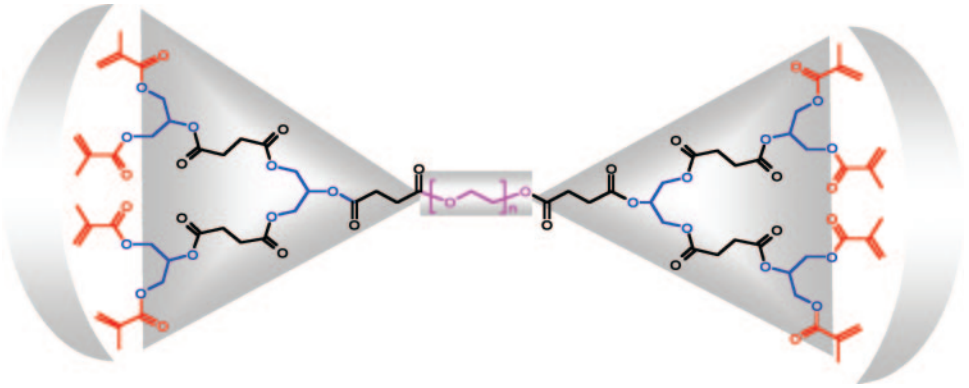

FIGURE 1. ABA triblock architecture of a first-generation (G1) dendritic polymer, $([G1]\text{-PGLSA-MA})_2\text{-PEG}$, consisting of natural metabolites such as glycerol and succinic acid (*triangle*), and nonimmunogenic poly(ethylene glycol) (*rectangle*). For the three different PEG formulations, 3,400, 10,000, and 20,000, n is 77, 227, and 454, respectively. The end groups are derivatized with photo cross-linkable methacrylate groups (*crescent*).

unique globular branched structure, these polymers exhibit low viscosities and high reactivities and are useful for the preparation of highly cross-linked hydrogels. In particular, we are preparing dendrimers that are composed of biocompatible building blocks (i.e., glycerol and succinic acid) as biodendritic hydrogel adhesives. Herein, we report the evaluation of three photo cross-linkable poly(glycerol-succinic acid)-*co*-poly(ethyelene glycol) dendrimers (Fig. 1) of various poly(ethyelene glycol) molecular weights to seal full-thickness 4.1-mm central lacerations and to secure penetrating keratoplasty (PKP) wounds in enucleated porcine eyes.

MATERIALS AND METHODS

Triethanolamine (TEOA) was purchased from Fluka (Milwaukee, WI), and eosin-Y (EY), and 1-vinyl-2-pyrrolidinone (VP) were purchased from Aldrich (Milwaukee, WI). Dulbecco's phosphate-buffered saline (PBS) was purchased from Invitrogen-Gibco (Carlsbad, CA). Physiologic saline solution was purchased from Alcon (Fort Worth, TX). An argon-ion laser on a handheld probe was used for photo-cross-linking (514 nm, 200 mW, 120 seconds; Ultima SE; Lumenis, Santa Clara, CA). Porcine eyes were purchased from Sioux-Preme Packing Co. (Sioux Center, IA).

Experiment Setup

For the central laceration, PKP, and India ink studies, extraocular tissue was first removed from an enucleated porcine eye, and then the eye was cut in half circumferentially. All uveal tissue was removed and the cornea-containing hemisection was mounted on the chamber modeled after that described by Thiel et al.[32] for measuring the leaking pressures of enucleated eyes. The saline solution was pumped into the chamber at a rate of 10 mL/h, which ultimately filled the eye chamber until the wound leaked. A cardiac transducer was attached to the eye chamber and used to monitor the pressure of an enucleated eye. The biodendrimers studied in this report, $([G1]\text{-PGLSA-MA})_2\text{-PEG}_{3,400}$, $([G1]\text{-PGLSA-MA})_2\text{-PEG}_{10,000}$, and $([G1\text{-PGLSA-MA})_2\text{-PEG}_{20,000}$, were prepared by the divergent method.[26] The biodendrimer materials were stored in a sealed bottle at −20°C and subsequently warmed to room temperature before use. The biodendrimers were dissolved in a sterile aqueous solution containing an eosin-based photoinitiating system (115 mM TEOA, 1% of 10 mM EY, and 1% VP). This biodendrimer solution can be delivered to the wound site easily via micropipette.

