In Vitro Sealing of Clear Corneal Cataract Incisions With a Novel Biodendrimer Adhesive

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Objective: To determine if a biodendrimer adhesive will seal a clear corneal cataract incision.

Design: An experimental study in which 2.75-mm clear corneal cataract incisions were made in 8 human donor eyes. The corneas were mounted on an artificial anterior chamber. Leaking pressure was determined in 6 corneas. These corneas were then treated with adhesive and leaking pressure was again measured in 4 of them. India ink was then applied to the 2 remaining treated and the 2 untreated corneas. Chamber pressure was cycled between 100 and 0 mm Hg. Optical coherence tomography was used to visualize the wound dynamics of a ninth cornea treated with adhesive, mounted, and pressure cycled in a similar fashion.

Results: The mean (SD) leaking pressure was 77 (14) mm Hg for the nonsealed wounds and 142 (22) mm Hg for the adhesive-sealed wounds. India ink entered the nonsealed wounds and anterior chamber when the intraocular pressure was cyclically raised and lowered, whereas no India ink entered the adhesive-sealed wounds. The optical coherence tomography–visualized corneal wound did gape under pressure cycling, but the adhesive remained intact and stretched to conform to the wound.

Conclusions: Biodendrimer adhesives may be used to seal cataract wounds to prevent leakage and influx of fluid.


With the advent of foldable and injectable intraocular lenses, sutureless clear corneal cataract surgery has become the preferred method for most ophthalmic surgeons. This technique allows for greater patient comfort, less inflammation, and more rapid visual recovery. However, several articles in the peer-reviewed literature support an association between clear corneal cataract surgery and an increased risk of endophthalmitis.

A meta-analysis of studies conducted between 1979 and 1991, a time period before sutureless cataract surgery was performed, found the incidence of endophthalmitis after cataract extraction to be 0.13%. A study examining outcomes of patients who had sutureless clear corneal cataract surgeries from 1992 to 1996 found an incidence of postoperative endophthalmitis of 0.29%. The same study showed an incidence of endophthalmitis with scleral tunnel incisions of 0.2%. In a retrospective case-controlled study from 2003, Cooper et al found a 3-fold greater risk of postoperative endophthalmitis associated with clear corneal incisions. More recently, the risk of endophthalmitis following clear corneal cataract surgery was shown to be as high as 0.38% by a multinational prospective study conducted by the European Society of Cataract and Refractive Surgery.

Using a laboratory model, McDonnell and colleagues have been able to study the morphology and behavior of clear corneal cataract incisions using optical coherence tomography (OCT) under varying intraocular pressures (IOPs) in ex vivo human and rabbit eyes. Sarayba and colleagues have further evaluated the self-sealing properties of these incisions in human globes using India ink during the application of external pressure and fluctuation of IOP. Both studies demonstrated that standard clear corneal cataract incisions tended to gape and cause influx of ocular surface fluid and/or India ink under a variety of conditions including lower IOPs and external manipulation. These findings support the hypothesis that unsutured clear corneal cataract incisions may not be self-sealing during the entire postoperative period. Postoperative phenomena such as transient hy-
potony, eye blinking, and/or eye rubbing could lead to a gaping or opening of the corneal incision, allowing ocular surface fluid and bacteria to enter the eye and thus increase the risk for endophthalmitis.

Given the disadvantages of traditional adhesives such as cyanoacrylate and fibrin,6-7 we used previously described experimental setups to evaluate a novel biodendrimer adhesive and its ability to seal clear corneal cataract incisions.6-7 Our objective also included studying the morphology of these clear corneal incisions in the setting of biodendrimer adhesive application.

