Use of Fibrin Tissue Adhesive in Conjunctival, Corneal, Cataract, and Refractive Surgery

a report by
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Sutures are a mainstay of almost all surgical fields. Despite an extensive history and widespread use, the universal trend toward simpler, quicker, and more comfortable surgical procedures has fostered the development of sutureless techniques. The first experimentation with fibrin in ocular tissue was in 1978,[1] and the first use of fibrin in human patients was to repair injuries to the lens.[2] These techniques had limited success because of rapid clot lysis by plasmin. With the commercial availability in the last two decades of fibrin adhesives that include the plasmin inhibitor aprotinin, fibrin has seen rapidly growing use in anterior segment surgery.

Fibrin tissue adhesive has been in use for over 25 years for the repair of splenic and liver rupture, and as an adjunct in cardiac surgery. Its 'off-label' use extends to many other abdominal and thoracic procedures, and its derivatives are commonly used in neurological and orthopaedic surgery. Currently, the most commonly used fibrin-based adhesive in ophthalmology is Tisseel VH Fibrin Sealant (Baxter BioSurgery, Deerfield, Illinois), whose use in ophthalmic applications is considered off-label. Tisseel consists of two parts that, when mixed, mimic natural clot formation. One part consists of human fibrinogen and bovine aprotinin, whereas the other part consists of human thrombin and calcium chloride. When the two parts are combined intra-operatively, the final stages of the coagulation cascade are initiated, and a strong, dense, cross-linked fibrin clot forms in about one minute. This clot adheres to rough (but not epithelialized) wound surfaces, and allows the gluing of tissues. Tisseel maintains its adhesive properties for about one week after surgery. The cost of Tisseel from Baxter is about $100 for a 1cc unit dose, making it a more expensive alternative to suture. Many surgeons feel that the savings in surgical time offset this cost, and to reduce this cost some surgeons will use a single unit dose in a sterile fashion for multiple procedures.

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Andrew Behesnilian is a second-year medical student at the David Geffen School of Medicine at UCLA, and is pursuing a career in ophthalmology. He is currently writing a manuscript evaluating the joint use of fibrin adhesive and amniotic membrane transplantation in pterygium surgery. He spent summer 2007 in the Republic of Armenia volunteering with the Armenian Eye Care Project (www.eyecareproject.com), and looks forward to returning there for volunteer work in the future as a practicing ophthalmologist.

Preparation, Handling, and Risks

Before use, Tisseel adhesive requires about 20 minutes of warming in a heating device provided without charge by Baxter. Its labeling states that it can be used for four hours after preparation. Most surgeons choose to dispense each part separately from a 1cc syringe. The material can be drawn up into the syringe from the vial using an 18-gauge needle. Many surgeons will then discard the needle and dispense the adhesive parts onto the eye directly from the hub of the syringe. If slower polymerization is desired for ease of use or complicated procedures, the thrombin portion of fibrin adhesive can be diluted 1:10 or even 1:100 with balanced saline solution (BSS). The calcium chloride in BSS makes it an ideal diluent. These dilutions will slow the adhesive's polymerization to about one and two minutes, respectively. Laboratory studies of Tisseel's tensile and shear strengths show that dilution of thrombin does not reduce its adhesiveness.[3]

Risks and Off-label Status

Like any blood product, fibrin adhesive carries a theoretical risk of disease transmission. However, Baxter's Tisseel has been in use worldwide for over 26 years in 11 million surgical procedures without any reported transmission of HIV, hepatitis, or prion-mediated disease.[4] Because Tisseel uses bovine aprotinin, there is a theoretical risk of sensitizing patients to bovine blood proteins. Though controversial, some animal evidence suggests this may predispose to future autoimmune disease.[5] Despite its widespread adoption, Tisseel's use in ophthalmology is not consistent with its US Food and Drug Administration (FDA) labeling, and is therefore considered 'off-label.'