Creating a 4.1-mm Central Laceration

A 2.75-mm slit, dual-bevel knife (Clearcut; Alcon) was used to make the initial central cornea incision. Next, a 4.1-mm implant dual-bevel knife (Clearcut; Alcon) was used to create a full-thickness 4.1-mm linear laceration perpendicular to the cornea. Both knives are disposable. In the control group, the leaking pressures were measured with no biodendrimer-based hydrogel adhesive present and with three interrupted 10-0 nylon sutures in a standard 3-1-1 suturing configuration. The control was tested in triplicate ($n = 3$). To seal the corneal laceration, we used a micropipette to apply 25 μL of a 10%, 20%, and 40% wt/vol (weight of biodendrimer/volume of solvent) solution of the adhesive formulation directly to the wound after removing excess water from the cornea with a sponge (Merocel; Medtronic ENT Surgical Products, Inc. Jacksonville, FL). Each formulation was tested in triplicate ($n = 3$). The solutions were cured with an argon-ion laser for 2 minutes with 1-second pulses, to form a transparent, and soft hydrogel adhesive that remained on the cornea. After the wound was sealed, a syringe pump was used for slow injection of physiologic saline (BSS; Alcon) into the eye chamber while the cardiac transducer monitored the pressure. The leaking pressure, as recorded by a cardiac transducer, was defined as the pressure at which a leak was observed in the wound. Statistical analysis was performed by Students' *t*-test.

Creating a PKP

In the PKP studies, an 8-mm diameter Hessburg-Barron vacuum trephine (Barron Precision Instruments, LLC, Grand Blanc, MI) was used to create a PKP wound. The corneal button created was then sutured on the existing eye with 8 or 16 interrupted 10-0 nylon sutures. Next, a micropipette was used to apply 100 μL of one of the adhesive solutions at 20% wt/vol to the PKP, to coat the sutures and wound interface. Each formulation was tested in triplicate ($n = 3$). The biodendrimer solutions were cured with a pulsed argon-ion laser for 2 minutes, to form the hydrogel adhesive. The leaking pressure for the control group, which received only sutures, was also measured. The chamber was filled with physiologic saline until a leak occurred, and the pressure was measured by a cardiac transducer.

Histology for India Ink Study

After the PKP wound was created on the enucleated porcine eyes ($n = 3$), the resultant autografts were sutured in place with 8 or 16 10-0 nylon sutures. Next, 100 μL of 20% wt/vol of the $([G1]\text{-PGLSA-MA})_2\text{-PEG}_{10,000}$ hydrogel adhesive was placed over the sutures to seal the wound interface further. The biodendrimer solution was photo cross-linked with an argon-ion laser for 2 minutes by using 1-second pulses. On the second set of enucleated porcine eyes ($n = 3$), only 8 or 16 10-0 nylon sutures were used to secure the 8-mm autograft with no application of the hydrogel adhesive. India ink was then generously applied with a 33-gauge needle and syringe to the surface of all the corneas to completely cover the wound area. The IOP was then lowered in a controlled fashion by slowly withdrawing the infusion syringe to an immeasurable level and then raising it to 50 mm Hg. This process was repeated six times. Excess India ink was washed away from the surface of the hydrogel adhesive. Next, visual inspection was performed to determine whether India ink entered the anterior chamber. The histologic sections for both sets of porcine eyes were obtained from Bio-Tek Research Consultants (Durham, NC). Images were taken from eosin-Y-stained sections.