METHODS

Eight fresh human donor eyes were obtained from the North Carolina Eye Bank. A triplanar clear-cornea cataract incision was made in each eye using a 2.75-mm keratome. A full-thickness circumferential excision of the posterior sclera was made just anterior to the vortex veins using scissors. The vitreous, retina, uvea, and lens were removed. The remaining corneal-scleral shell was mounted on a 2-port artificial anterior chamber and secured in place. The chamber was constructed of rigid plastic and stainless steel by the Ophthalmic Biophysics Department at Duke University Eye Center. All air was flushed from the system and the transducer was zeroed with the system open to atmospheric pressure with the eye soft. The system was closed and the pressure remained at zero. One port was attached via rigid tubing to a microinfusion pump (KD Scientific, Holliston, Massachusetts). The other port was attached via rigid tubing to a pressure monitor (model CMS 24 Omnicare; Hewlett Packard, Palo Alto, California). An infusion of balanced salt solution was then initiated at a rate of 10 mL/h (2.78 µL/s). Six of the 8 eyes were set up with this system and viewed under an operating microscope. As soon as a leak was visualized, the pressure was recorded (ie, leaking pressure).

Infusion was then stopped and the surfaces of the 6 eyes were dried. The biodendrimer adhesive was applied to the corneal wounds of these same 6 eyes. The polymer was provided by Grinstaff et al. The synthetic procedure to prepare the polymeric adhesives has been reported.18 The materials were stored at −20°C under nitrogen in a sealed bottle and warmed to 37°C before use. The adhesive was a 2-component self-gelling polymer that cures upon mixing the separated components. The components consisted of a dendritic polymer synthesized from the amino acids lysine and cysteine and a linear polymer—poly(ethylene glycol)-butyric dialdehyde.18 To prepare the hydrogel, the dendron was mixed with poly(ethylene glycol butyric dialdehyde) of 3400 molecular weight in 4-(2-hydroxyethyl)-1-piperazineethanesulfonylic acid (HEPES) buffer at a pH of 7.4 for approximately 5 seconds using a 4.1-mm keratome blade. The mixed solution was then applied to the wound edge using the bottom side of the keratome blade. The total concentration of polymer in solution was 50% wt/vt. When the hydrogel precursors were applied to the wound, the solution cured, formed a hydrogel, and sealed the wound in less than 1 minute forming a clear, soft, flexible hydrogel adhesive. Curing time was measured by infrared spectroscopy (rheology).

The leaking pressures of the nonsealed wounds were 68, 77, 60, 80, 75, and 100 mm Hg (mean [SD], 77 [14] mm Hg). The leaking pressures of the adhesive-sealed wounds were 173, 124, 128, and 141 mm Hg (mean [SD], 142 [22] mm Hg). In the 2 nontreated eyes, India ink was visualized entering the wound and the anterior chamber when the IOP was cyclically raised and lowered (Figure 1). In the adhesive-sealed eyes, no India ink was visualized entering the wound or anterior chamber when the IOP was cyclically raised and lowered. Of note, ink seemed to enter at low pressures. Hematoxylin-eosin staining revealed India ink particles throughout the wounds in the nonsealed group. No ink particles were found in the wounds of the adhesive-sealed group (Figure 3).

Optical coherence tomography demonstrated a smooth homogeneous layer of adhesive covering the wound. With cyclic raising and lowering of IOP, real-time imaging with OCT revealed minimal, then extensive, gapping of the wound (Figure 3). However, because of its elastic characteristics, the polymer stretched to conform to the wound and was not disrupted or dislodged. Even with visualized wound gapping, no leakage around the adhesive was observed.

References:

Although clear corneal incisions may be demonstrated to be self-sealing at the time of surgery, it appears that these wounds are susceptible to gaping when subjected to IOP fluctuations or mechanically induced external pressure. These findings provide a possible mechanism whereby ocular surface fluid and microorganisms can enter the eye following cataract surgery and potentially explain the increased incidence of endophthalmitis associated with sutureless clear-corneal surgery. Tissue adhesives offer an attractive alternative to sutures and already have an established role in ophthalmology, particularly in the management of corneal perforations. Initially presented by Coover et al in the 1960s, authors such as Webster et al reported the use of cyanoacrylate glue for corneal perforations. Since then, similar cyanoacrylate adhesives have been used on the cornea as an off-label use and have proven to be an effective therapeutic option in certain ophthalmic settings. These settings include the emergent treatment of small corneal perforations and prophylactic treatment of progressive corneal thinning disorders. The goal of tissue adhesive therapy frequently is to provide immediate restoration of structural integrity and occasionally to prevent further corneal thinning. In either case, cyanoacrylate adhesives can lead to permanent corneal healing or at least offer temporary closure for anticipation of further surgical intervention that may be necessary (ie, corneal patch grafting, lamellar keratoplasty, and even therapeutic penetrating keratoplasty). Some investigators even performed laboratory and clinical investigations to evaluate a newer formulation of commercially available cyanoacrylate glue to seal clear corneal cataract incisions in cataract surgery. Although the adhesive proved successful as a temporary wound barrier, many of the patients experienced foreign-body sensation as well as conjunctival hyperemia.

