Handout:
Sutureless Lamellar Keratoplasty

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PUBLICATIONS:

Human Fibrin Tissue Glue for Corneal Lamellar Adhesion in Rabbits: A Preliminary Study

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Purpose: To evaluate the use of a human fibrin tissue adhesive in the adherence of corneal lamellar flaps in rabbit eyes.

Methods: Corneal flaps were made using a microkeratome in both eyes of six New Zealand white rabbits. In the right eyes, the flaps were glued with fibrin tissue adhesive; in the left eyes, flaps were allowed to heal without adhesive (controls). All eyes were treated with antibiotics and steroids once daily for 10 days. Slit-lamp biomicroscopy was performed 1 and 10 days after surgery. The rabbits with surviving flaps were euthanized and the corneas obtained for histopathologic examination 10 days after surgery.

Results: Slit-lamp examinations showed no interface deposits and no other signs of corneal toxicity. Histologically, a few inflammatory cells were seen in both the experimental and control eyes, and microscopic gapping and tissue debris were observed in three of the six control eyes.

Conclusions: Human fibrin tissue glue was well tolerated in these eyes, with no or minimal corneal toxicity. Further studies are needed to determine the tensile strength of the adhesive bond in the cornea.

The fibrinogen-thrombin adhesive system, which has been used in ophthalmology since the early 1980s, was first used to fill injuries of the lens. 1 It was not until the 1990s that a more general study of potential ophthalmic applications of this adhesive was undertaken, 2 in part because the adhesive became available commercially, but more importantly, because at that time, the fibrin was combined with aprotinin to retard dissolution of the adhesive bond.

Some of the uses evaluated included closure of the conjunctiva 3 as well as reattachment of the extraocular muscles 4 in strabismus surgery, conjunctival closure in glaucoma surgery, 5 closure of the scleral tunnel after cataract surgery, 6 and enhancement of healing and stabilization of radial keratotomy wounds. 7,8 Fibrin glue has also been used with amniotic membrane grafts to seal corneal perforations. 9 To our knowledge, however, our study is the first trial of a commercially available fibrin-aprotinin tissue adhesive for corneal lamellar reattachment.

When the epithelium is disrupted during lamellar keratectomy performed with a microkeratome, adhesion of the corneal flap is dramatically reduced and is not re-established until the surface of the flap is re-epithelialized by the fluid-impermeable epithelium, just as laser-assisted in situ keratomileusis (LASIK) flaps with large epithelial defects adhere less well and have more epithelial ingrowth. 10–12 If a tissue adhesive could be used safely to enhance reattachment of the flap, it might not only permit more reliable flap adhesion but also could shorten the procedure time and might reduce astigmatism compared with corneal suturing. The purpose of this study was to determine whether a fibrin adhesive can help microkeratome flaps adhere to the stroma underneath, with the goal of permitting sutureless lamellar keratoplasty.

METHODS

Tissue Adhesive

The tissue adhesive (Tisseel VH Fibrin Sealant; Baxter Healthcare Corp., Glendale, CA), which is an FDA-approved, commercially available product that is provided in kit form, was prepared for use according to the manufacturer's instructions. Briefly, the freeze-dried sealer protein concentrate was reconstituted with the fibrinolysis inhibitor solution, and the freeze-dried thrombin solution was reconstituted with a calcium chloride solution. Then equal amounts of the two components were transferred to the sterile surgical field and loaded into a double-chambered syringe.

Surgical Procedure

All animals involved in this study were treated in accordance with the ARVO Resolution on the Use of Animals in Ophthalmic and Vision Research. Six New Zealand white rabbits weighing 3 to 6 lb each were used. The animals were anesthetized with 2 mL ketamine injected intramuscularly (100 mg/mL; Schering-Plough, Kenilworth, NJ). The corneal epithelium was mechanically scraped from both eyes. A microkeratome (Automatic Corneal Shaper, Bausch & Lomb, San Dimas, CA) was used to create a nasally hinged corneal flap approximately 160 µm thick in each eye. All flaps were irrigated, and any debris present in the interface was washed away with saline solution (BSS, Alcon Surgical, Fort Worth, TX). In the right eyes, the flaps were reposited with tissue adhesive. The flap was held down with a Paton spatula, and the adhesive was instilled under the flap through a cannula from a double syringe that mixed the components. In the left eyes, the flaps were reposited without tissue adhesive. Topical antibiotics (Ocuflox, Allergan, Irvine, CA) and topical steroids (Pred Forte, Allergan) were applied to each eye once a day for 3 days after surgery.