Other Fibrin Adhesive Products

Evicel, a fibrin adhesive made exclusively from human proteins, may avoid the risk of exposure to bovine blood proteins. This product's labeling does not exclude ocular use, and it is available from Johnson & Johnson's Ethicon division as Evicel. Unfortunately, this product has not been widely used in ophthalmology. VitaGel (Angiotech Pharmaceuticals, Vancouver, British Columbia) is a fibrin adhesive made from a patient's own serum. Because this product requires significant preparation time and is not currently configured for microsurgical use, it has not been used widely in ocular surgery.

Pterygium Excision with Conjunctival Autograft

Fibrin adhesive was first popularized in pterygium surgery with conjunctival autografts using a technique described by Koranyi in 2004.[6] In this

Figure 1: Pre-operative Photograph of Pterygium

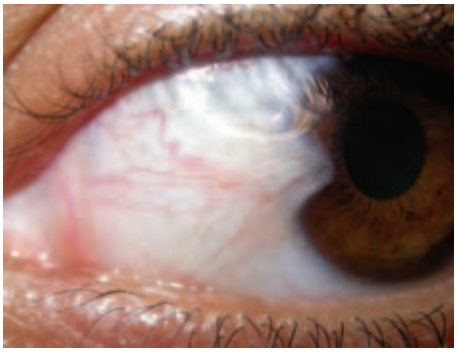


Figure 2: One Week after Pterygium/ Autograft Surgery Using Fibrin Tissue Adhesive

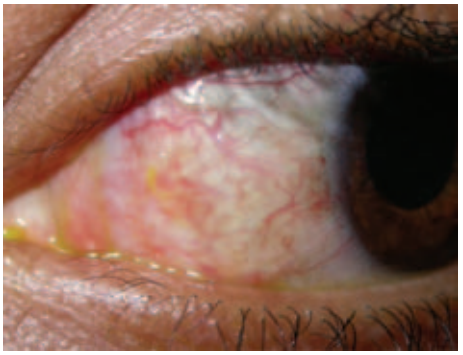


Figure 3: Conjunctivochalasis

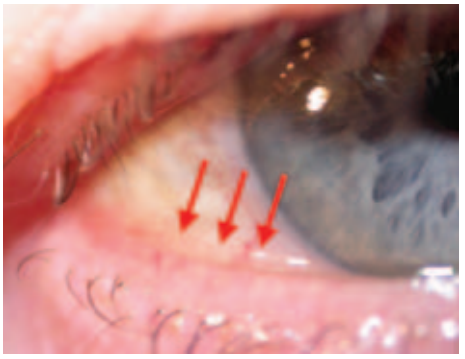


Figure 2: This patient has no discomfort and only minimal signs of healing of the graft, which was harvested from the superior bulbar limbal region. Figure 3: Note redundancy of bulbar conjunctiva at the lower lid margin (arrows).

procedure (video available at www.amtsurgery.com), the surgeon removes the pterygium and harvests an autograft in a routine fashion. The autograft is laid stromal-side up on the cornea with its limbus aligned with the limbus of the recipient site. A small drop of thrombin is applied to the dry, bare sclera. Similarly, a small drop of fibrinogen is applied to the stromal side of the autograft. Using forceps, the surgeon inverts the autograft onto the bare sclera site, mixing the two components of the adhesive. The edges of the wound are apposed to the surrounding conjunctival edge by using a 'squeegee' motion with smooth forceps to stretch the graft to fill the bare sclera site. This must be done before the adhesive has polymerized significantly, which takes from 15 seconds to about two minutes, depending on the degree of thrombin dilution used by the surgeon (see above). This technique resulted in significantly less pain than suture, and the average surgery time was cut in half (see *Figures 1* and *2*). Others have found that the rate of recurrence in these cases was comparable to suture.[7]