In general, cyanoacrylate-based corneal adhesives as a class have limitations regarding their ease of applicability and effectiveness. The methods of application vary (eg, direct application with a tuberculin syringe, initial placement of adhesive on a piece of sterile draping). They can also be cumbersome, often requiring numerous instruments and equipment such as cotton-tipped applicators, cellulose sponges, and eyelid speculum. The technique requires the adept and delicate application of a precise amount of adhesive in a dry environment to facilitate adhesive solidification and wound closure. Excessive amounts of glue can predispose the glue to pre-
mature dislodgement (from normal eyelid movement on the cornea) and can also cause foreign-body sensation. A wet application surface can prevent glue adhesion and solidification. Following the procedure, a bandage contact lens is frequently placed over the glue and cornea to minimize the chance for dislodgment due to eyelid movement and to reduce patient discomfort. Therapeutic effectiveness is often restricted to small corneal perforations of limited size (usually <1-2 mm) because of the inability to solidify, and hence close, larger perforations. Furthermore, complications with traditional corneal adhesives have also been reported and include cataract formation, corneal infiltration, granulomatous keratitis, glaucoma, and even retinal toxicity.8-11

The off-label use of fibrin-based adhesives (ie, Tisseel; Baxter, Deerfield, Illinois) in ophthalmology has attracted increasing attention for securing conjunctival autografts in pterygium surgery and for sealing laser in situ keratomileusis (LASIK) flaps from recurrent epithelial ingrowth.12,13 They have also been used in an ex vivo setting to demonstrate their effectiveness in sealing clear corneal cataract incisions.26 These adhesives typically require the combination of a fibrinogen and thrombin compound to form an adhesive. After warming these solutions in a specially designed heating unit, these 2 components can then be mixed together to form a solid coagulum on the ocular surface.13 The advantage of fibrin-based adhesives is its tolerability on the ocular surface. However, disadvantages such as the preparation time (up to 20-30 minutes), curing time (up to 3-5 minutes to form a solid coagulum and up to 8-10 minutes for complete drying), and cost (approximately $80/mL) preclude their practical use for sealing clear corneal incisions in routine cataract surgeries. Furthermore, because of the human and bovine sources of the components, fibrin-based adhesives like Tisseel carry the potential risk of viral and/or prion disease transmission.

The introduction of an adhesive specifically designed for ophthalmic use could potentially avoid the drawbacks of traditional suture and the limitations of currently available adhesives. Biodendrimers represent a novel class of dendritic polymers that possess many of the characteristics needed for an ideal ophthalmic adhesive.18,27,28 Dendrimers are polymers that contain a central core from which the polymers branch outward in a treelike structure. A biodendrimer is composed of biocompatible monomers and can be completely synthesized in the laboratory without the need for biologic components. They are highly ordered, with a single molecular weight, and exhibit numerous end groups for functionalization.18 Unlike sutures, biodendrimers are applied only to the surface of the cornea. Thus they are not traumatic, do not serve as a nidus for infection, and do not need to be removed. They can be applied to the wound and completely cure in less than 30 seconds.18,29

In this study we have demonstrated that a biodendrimer adhesive can effectively seal a clear corneal cataract wound. In each of the wounds tested, the adhesive was easily applied using a keratome. In this experiment, a mixing process vs laser activation was used to cross-link the 2 components of the biodendrimer adhesive to simplify the procedure and eliminate the need for an argon laser. When mixed, the adhesive was immediately viscous, stayed at the area where it was applied without runoff, and cured in less than 30 seconds. When polymerized, the biodendrimer adhesive formed a smooth homogeneous hydrogel layer on the wound, in sharp contrast to cyanoacrylate, which cures unevenly, creating a rough elevated surface.