Slit-Lamp Biomicroscopy and Histology

Slit-lamp examination and photography were carried out on days 1 and 10 after surgery. Rabbits with surviving flaps were killed on day 10, and the corneas were processed for histopathologic examination. Corneas were processed on a masked basis. Tissues were fixed in a solution of paraformaldehyde and glutaraldehyde (2%), placed in 2% osmium solution, dehydrated in increasing concentrations of alcohol to 100%, infiltrated in plastic (Embed 812, Electron Microscopy Sciences, Fort Washington, PA), polymerized at 60°C for 48 hours, and sectioned on a microtome (MT-700; Sorval).

RESULTS

Of the six flaps glued to the cornea with the tissue adhesive, one was dislocated and five remained in place until the end of the study (day 10 after surgery). On day 10, the five eyes with the surviving flaps had clear corneas on slit-lamp examination. Histopathologic examination of these eyes at 10 days showed no gapping or debris in the interface (Fig. 1). Only minimal reactive fibroblastic transformation of some keratocytes at the interface was seen; this was considered part of the normal healing process (Table 1).

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TABLE 1. Clinical and Histologic Results With Tissue Adhesive*Rabbit sacrificed on first postoperative day.

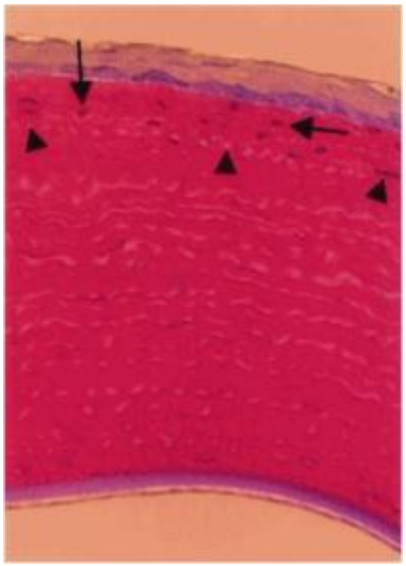

FIG. 1. Histopathologic specimen from rabbit cornea with flap bonded with tissue adhesive. No gapping or tissue debris is visible 10 days after surgery. Some reactive fibroblastic transformation of the keratocytes (arrows) is seen above the interface (arrowheads), which is thought to be a part of the normal healing process. Toluidine blue and basic fuchsin, original magnification ×10.

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In the control eyes, with no adhesive, three of the six flaps were dislocated. The three eyes with surviving flaps at 10 days were clear. On histopathologic examination, one of the three corneas showed microscopic gapping, and all three showed tissue debris at the interface (Table 2 and Fig. 2).

TABLE 2. Clinical and Histologic Results Without Tissue Adhesive*Rabbit sacrificed on first postoperative day.†Infection.

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FIG. 2. Histopathologic specimen from rabbit cornea with flap not bonded with tissue adhesive (control). Gapping (arrowheads) and tissue debris are seen at the interface (arrow) 10 days after surgery. Toluidine blue and basic fuchsin, original magnification ×10.

DISCUSSION

The results of this study showed that the tissue adhesive was biocompatible with the corneal stroma in terms of the complete absence of clinical and histologic inflammation, and attachment of the flap was improved. Since no sutures were used, potential complications related to suturing were avoided, and surgery time was probably shortened.

However, this tissue adhesive is not ideal. It is of human origin and, therefore, despite all U.S. Food and Drug Administration approval precautions, it might harbor viruses. The reconstitutional process is tedious, critical, and time-consuming, and there is rapid, irreversible clotting once it is applied to the surface, with little "working time."

