

Comparison of Sutures and Dendritic Polymer Adhesives for Corneal Laceration Repair in an In Vivo Chicken Model

John P. Berdahl, MD; C. Stark Johnson, MD; Alan D. Proia, MD, PhD; Mark W. Grinstaff, PhD; Terry Kim, MD

Objective: To compare clinical and histologic healing of corneal lacerations repaired by sutures or a new polymeric adhesive.

Methods: A central full-thickness 4.1-mm laceration was made in the right eyes of 60 white leghorn chickens. Half of the wounds were treated with biodendrimer polymer adhesive and half were closed with 3 interrupted 10-0 nylon sutures. Slitlamp examination was performed at 6 hours, daily for 7 days, and weekly for 21 days. Animals were humanely killed at days 1, 3, 7, and 28 for histologic examination to evaluate corneal healing.

Results: Histologic observations on days 1, 3, and 7 showed glued wounds filled with fibrin, then hyperplastic epithelium, and subsequently scar tissue. Scarring was

more prominent at day 7 in glued corneas; however, by day 28, sutured corneas exhibited more inflammation and scarring and much more irregular anterior corneal surfaces. Clinically, all glued corneas remained clear while nearly all sutured corneas had some degree of corneal scarring persisting through day 28. The procedure was about 5 times faster with sealant than with sutures.

Conclusion: Corneal lacerations treated with adhesive heal favorably compared with sutures.

Clinical Relevance: Biodendrimer adhesives represent a safe, effective, and technically easier alternative to traditional suture repair of corneal perforations.

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FULL-THICKNESS CORNEAL wounds are a common ophthalmic situation with potentially disastrous sequelae, including corneal scarring, astigmatism, endophthalmitis, and blindness. Whether iatrogenic, traumatic, or due to infection or inflammation, full-thickness corneal defects warrant immediate attention to prevent inflow or outflow

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of fluid through the wound. Outflow of aqueous humor can result in a flat anterior chamber causing cataract, peripheral anterior synechiae, hypotony maculopathy, or suprachoroidal hemorrhage. Inflow of fluid can carry microorganisms and result in endophthalmitis, even if the anterior chamber remains formed.¹

Depending on the character and cause of the perforation, different approaches to repair may be taken. Suturing is the traditional treatment, whereas repair with cyanoacrylate or fibrinogen adhesives has served as another alternative. Biodendrim-

ers are a promising new alternative tissue sealant. These polymers belong to a class called *dendrimers*, which are globular polymers containing a central core from which the polymers branch outward in a tree-like structure. A biodendrimer is unique because it is composed of biocompatible monomers that allow in vivo applications ranging from wound repair and tissue engineering to drug delivery.²⁻⁸

These single-molecular-weight polymers are highly ordered and exhibit numerous end groups for functionalization. Unlike sutures, laser-activated biodendrimer adhesives can be applied in an office or emergency department setting. Adhesive is applied only to the surface of the cornea and thus is not traumatic, does not create artificial tension lines, requires minimal technical skill, does not require removal, and is not a nidus for infection. Unlike cyanoacrylate and fibrin-based adhesives, biodendrimers are easy to work with and provide a transparent flexible seal with no ocular toxic effects.

In vitro experiments with enucleated eyes have shown that biodendrimers ap-

Author Affiliations:

Departments of Ophthalmology (Drs Berdahl, Johnson, Proia, and Kim) and Pathology (Dr Proia), Duke University, Durham, North Carolina; and Department of Biomedical Engineering and Chemistry, Boston University, Boston, Massachusetts (Dr Grinstaff).