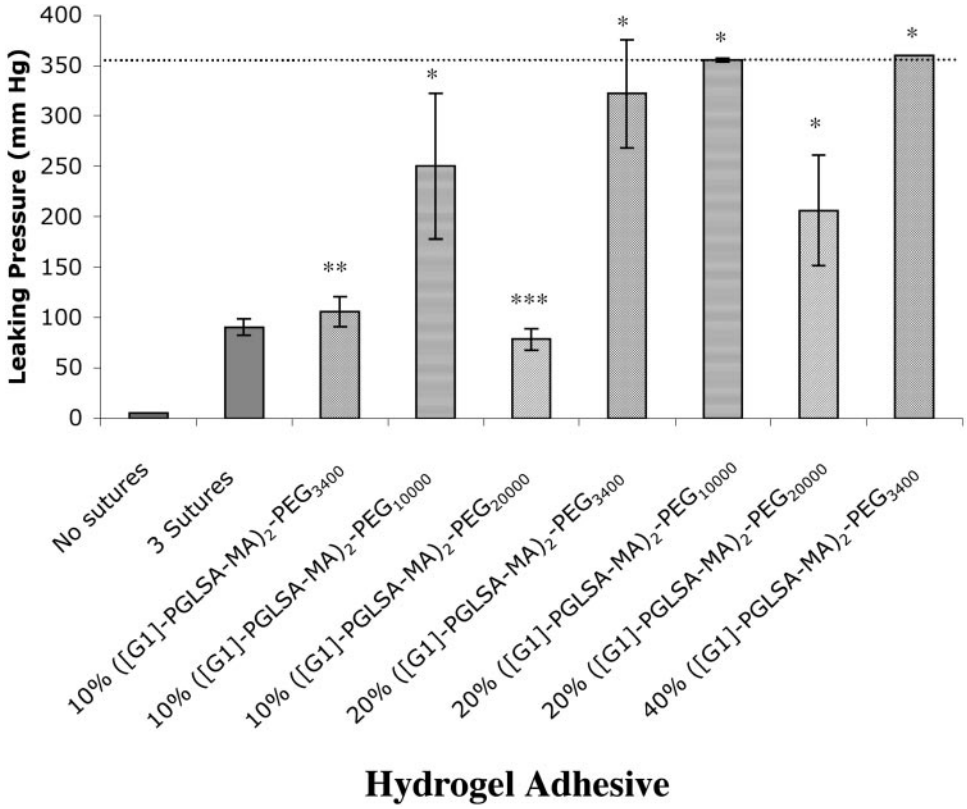

FIGURE 2. Leaking pressures for the 4.1-mm central lacerations with three different hydrogel adhesives at 10%, 20%, and 40% wt/vol. All adhesives were evaluated in enucleated porcine eyes ($n = 3$ per formulation). *Dashed line*: detection limit of the cardiac transducer. $^{*}P < 0.02$, $^{**}P = 0.141$, and $^{***}P = 0.02$ compared with the three-suture control group.

RESULTS

Leaking Pressures for the 4.1-mm Central Laceration Study

For the central laceration study, the ([G1]-PGLSA-MA)$_2$-PEG$_{3,400}$ formulation was evaluated at 10%, 20%, and 40% wt/vol, whereas the ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$, and ([G1]-PGLSA-MA)$_2$-PEG$_{20,000}$ formulations were both tested at 10% and 20% wt/vol. The ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$ and ([G1]-PGLSA-MA)$_2$-PEG$_{20,000}$ biodendrimer formulations were not evaluated at 40% wt/vol, because of a lack of solubility at this high concentration. Each formulation was tested in triplicate ($n = 3$). The leaking pressures for the sealed central lacerations are shown in Figure 2. For the ([G1]-PGLSA-MA)$_2$-PEG$_{3,400}$, ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$, and ([G1]-PGLSA-MA)$_2$-PEG$_{20,000}$ formulations at 10% wt/vol, the reported average was 106 ± 15, 250 ± 71.9, and 78 ± 11 mm Hg, respectively. The 20% wt/vol of the ([G1]-PGLSA-MA)$_2$-PEG$_{3,400}$, ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$, and ([G1]-PGLSA-MA)$_2$-PEG$_{20,000}$ formulations held to pressures of 322 ± 54, 355 ± 2.1, and 206 ± 55 mm Hg, respectively. For the 40% wt/vol ([G1]-PGLSA-MA)$_2$-PEG$_{3,400}$ formulation, the leaking pressure recorded was greater than 360 mm Hg, which is the upper limit of the cardiac transducer. The control without any sutures leaked at pressures less than normal IOP, and the leaking pressure for the control with three interrupted 10-0 nylon sutures was 90 ± 8 mm Hg. Based on these data, the ([G1]-PGLSA-MA)$_2$-PEG$_{3,400}$ adhesive at 20% and 40% wt/vol and the ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$ adhesive at a 20% wt/vol were the most successful at sealing a 4.1-mm central laceration. Although, the 10% wt/vol ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$ and the 20% wt/vol ([G1]-PGLSA-MA)$_2$-PEG$_{20,000}$ adhesives showed high leaking pressures, they were difficult to work with. The low viscosity of the 10% wt/vol ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$ prevented the biodendrimer solution from completely remaining on the wound site, whereas the higher viscosity of the 20% wt/vol ([G1]-PGLSA-MA)$_2$-PEG$_{20,000}$ made the application of the solution difficult. The 40% wt/vol ([G1]-PGLSA-MA)$_2$-PEG$_{3,400}$ biodendrimer solution was very viscous and cross-linked prematurely before application of the material on the tissue was complete. Forceps were needed to remove the material from the tissue after placement.