In the control group, the presence of tissue debris in the absence of microscopic gapping in two corneas may have been the result of early postoperative dehiscence. The lamellar adhesion takes place mainly through physical forces, in addition to the chemical bond that occurs in tissues containing collagen. 13 The tensile strength of the bond was tested in dogs whose aorta was incised and subsequently sealed with the adhesive; the results showed that the adhesive could withstand high hemodynamic strain. 13

Although presumably the tensile strength of the bond is not great, it should be adequate to affix tissue that is simply applied to a surface and not subjected to much lateral stress. The adhesive is permeable to metabolites, optically clear, permits healing, and disappears within days or weeks, although the exact duration in the cornea is not known.

The swelling pressure of the cornea is also the pressure that tends to hold the layers together as fluid is pumped out of the stroma and the epithelial and endothelial surfaces resist fluid inflow. The pioneering work of Ytteborg and Dohlman 14 and the subsequent work of Klyce et al., 15 as summarized in The Cornea, 16 indicate that this swelling pressure can be diminished by inflow of fluid from either surface. The restoration of an impermeable epithelial surface favors the restoration of the swelling pressure within the cornea, tending to hold the impermeable surfaces together, and also favors adhesion of the LASIK flap. Although other phenomena may be involved in lamellar flap adhesion, the restoration of stromal dehydration and the swelling pressure that helps to hold the layers together play an important role in this process.

In the case of a lamellar transplant, tissue adhesion is required only until the epithelium resurfaces the graft and re-establishes tight junctions across the surface of the cornea, after which it will adhere like any other microkeratome-cut free cap. Epithelium that is impermeable to aqueous fluids allows the natural swelling pressure and endothelial pump of the cornea to pull the tissue together. Anatomical healing of connective tissue is not required for initial flap adhesion, just as it is not required in LASIK.

A good tissue adhesive has great potential for use in ophthalmic surgery. It could eliminate even the occasional use of sutures after cataract surgery, permit the adhesion of amniotic membrane over corneal ulcers as a simple outpatient procedure done at the slit lamp, attach conjunctival flaps after excision of pterygia, repair lamellar corneal defects, and substitute for sutures in attaching the conjunctiva after surgery. For removal of superficial corneal scars, microkeratome-cut donor tissue affixed to a microkeratome-cut lamellar bed may be superior to phototherapeutic keratectomy in terms of uniformity of scar removal and postsurgical optics. We think that this new tissue adhesive offers significant potential benefits in ophthalmology.

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Key Words: adhesive; cornea; lamellar

Human fibrin tissue adhesive for sutureless lamellar keratoplasty and scleral patch adhesion[*1]

a pilot study

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Abstract

Purpose

To determine whether a fibrin adhesive can facilitate the performance of sutureless lamellar keratoplasty and attachment of amnion to bare sclera.

Design

Prospective, noncomparative case series.

Participants

Six patients, 5 of whom underwent lamellar keratoplasty and 1 who received an amniotic patch of the sclera and cornea. Institutional review board approval was not required for these therapeutic treatments.

Methods

In 5 patients, the epithelium was removed from the corneal surface, a free cap, 200-μm thick, was cut with a microkeratome, and a human fibrin tissue adhesive (Tisseel VH Fibrin Sealant; Baxter Healthcare Corporation, Glendale, CA) was applied to the cut surface of the corneal stroma. A 200-μm thick, microkeratome-cut lamellar graft was placed in the stromal bed without sutures, and a bandage soft contact lens was applied. The lens was left in place for 1 week and then removed. In 1 patient, the adhesive was applied to bare sclera for attachment of amniotic membrane after removal of a conjunctival melanosis. All patients were followed up for 3 months after surgery.

Main outcome measures

Tissue adhesion, corneal clarity, and visual acuity.

Results

All 5 lamellar grafts healed and remained clear, although final visual acuity varied with visual potential and astigmatism. The amniotic membrane graft also adhered well to the bare sclera.

Conclusions

The fibrin adhesive provided satisfactory attachment without sutures for lamellar keratoplasty and amniotic patching. It should be effective for sealing of clear cornea incisions, LASIK flaps, and conjunctival and skin grafts. An adhesive that has been designed specifically for ophthalmic applications and is more convenient to use would be desirable.