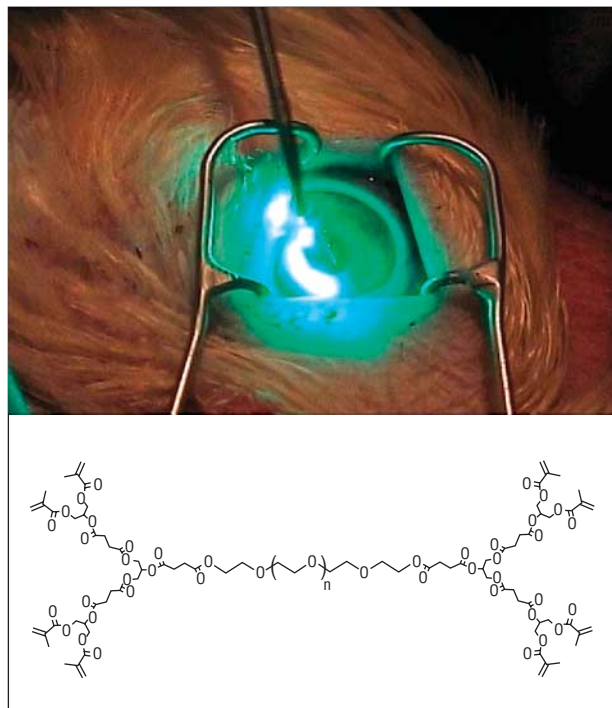


Figure 1. Use of the argon ion laser-activated biodendrimer polymer. A, Laser activation of the polymer. B, Chemical structure of the polymer.

plied to full-thickness corneal lacerations and corneal autografts create a watertight seal that is able to withstand extreme elevations in intraocular pressure.^{2,9,10} This experiment was designed to test these biodendrimers in vivo and compare wound healing with that after traditional suture repair. We report herein the results of the first randomized prospective experiment, to our knowledge, to compare the clinical and histologic healing response of corneal lacerations repaired by either traditional suture or the argon ion laser-activated biodendrimer polymer ([G1]-PGLSA-MA)₂-PEG in an in vivo chicken model.

METHODS

All experiments adhered to the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research. The animals were anesthetized with an intramuscular injection of ketamine hydrochloride (60 mg/kg) and xylazine hydrochloride (5 mg/kg) for all procedures. Central full-thickness linear corneal wounds were made in white leghorn chickens (*Gallus gallus domesticus*) with a 4.1-mm keratome. Seidel positivity was checked to ensure that wounds were not self-sealing.

A total of 60 chickens were used for this experiment. The right eyes of 30 chickens received approximately 10 μ L (enough volume to cover the wound) of a 2-mL 50% wt/wt polymer solution containing 5 μ L of 0.5% ethyl eosin in 1-vinyl-2-pyrrolidinone (photoinitiator) and 50 μ L of 5M triethylaluminum (cocatalyst). After the wound site was dried with a cellulose sponge, this solution was applied directly to the corneal perforation with a 30-gauge cannula attached to a 1-mL syringe. The epithelium was not removed. With the use of a handheld probe, the polymer was photocrosslinked with approximately fifty 1-second applications of low-intensity argon laser irradiation (diffuse beam; $\lambda_{\text{max}} = 514$ nm; 200 mW) to produce a clear dendritic seal (**Figure 1**). The beam diameter on a handheld

probe varies according to the distance of the probe end from the applied surface. For our procedures, the probe end was consistently held approximately 2.5 cm from the adhesive, and the laser beam was applied directly to the adhesive at the wound edges without reapproximation. The right eyes of the other 30 chickens received 3 interrupted 10-0 nylon sutures. All procedures were performed by a single surgeon trained in cornea surgery (C.S.J.). Each procedure was timed. Slitlamp examination of wound integrity, corneal clarity, Seidel positivity, and anterior chamber inflammation were evaluated at 6 hours and 1, 2, 3, 4, 5, 6, 7, 14, 21, and 28 days after surgery.

Animals were humanely killed with an intravenous overdose of pentobarbital sodium at day 1 (3 in the polymer group, 4 in the suture group), day 3 (10 in each group), day 7 (10 in each group), and day 28 (6 in each group). Masked histologic examination was performed to determine the time course and extent of corneal healing, although the use of sutures prevented true masking of the histologic observations. One animal in the polymer group died during the surgery; hence, only 3 chickens in the polymer group were killed on day 1.

The eyes were enucleated and fixed in 10% formalin, and the corneas were embedded in paraffin for histologic examination. The extent of inflammation and quality of epithelial, stromal, and endothelial healing were evaluated at each time point.

RESULTS

CLINICAL RESULTS

Intraoperatively, all wounds were confirmed to be Seidel positive. After application and photopolymerization of the biodendrimer polymer or suture placement, all anterior chambers quickly reformed. Seidel testing showed slight leakage immediately after closure in 1 of the adhesive-treated eyes and none of the sutured eyes.