Leaking Pressures for the PKP Studies

According to the results obtained from the 4.1 mm central laceration study, the ([G1]-PGLSA-MA)$_2$-PEG$_{3,400}$ at 20% and 40% wt/vol, the ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$ at 10% and 20% wt/vol, and the ([G1]-PGLSA-MA)$_2$-PEG$_{20,000}$ at 20% wt/vol hydrogel adhesives showed the highest leaking pressures. Of the five formulations, the 10% wt/vol ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$ was not viscous enough to remain on the wound site completely and cross-link into a strong gel after polymerization, whereas the 40% wt/vol ([G1]-PGLSA-MA)$_2$-PEG$_{3,400}$ was too viscous to be applied evenly around the wound and partially polymerized during application. Consequently, the three remaining adhesives at 20% wt/vol were evaluated in securing a PKP with 16 sutures, which is most commonly used today. Each formulation was tested in triplicate ($n = 3$). After creating a PKP, 16 sutures were initially placed, followed by application and photo cross-linking of the hydrogel adhesive. The data for this PKP study are shown in Figure 3. An autograft sealed with 16 sutures alone held to 45 ± 10 mm Hg. Application of the 20% wt/vol ([G1]-PGLSA-MA)$_2$-PEG$_{3,400}$, ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$, and ([G1]-PGLSA-MA)$_2$-PEG$_{20,000}$ led to leaking pressures of 103 ± 13, 114 ± 7, and 98 ± 14 mm Hg, respectively (Fig. 3). The autograft sealed with 16 sutures and the biodendrimer-based hydrogel adhesive (Fig. 4) provided a secure interface.

Next, we determined the leaking pressures of a corneal autograft initially secured with only eight sutures followed by the application and photo cross-linking of the three hydrogel