There has been a prolonged search for a bioadhesive that can successfully supplement or supplant sutures in ophthalmic surgery as well as in other medical specialties. Some of the potential advantages of sutureless surgery in ophthalmology include shortening the duration of surgical procedures, increasing patient comfort, and reducing the possibility of postoperative epithelial ingrowth beneath flaps and grafts.

Cyanoacrylate adhesives have been used in ophthalmology since 1963[1] for various purposes, including application to the corneal surface to seal corneal perforations [2] and to attach methyl methacrylate contact lenses. [3] Cyanoacrylate adhesives have the advantage of internally polymerizing so that external drying is not required; different cyanoacrylates have different viscosities and working time parameters. The disadvantage of cyanoacrylates is that they form a solid, impermeable plastic in situ. Although tissue may adhere to both sides of the material, the plastic persists as a foreign body that typically is extruded when located near the surface of the cornea. Furthermore, the cyanoacrylate polymers are not permeable to fluids and metabolites, so nutrients cannot traverse the cornea, and tissue superficial to the adhesive becomes necrotic. The use of cyanoacrylates on the surface of the cornea continues to be valuable, but their use as a tissue adhesive generally is not satisfactory and has largely been abandoned.

Another tissue adhesive used in recent years is mussel adhesive protein, a decapeptide from the common blue mussel (*Mytilus edulis*) that can be polymerized.[4] Although initially promising, this adhesive was found to have inadequate tensile strength and to cause sufficient inflammation so that its use never became widespread.

Experience with cyanoacrylates and mussel adhesive protein helped to clarify the properties necessary for a useful ophthalmic adhesive. Ideally, an ocular adhesive (1) would allow sufficient working time before totally “setting” in situ, (2) would have adequate tensile strength to maintain corneal integrity, (3) would be clear to permit vision, (4) would be permeable to fluids and metabolites to prevent necrosis, (5) would not cause inflammation, and (6) eventually would disappear to permit healing at the adhesive interface.

Fibrin adhesives have been tested experimentally in the eye as far back as the 1970s.[5] In the 1990s, when fibrin was combined with aprotinin to retard the dissolution of the fibrin adhesion, interest was revived and a number of studies of ophthalmic applications

were published, including closure of the conjunctiva in strabismus surgery [6 and 7] and glaucoma surgery, [8] closure of the scleral tunnel after cataract extraction, [9] and stabilization of radial keratotomy wounds. [10] Tisseel VH Fibrin Sealant (Baxter Healthcare Corporation, Glendale, CA) is a commercially available fibrin adhesive approved by the U. S. Food and Drug Administration as an adjunct to hemostasis in cardiopulmonary surgery bypass and in treatment of splenic injuries, but not for ocular surgery. A preliminary study in which this adhesive was used to attach corneal flaps in de-epithelialized rabbit corneas indicated that it was well tolerated, did not cause inflammation, permitted adherence of the corneal flap, and provided an interface that healed after the disappearance of the adhesive. [11]

We report here the successful use of this commercially available fibrin adhesive to secure microkeratome-cut "free-cap" lamellar keratoplasties using only topical anesthetic and no sutures in 5 patients, as well as to affix amnion to a bare scleral wound in one additional patient. Although the use of fibrin adhesive to seal corneal perforations with amniotic membrane grafts has been reported previously,[4 and 12] to our knowledge, this is the first report of the use of a fibrin–aprotinin tissue adhesive in clinical corneal lamellar graft attachment.

Materials and methods

The tissue adhesive was reconstituted according to the manufacturer's instructions. Transparent dressing strips (Tegaderm; 3M Canada, London, Ontario, Canada) were placed on the upper and lower lids. For lamellar keratoplasty, topical proparacaine was instilled in the patient's eye and the epithelium was removed mechanically. A microkeratome (Automatic Corneal Shaper; Bausch & Lomb, San Dimas, CA) was used to create a 200-μm thick cut in the patient's cornea using a 9.5-mm diameter ring. The donor cornea was de-epithelialized in the same manner, and the graft was cut with the same instrument and to the same thickness using an 8.5-mm diameter ring. The reconstituted adhesive was applied to the bed, and the donor graft was pressed rapidly and firmly onto the bed before the adhesive hardened. A bandage soft contact lens was placed on the eye and left in place for 7 days. Ofloxacin 3% (Ocuflox; Allergan, Irvine, CA) and prednisolone acetate 1% (Pred Forte; Allergan) were applied twice daily for 7 days. Excess adhesive that extruded from the interface during surgery in some eyes was rubbed off with a sponge or left to disappear.