On postoperative day 1, all eyes were Seidel negative and all anterior chambers remained formed (**Table**). Mild to moderate anterior chamber inflammation was evident in similar proportions in each treatment group. No evidence of a toxic response to biodendrimer sealant or sutures was observed during clinical examinations. The adhesive had degraded by day 14. All corneas treated with the polymer remained clear (with the exception of a faint linear scar in the incision tract), whereas nearly all of the sutured corneas had some degree of corneal scarring that persisted through day 28 (**Figure 2**). Average repair time after corneal injury for each eye was approximately 1 minute for the adhesive group and 5 minutes for the suture group.

HISTOLOGIC RESULTS

Histologic examination of wounds from each group demonstrated healing at a similar rate and in a similar order (**Figure 3**). On day 1, we examined 3 eyes from the adhesive group and 4 eyes from the sutured group. The epithelium began migrating over the wounds as a monolayer in both groups. All wounds in both groups remained full thickness with juxtaposed edges and hyperplastic epithelium filling the anterior portion of the wounds. Adhesive-treated wounds had very clean wound edges and

Table. Clinical Observations of Chicken Corneas at Days 1, 3, 7, 14, 21, and 28

	Cornea	Wound	Anterior Chamber Formation	Anterior Chamber Inflammation
		Adhesive		
Day 1 (n=30) ^a	Clear, 26; haze, 3	Intact, 29	Formed, 29	None, 25; mild, 4
Day 3 (n=26)	Clear, 26	Intact, 25; CNV, 1	Formed, 26	None, 21; mild, 5
Day 7 (n=16)	Clear, 16	Intact, 16	Formed, 16	None, 12; mild, 3; moderate, 1
Day 14 (n=6)	Clear, 6	Intact, 6	Formed, 6	None, 6
Day 21 (n=6)	Clear, 6	Intact, 6	Formed, 6	None, 6
Day 28 (n=6)	Clear, 6	Intact, 6	Formed, 6	None, 6
		Suture		
Day 1 (n=30)	Clear, 3; haze, 27	Intact, 27; broken suture, 3	Formed, 29; shallow, 1	None, 29; mild, 1
Day 3 (n=26)	Clear, 4; haze, 22	Intact, 23; broken suture, 3	Formed, 24; iris to wound, 2	None, 22; mild, 2; severe, 2
Day 7 (n=16)	Clear, 3; haze, 13	Intact, 10; broken suture, 6	Formed, 15; iris to wound, 1	None, 14; mild, 1; severe, 1
Day 14 (n=6)	Mild haze, 6	Intact, 0; broken suture, 2; mild stromal edema, 4	Formed, 6	None, 5; mild, 1
Day 21 (n=6)	Clear, 1; mild haze, 5	Intact, 2; broken suture, 2; mild stromal edema, 2	Formed, 6	None, 5; mild, 1
Day 28 (n=6)	Mild haze, 6	Intact, 0; broken suture, 2; mild stromal edema, 3; moderate stromal edema, 1	Formed, 6	None, 5; mild, 1

Abbreviation: CNV, corneal neovascularization.

^aOne animal died during the surgery, so findings are given for 29 animals.