The hydrogel polymer adhered strongly to the cornea and did not easily dislodge with IOP fluctuation or mechanical external pressure as confirmed by real-time OCT imaging of the corneal wound. The adhesive hydrogel maintained its tight adherence to the cornea despite large nonphysiologic increases in eye pressure. McDonnell et al6 demonstrated that as the eye pressure increases, beveled wounds tend to become more approximated. However, as this study supports, if the pressure is raised sufficiently high, even carefully constructed nonsealed beveled wounds will leak. The leaking pressure of wounds sealed with the biodendrimer adhesive was significantly higher than nonsealed wounds (mean, 142 vs 78, respectively). As hard lid squeezing can raise the IOP to nearly 90 mm Hg,30 the increase in leaking pressure provided by the adhesive may have clinical significance. If the postoperative eye is subjected to leaking due to intermittent elevated eye pressure, healing time may be delayed.

Aqueous leakage itself does not, in theory, increase the risk of endophthalmitis, but the relative hypotony that follows and the cycling of the pressure from high to low presents a dynamic physical state where pathogens can enter the eye. In the studies of McDonnell et al,8 the cycling from elevated to depressed IOP resulted in the influx of india ink particles from the surface of the eye into the anterior chamber. That same phenomenon was confirmed in our study in the wounds that were not sealed with adhesive. Conversely, all of the corneal wounds that were sealed with adhesive showed no evidence of india ink influx into the anterior chamber during IOP fluctuation. Histopathology confirmed the absence of india ink particles within the corneal wounds that were sealed with adhesive.

For each eye we tested, application of the biodendrimer adhesive provided a strong seal on the eye against high IOP and also prevented any influx of extracocular content through the wound during IOP fluctuations. Real-time OCT imaging clearly demonstrated corneal wound gaping at extreme pressures, high or low. Yet even with wound gaping, the adhesive maintained its adherence to the corneal wound and was able to prevent leakage of intraocular fluid.

With the proven role of tissue adhesives in various corneal procedures, there is no question that improvements made either to the composition and/or to the method of application of tissue adhesives could lead to a more ideal ophthalmic adhesive. Tissue adhesives that are specifically engineered for ophthalmic use could potentially supplant sutures and provide a true sealing of the corneal incision to prevent wound leakage and provide a potential microbial barrier. Biodendrimers are a novel class of polymers that provide a promising alternative as an ophthalmic tissue sealant. In vitro experiments in human cadaver eyes have shown that bioden-
drimers applied to a 4.1-mm full-thickness corneal laceration create a seal that is able to withstand extreme elevations in IOP without breaking. In vitro studies using human eye bank eyes have also demonstrated the ability of these biodendrimers to close 3-mm clear corneal cataract incisions more effectively than sutures, as evidenced by higher leaking pressures.

Although these in vitro studies have been able to show the effectiveness of our biodendrimer adhesive in sealing clear corneal cataract incisions, further in vivo studies are required to determine clinically relevant and important issues such as its duration on the eye, its propensity for inducing inflammation, and its tolerability on the ocular surface. Recent studies comparing these new biodendrimer adhesives with conventional sutures in repairing corneal lacerations in an in vivo chicken model have been conducted and confirm the safety, duration, and effectiveness of these dendritic polymers. However, the experimental data does demonstrate that, theoretically, corneal adhesives specifically tailored for ophthalmic use could offer a practical alternative to sutures and represent a paradigm shift in wound closure. Further studies are warranted to support the role of adhesives to seal cataract incisions, with the goal of improving wound integrity and closure and potentially decreasing the risk for endophthalmitis.

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REFERENCES