Amnionic Membrane Transplantation

Amnionic membrane transplant (AMT) tissue, derived from human placenta, has been used routinely for almost a decade in ocular surface surgery to promote healing while suppressing inflammation and scar formation. The first report of ophthalmic AMT use was in the 1940s for the treatment of sterile corneal ulceration.[8] For pterygium surgery, many surgeons prefer to use AMT to cover the bare sclera instead of a conjunctival autograft, because AMT does not require damaging the limbal conjunctiva in a donor site and offers a quicker procedure, possibly with less pain because only one region of conjunctiva is injured. Though studies vary among surgeons and studies, recurrence rates with amnion are generally comparable to those with conjunctival autograft (CA), regardless of the type of AMT used.[9]

Another common use of AMT is for treatment of conjunctivochalasis. Conjunctivochalasis consists of relaxation (redundancy) of conjunctiva with loss of underlying Tenon's fascia, which normally anchors the conjunctiva to the globe. It generally occurs in patients over 50 years of age, frequently with a history of recent cataract surgery. Conjunctivochalasis causes a painful foreign body sensation that can be localized to the area of redundant conjunctiva at the lid margin (see arrows, *Figure 3*). Surgical treatment involves removing 1–2mm of conjunctiva while preserving about 1mm of intact limbal conjunctiva. The remaining bulbar conjunctiva recedes toward the limbus, leaving a wider area of bare sclera. The resulting conjunctival defect can be grafted with amnionic membrane, which is secured in place with fibrin tissue adhesive (see *Figures 4a–c*). In properly selected cases, pain can be eliminated by this procedure. The ocular surface usually heals quickly with epithelialization in about seven days (see *Figure 5*).

AMT is available under FDA regulation from three commercial sources in the US. Two of these products, AmbioDry (IOP, Inc., Costa Mesa, California) and Acelagraft (Oasis Medical, Inc., Glendora, California), are freeze-dried and shelf-stable, while the third, AmnioGraft (Bio-Tissue, Inc., Miami, Florida), is cryopreserved wet amnion requiring refrigeration.

In the past, amnion was adhered to the ocular surface exclusively with sutures. However, fibrin adhesive has greatly simplified this procedure by providing rapid adhesion across the entire surface of amnion, rather than just at the edges with sutures. The technique for gluing AMT to the ocular surface depends on the type of amnion used (dry or wet). For more information on surgical technique, contact each product's manufacturer.

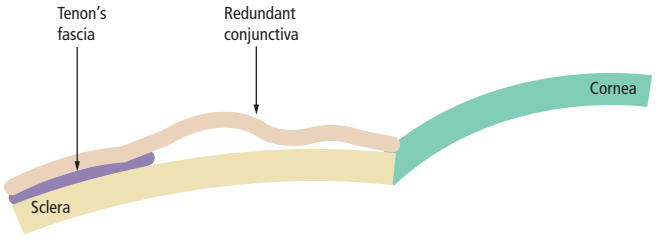
Uses in Corneal Surgery

Automated lamellar keratoplasty has been used to treat corneal irregularity caused by previous trauma or surgery. Rather than suture, Kaufman[10] described a technique in which fibrin adhesive was used to secure the graft. This technique involves using a microkeratome to remove the anterior cornea of both the recipient eye and a donor (whole globe or corneoscleral rim mounted on an artificial anterior chamber). The donor lamellar button is placed on the recipient site, and both components of fibrin adhesive are placed in the interlamellar interface. The excess fibrin adhesive is 'squeegeed' out of the interface with a blunt spatula on the surface of the cornea.