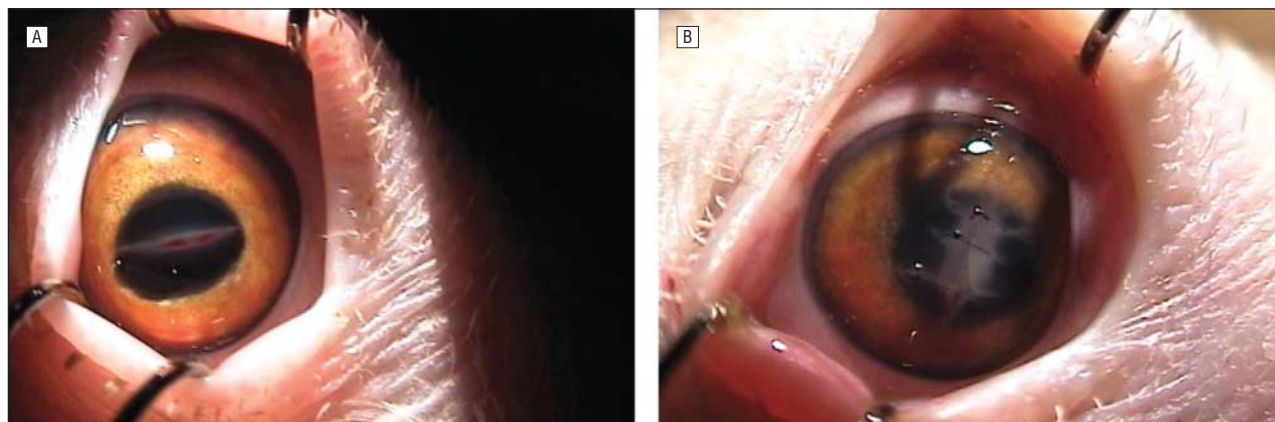


Figure 2. Postoperative day 5 corneas. A, Adhesive. B, Sutured.

minimal stromal inflammation. Adhesive-treated wounds had more even anterior surfaces than those with sutures. One suture had bacterial colonies surrounding it.

On day 3, 10 eyes from each group were examined. The epithelium had completely migrated over 9 of 10 wounds in each group. Corneas that had been repaired with adhesive had better approximation of the wound edges compared with corneas repaired with sutures, with a much more regular anterior surface of the cornea. Despite the better approximation of the wound edges, there was much more hyperplastic epithelium plugging the anterior portion of the wound, along with much more fibrinous/proteinaceous exudate plugging the posterior edge of the wound. Endothelial cells began covering the posterior stromal surface in both groups.

Day 7 histologic analysis included 10 eyes from each group. The epithelium covered all wounds in both groups. The wounds in both groups were filled with scar tissue, manifest as an increased number of keratocytes and irregular stroma. Although scarring was wider in adhesive-

treated wounds, there was less stromal inflammation than that associated with the sutured wounds. Duplication of Descemet membrane was noted and the endothelium covered the posterior corneal surface in all eyes of both groups. Adhesive-treated wounds tended to have anterior edges that were more even.

On day 28, 6 eyes in each group were examined. The epithelium remained intact in all eyes. In both groups, the entire length of all wounds was completely adherent by scar and apposed. Adhesive-treated wounds had wider scars on average than the sutured group. However, multiple prominent scars were evident at the suture placement site. The sutured wounds had a more irregular anterior surface and more stromal inflammation than did adhesive-treated wounds. Descemet membrane was normal and endothelial cells completely covered the posterior surface in both groups. Corneal thickness was normal in both groups.

There was no clinical or histologic evidence of epithelial downgrowth in either group.