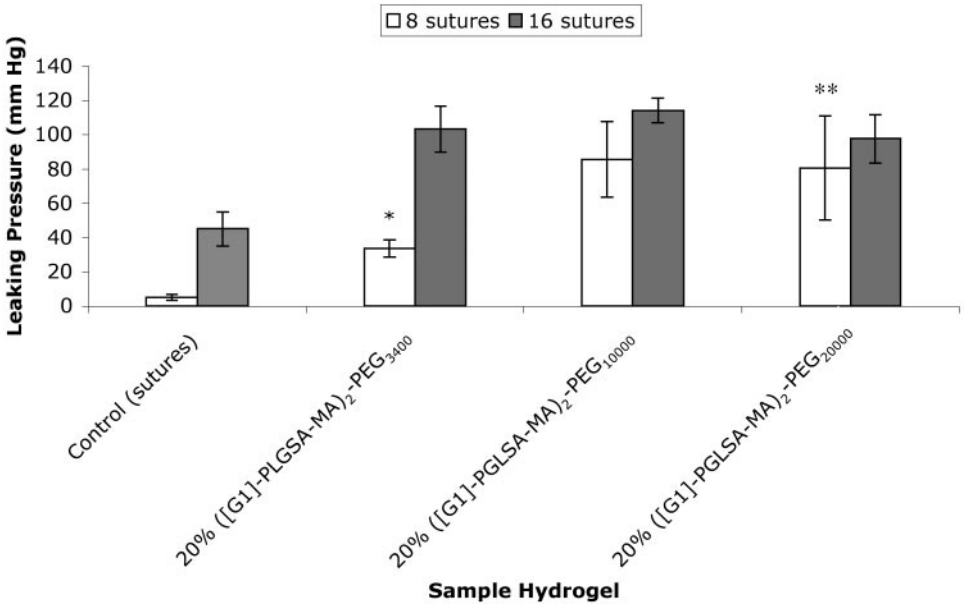

FIGURE 3. Leaking pressures for PKP autografts sealed with either 8 or 16 10-0 nylon sutures and the three different biodendrimer adhesive formulations at 20% wt/vol. All the adhesives were evaluated in enucleated porcine eyes ($n = 3$ per formulation). All samples are significant ($P < 0.02$) compared with the 16-suture control group, unless otherwise noted. $^{*}P = 0.11$ and $^{**}P = 0.08$ when compared with the 16-suture control group.

adhesives at 20% wt/vol. Using a minimum number of sutures and an adhesive to secure a PKP would lessen tissue trauma induced by suturing, provide a strong seal at the wound interface and reduce overall surgery time. The data for this study are shown in Figure 3. Sealing the wound with 20% wt/vol of the ([G1]-PGLSA-MA)$_2$-PEG$_{3,400}$, ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$, and ([G1]-PGLSA-MA)$_2$-PEG$_{20,000}$ systems afforded leaking pressures of 34 ± 5, 85 ± 22, and 81 ± 30 mm Hg, respectively. For reference, the autograft sealed with eight sutures had a leaking pressure of less than normal IOP. After photo cross-linking, we needed forceps to remove the hydrogel adhesives.

Histologic Sections with India Ink

In addition to reducing the number of necessary sutures, the use of a hydrogel adhesive may serve as a barrier against microbes and possibly reduce the risk of postoperative infections. The barrier function of the adhesive was tested using India ink according to a method described by McDonnell et al.[33] In this method, the adhesive was applied to the PKP with 8 and 16 sutures, and the IOP was raised and lowered. As shown in Figure 5A and 5B, when India ink was applied to a PKP with 8 and 16 sutures and no hydrogel adhesive, the ink was found to be present along the epithelium and in the wound tissue interface. This indicates the potential for ocular surface fluid and microbes to enter the wound site and anterior chamber. However, when the 20% wt/vol of ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$ adhesive was applied to the autograft with 8 and 16 sutures, the dye was absent in the wound tissue interface, indicating that the wound site was sealed (Figs. 5C–5D). The hydrogel adhesive also remains on the wound interface during cyclical raising and lowering of the IOP.

DISCUSSION

The goal of this study was to evaluate the effectiveness of new light-activated biodendrimer-based hydrogel adhesives in securing large central corneal lacerations and autografts. These adhesives showed good adhesion to the epithelium, significant wound repair strength in withstanding high IOP, ease of application, and barrier properties that prevented ocular surface fluid from entering the wound.

A series of ([G1]-PGLSA-MA)$_2$-PEG polymers of various PEG molecular weights (3,400 to 20,000 g/mole) and formulation concentrations (10, 20, and 40% wt/vol) were evaluated for the repair of 4.1 mm central corneal lacerations. The 20% wt/vol ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$, and ([G1]-PGLSA-MA)$_2$-PEG$_{20,000}$, and the 20% and 40% wt/vol ([G1]-PGLSA-MA)$_2$-PEG$_{3,400}$ biodendrimer formulations remain on the wound site and can be easily photo cross-link to seal the wound. Two general trends were observed during this experiment. First, as the concentration increased for all the biodendrimer formulations, the viscosity increased, which allowed the adhesive solutions to re-