Laser-assisted *In Situ* Keratomileusis—Epithelial Ingrowth and Flap Dislocations

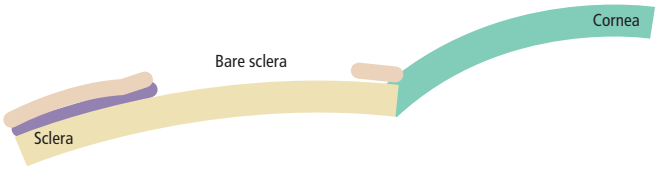
Recurrent epithelial ingrowth after laser-assisted *in situ* keratomileusis (LASIK) surgery is one of the most frustrating complications of this procedure. Anderson and Hardten[11] first described a technique, which has since been widely used, for placing fibrin adhesive sparingly on the ocular surface to seal

Figure 4a: Conjunctivochalasis



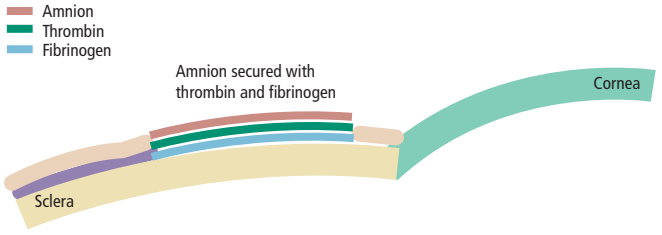
The redundant conjunctiva near the limbus has no anchoring Tenon's fascia.

Figure 4b: After a 1–2mm Strip of Conjunctiva is Removed



About 1mm of limbal tissue is spared and the remaining conjunctiva recedes toward the fornix.

Figure 4c: Amnionic Membrane Fills the Defect

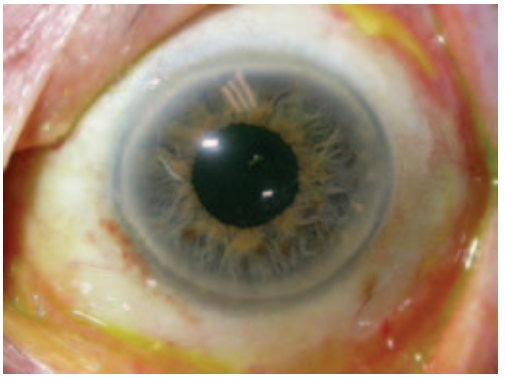


The amnionic membrane is held in place with a thin layer of fibrin adhesive, composed of thrombin and fibrinogen.

the entry portal for epithelial cells that allows this complication. In this application the adhesive is delivered through Baxter's 'duploject' application system, with care taken to deliver equal amounts of each component.

Flap adherence problems (dislocations) in the first 24 hours after LASIK can occur with eye rubbing, tight eyelids, or under dry conditions. In

Figure 5: Two Weeks after Extensive (360-degree) Conjunctival Recession with Amnionic Membrane Transplantation



The ocular surface is re-epithelialized and painful, recurrent foreign body symptoms have been eliminated in this patient.

cases of repeated dislocations, fibrin adhesive has been placed in the flap interface with good success.[12] In this method, the edge of about one-third of the flap is reflected centrally onto itself. Less than one drop of thrombin is placed on the exposed stromal bed. This is accomplished by forming a bead of thrombin on the tip of a cannula, then touching that droplet to the stromal surface and using the cannula to spread the droplet over the entire exposed surface. A similar procedure allows placement of less than a drop of fibrinogen on the underside of the reflected flap. The flap is then laid back in place with a 'squeegee' motion to remove excess fibrin material before it polymerizes, and a bandage contact lens is placed. This can be repeated in two or three different meridians. Often it is only necessary to use adhesive under the superior portion of the flap, since downward pressure from the eyelid is the most common cause of these dislocations.

Cataract Surgery

Clear corneal incisions in cataract surgery have become standard practice, but several authors[13] have suggested that post-operative bacterial endophthalmitis is more common among patients having these incisions than those receiving the older scleral tunnel technique.[14] Kim[15] and Henrick[16] have demonstrated that fibrin adhesive showed promise for closure of scleral tunnel cataract incisions, and preliminary evidence on eye bank corneas suggests it may also have value for closing clear corneal incisions with a simple technique using readily available instruments, which may help reduce the risk of infection.[17] Further study on the ideal method for applying adhesive and its possible intraocular toxicity is ongoing. ■

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