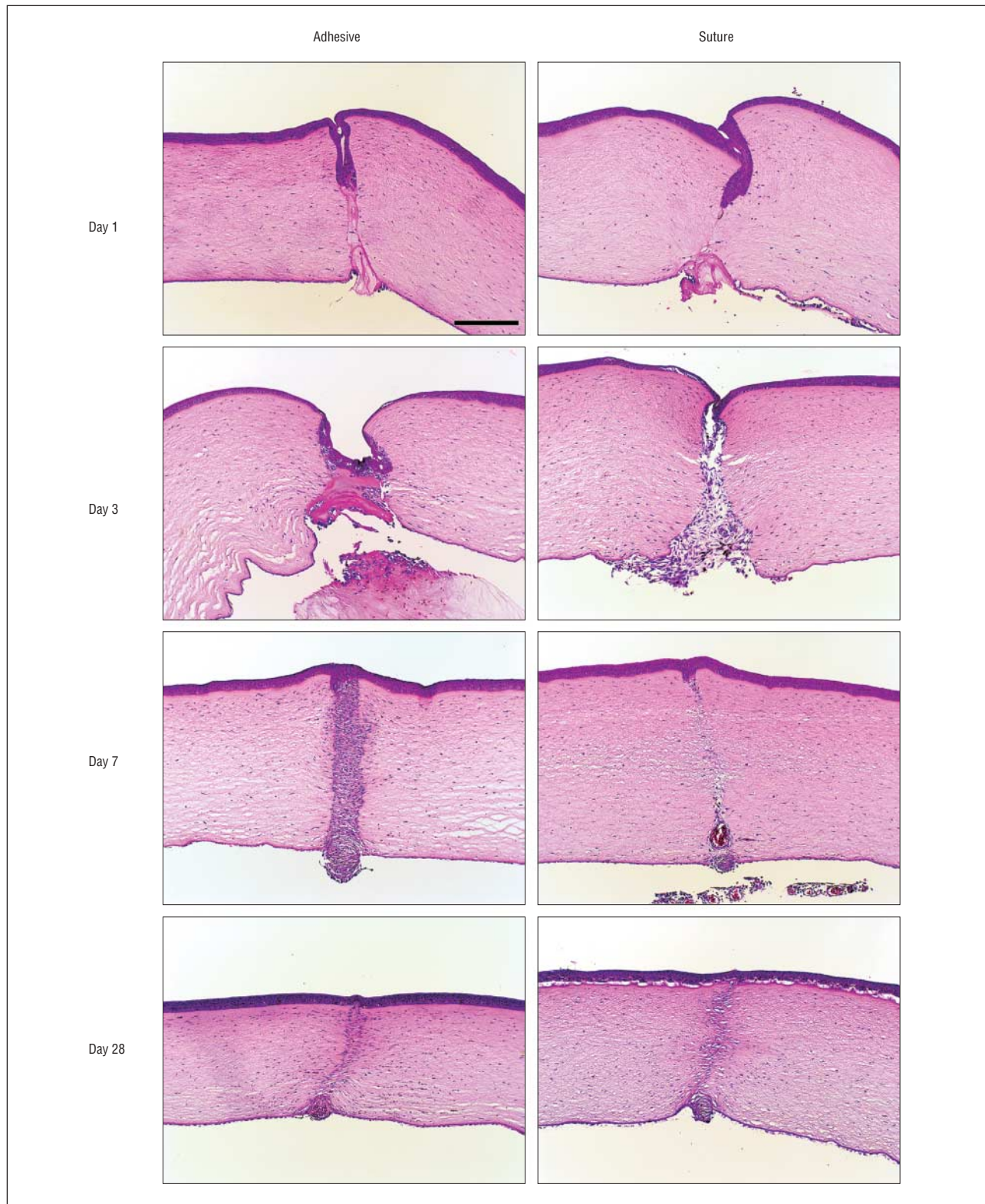


Figure 3. Histologic appearance (original magnification $\times 10$). Scale bar indicates 200 μm .

COMMENT

Corneal wound healing studies have been performed on primates,¹¹⁻¹⁴ cats,¹⁵⁻¹⁸ dogs,¹⁸ rats,¹⁹ chickens, and rabbits.^{20,21} Of these animal models, the primate eye is gen-

erally accepted as the most similar to the human eye.²² However, these initial *in vivo* experiments did not justify the use of such a primate model. Rabbits have been the most commonly used animal for *in vivo* experiments,^{20,21} but significant limitations exist. Rabbit cor-

neas lack a Bowman layer,²³ and the blood-aqueous barrier is easily disrupted by mechanical manipulation.²⁰ In rabbits, perforating corneal injuries are sealed within hours with a fibrin plug, quite unlike human corneas.²⁴ Consequently, we chose the white leghorn chicken (*Gallus gallus domesticus*) model. Recently, the chicken cornea has become a widely accepted model,²⁵⁻²⁸ and the Commission of the European Communities has recognized the chicken as a preferred model for assessing eye irritation.²⁹ Although other animals appear more phylogenetically similar to humans, the structure, composition, and physiological features of the chicken cornea are remarkably comparable.²⁷ The chicken cornea is one of the few models with a definable Bowman layer³⁰ and has a very stable blood-aqueous barrier, which eliminates an important confounding variable in studying ocular tissue response to perforating injury.²⁰ The anatomic layers in the human cornea all exist in the chicken cornea and are similarly proportioned, with a comparable endothelial cell density.²⁷ As a result, the chicken eye appears to be an optimal and accessible model for predicting human ocular responses to perforating injuries.