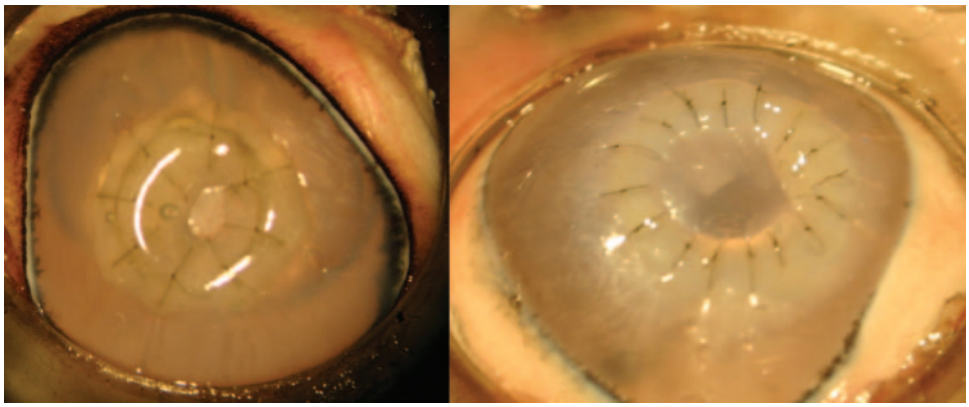

FIGURE 4. Photographs of a secured autograft in an enucleated porcine eye after placement of 8 or 16 interrupted 10-0 nylon sutures followed by application and photo cross-linking of the hydrogel adhesive.

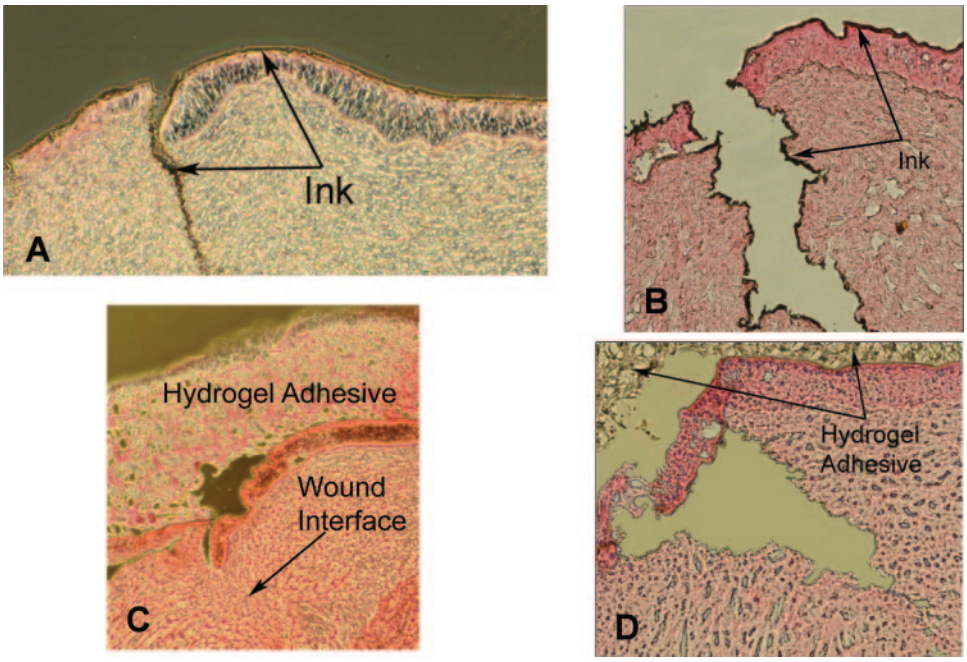

FIGURE 5. Histologic sections of India ink on an autograft with (**A**) 16 sutures and no hydrogel adhesive, (**B**) 8 sutures and no hydrogel adhesive, (**C**) 16 sutures and hydrogel adhesive on top of the epithelium, and (**D**) 8 sutures and hydrogel adhesive on top of the epithelium. (**A**, **B**) Ink appears along the epithelium and in the wound site; (**C**, **D**) Lack of dye at the wound site. India ink was washed away from the surface of the hydrogel during the staining process (**C**, **D**).