The application of a biodendrimer adhesive was as effective as traditional suturing in closing full-thickness corneal wounds, and no difference in postoperative complications between the groups was observed. However, some differences in the healing response deserve mention. One wound in the adhesive group remained Seidel positive immediately after closure. Because of the small sample size, commenting on the significance of this difference is not possible, but initial leakage may have occurred as a result of incomplete application of the adhesive. However, all anterior chambers reformed immediately despite Seidel positivity, and all wounds became Seidel negative by day 1. Clinically, leakage is often noted intraoperatively in sutured eyes, and additional sutures may be placed or loose sutures replaced. Similarly, there is no contraindication to reapplication of polymer if a leak is noted.

The polymer is applied at the surface of the wound, which likely explains the wound separation observed in the corneas on day 3. This was manifest histologically as hyperplastic epithelium plugging the anterior portion of the wound and fibrinous exudate within the posterior aspect of the wound. On day 7, this wound separation resulted in broader scars in the glued corneas than in the sutured corneas. Clinically, wounds that received the polymer sealant had minimal corneal haze on day 1, and by day 3 all of the eyes were clear (with the exception of a faint linear scar in the incision tract). In contrast, suture-treated eyes had significant corneal scarring that only became mild by day 28. Corneal scarring can limit visual acuity and clinical examination. Wounds receiving polymer sealant had less surface irregularity, which may lead to less astigmatism. Corneal topography would have been helpful to characterize astigmatism and to confirm the apparent smoothness of the corneal surface evident on histologic examination. Although the corneal scar was wider in the adhesive-treated group, prominent individual scars were observed at the suture sites in the sutured group, and this, together with the increased haze, indicate that the polymer sealant was at least

as good for closing the corneal incisions as the traditional suture method.

Although both suturing and adhesive repair of corneal lacerations can be effective, each has significant drawbacks. Suturing requires technical skill and access to an operating room. Suture placement deforms the cornea, creating artificial lines of tension, and inflicts trauma, especially when multiple passes are made. Loose or broken sutures require removal, act as a nidus for infection, and may incite corneal inflammation and vascularization.³¹ Sutures can produce uneven healing with resultant regular or irregular astigmatism.³² Application of cyanoacrylate glue is difficult because it immediately solidifies on contact with water and can cause complications such as cataract, corneal infiltrates, keratitis, glaucoma, and retinal toxic effects.³³⁻³⁷ Cyanoacrylate is opaque, obscuring both vision and clinical examination while in place. Moreover, cyanoacrylate is stiff and abrasive, making it an irritant and easily dislodged. Fibrinogen glue has limited utility because of the need for autologous fibrinogen, potential for viral transmittance, long preparation times (30 minutes), slow setting times (minutes), expense, and the general difficulty in its use to close corneal wounds.³⁸

The biodendrimers used in this experiment required argon-laser application for polymerization, adding time and an additional piece of equipment to the process. An advantage of using the laser-activated system is complete control of the adhesive formation since it takes place only at the site of laser irradiation. The adhesive can also be easily and readily applied to the wound site because it is a low-viscosity solution and does not polymerize on tissue contact (as with cyanoacrylate glue) or on mixing (as with fibrin glue). In addition, dendritic adhesives form a protective barrier that prevents fluid movement in and out of the wound and, as such, may act as a microbial barrier to infection.⁹ The outcomes observed with the biodendrimer-based adhesive favor its use for the repair of corneal wounds caused by surgery, infection, or injury. "Self-gelling" biodendrimer adhesives, which do not require light, are currently being investigated and, when tested *in vitro*, performed satisfactorily.^{39,40}

The ease of application, as well as the ability to quickly and precisely seal a wet or dry corneal wound, suggests that these materials may prove to be superior to current treatment with either sutures or cyanoacrylate glue. The adhesive's rheologic properties allow rapid yet controlled placement, swiftly securing the tissue in place and restoring intraocular pressure on exposure to light. The adhesive acts locally without signs of toxic effects, may provide a mechanical barrier to microbes, and persists long enough to allow wound healing. The elastic mechanical properties maintain the structural integrity of the eye and may induce less astigmatism. These advantageous properties may encourage widespread use of this sealant for corneal wounds caused by surgery, infection, or injury in addition to other ophthalmologic applications such as closure of leaking blebs and sclerectomies.

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Correspondence: Terry Kim, MD, Department of Ophthalmology, Cornea and Refractive Surgery, Duke University Eye Center, 2351 Erwin Rd, Box 3802, Durham, NC 27710 (kim00006@mc.duke.edu).

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