main on the wound site before photo cross-linking. Also, an increase in concentration, within one biodendrimer formulation, led to cross-linked hydrogels that withheld higher leaking pressures. Second, as the molecular weight of the PEG-based biodendrimers was increased from ([G1]-PGLSA-MA)$_2$-PEG$_{3,400}$ to ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$, the leaking pressure increased, as observed for the 10% and 20% wt/vol concentrations. On the other hand, as the molecular weight of the PEG-based biodendrimers was further increased from ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$ to ([G1]-PGLSA-MA)$_2$-PEG$_{20,000}$ the leaking pressure decreased, as seen for the 10% and 20% wt/vol concentrations. The 20% wt/vol ([G1]-PGLSA-MA)$_2$-PEG$_{20,000}$ solution was difficult to work with, due to problems with solution preparation (i.e., inhomogeneous) and application (i.e., high viscosity). This is consistent with the large SD, where the leaking pressures ranged from 155 to 264 mm Hg.

Based on the central laceration results, we anticipated that the ([G1]-PGLSA-MA)$_2$-PEG$_{3,400}$, ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$, and ([G1]-PGLSA-MA)$_2$-PEG$_{20,000}$ adhesive formulations at 20% wt/vol may be suitable in securing a PKP with 16 sutures. We examined an autograft sealed with 16 sutures followed by the application and photo cross-linking of the hydrogel adhesives. These 20% wt/vol formulations were easy to apply and remained on the wound site after application. The three adhesive formulations were found to hold pressures at or above 100 mm Hg.

Next, we determined the leaking pressures for a corneal autograft secured with eight sutures and the ([G1]-PGLSA-MA)$_2$-PEG adhesive. The 20% wt/vol of the ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$ and ([G1]-PGLSA-MA)$_2$-PEG$_{20,000}$ formulations held to higher pressures than the eight-suture control group and did not leak until pressures greater than 80 mm Hg. On the one hand, the leaking pressure for these formulations was also greater than that in the 16-suture control group. The 20% wt/vol ([G1]-PGLSA-MA)$_2$-PEG$_{3,400}$ formulation leaked at a lower pressure, although the leaking pressure was still higher than the control with eight sutures. During application of the 20% wt/vol of all three formulations, the best results were observed when the adhesive completely covered the wound site and all sutures. Based on these findings, the two best candidates for securing PKPs using a minimum amount of sutures are the ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$ and ([G1]-PGLSA-MA)$_2$-PEG$_{20,000}$ at 20% wt/vol.

Next, India ink was used as a model to visualize the flow of surface ocular fluid across the wound interface and into the anterior chamber of enucleated porcine eyes. The flow of surface fluid across the cornea and into the wound site may lead to postoperative infections.[34] The 20% wt/vol of the ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$ formulation, with either 8 or 16 sutures, was evaluated for preventing the influx of surface fluid across the cornea and into the wound interface of the PKP. These results were compared with the typical surgical procedure, in which 16 interrupted 10-0 nylon sutures are used to secure the corneal autograft. The corneal histologic sections show the presence of India ink at the wound interface when the autograft is secured with only 8 or 16 sutures, and a lack of India ink at the wound interface when the adhesive is applied to the autograft with either 8 or 16 sutures. The presence of the biodendrimer-based adhesive on the wound interface serves two purposes. First, the adhesive provides an additional seal to aid the sutures in preventing the eye from leaking at high pressures. Second, the adhesive is a barrier against the potential influx of surface fluid into the wound site.

In conclusion, we have developed and evaluated biodendrimer-based hydrogel adhesives for repairing corneal wounds. Overall, we have shown that the ([G1]-PGLSA-MA)$_2$-PEG$_{10,000}$ is a versatile adhesive in sealing a central laceration and a PKP corneal wound ex vivo. The ease of application and uniform curing allow for control when repairing the wound with the hydrogel adhesive. The biodendrimer adhesive is soft, smooth, transparent, and has a rubbery consistency on cross-linking. These physical characteristics are an advantage over cyanoacrylate glues that have a rough texture and often require a bandage contact lens to be placed over the glue to improve patient comfort and tolerance. Furthermore, these biodendrimer-based hydrogel adhesives may also be effective in preventing postoperative microbial infections since the wound site is sealed with a protective hydrogel barrier. These positive results are likely to encourage further development and evaluation of adhesives for the repair of corneal wounds. Ultimately, the reduction or elimination of sutures through the use of

ocular adhesives may have a significant impact on ocular surgery.

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