For attachment of the amnion patch, the amniotic tissue was cut to size and placed on the bare scleral bed. The adhesive was injected beneath the patch using the double syringe, and the amnion then was maneuvered into place and pressed firmly against the scleral base.

Institutional review board approval was not required for these therapeutic treatments.

Patient data, indications for surgery, surgical procedures, and type of donor material are described in Table 1. Patients were followed up for a minimum of 3 months after surgery.

Table 1. Patient Data and Procedure Performed

Patient No.	Gender	Age (yrs)	Diagnosis	Procedure	Donor Material
1	F	66	Corneal stromal scar	Lamellar keratoplasty	Frozen globe p −85° C for 36 d
2	F	74	Corneal stromal scar	Lamellar keratoplasty	Refrigerated glo 4° C for 12 day
3	F	17	Atypical conjunctival melanosis	Excision of lesion and superficial sclera with safety margin, cauterization, and amniotic membrane graft	Frozen amniotic
4	M	71	Corneal stromal scar after penetrating keratoplasty for ammonia burn	Lamellar keratoplasty	Frozen globe p −85° C for 45 d
5	F	82	Recurrent band-shaped keratopathy after penetrating keratoplasty	Lamellar keratoplasty	Frozen globe p −85° C for 70 d
6	F	45	Corneal scar in lower half of cornea	Lamellar keratoplasty	Refrigerated glo 4° C for 24 hou

F = female; M = male.

Results

All of the lamellar keratoplasty grafts and recipient corneas remained clear, without inflammation. At 1 month after surgery, all patients who received lamellar keratoplasty grafts showed improvement in best contact lens-corrected visual acuity (Table 2). In patient 5, who had recurrent band keratopathy, best contact lens-corrected visual acuity improved from 20/400 before surgery to 20/30−2 at 3 weeks after surgery (Fig 1). Patient 4, who underwent lamellar keratoplasty for a stromal scar after penetrating keratoplasty for a severe ammonia burn, also demonstrated a visual acuity of 20/30−2 at 3 weeks after surgery. Subsequently, the patient required a tarsorrhaphy to re-establish epithelial integrity after the initially healed epithelium developed a defect.

Table 2. Best Contact-Lens Corrected Visual Acuity* before and after Sutureless Surgery with Tissue Adhesive

Patient No.	Before Surgery	After Surgery
1	20/200	20/40
2	20/50	20/40†
3‡	20/20	20/20
4	20/200	20/30-2
5	20/400	20/30-2
6	20/400§	20/200

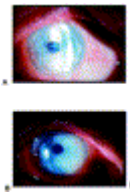
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Figure 1. Patient 5. **A,** Preoperative recurrent band keratopathy after penetrating keratoplasty. **B,** Two weeks after sutureless lamellar keratoplasty with a commercially available fibrin tissue adhesive.

In patient 3, who underwent excision of a melanosis, the amnion placed over the extensive scleral resection adhered without incident and without inflammation (Fig 2). Best contact lens-corrected visual acuity in this patient was 20/20 before and 1 month after surgery (Table 2).

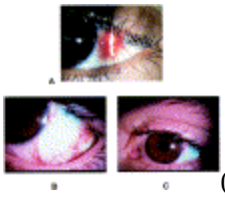
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Figure 2. Patient 3. **A,** Conjunctival melanoma. **B,** One week after surgery for excision of the melanosis and placement of an amniotic membrane graft attached with the use of a fibrin tissue adhesive, the amniotic membrane is in place. **C,** Two weeks after surgery, the conjunctiva is beginning to heal.

Discussion

For an adhesive to be effective in lamellar keratoplasty surgery, we believe it must hold the lamellar cap in place until the epithelium resurfaces the cornea and develops new tight junctions that exclude fluid. This theory is based on the assumption that LASIK flaps and microkeratome-cut lamellar corneal caps adhere to the stromal bed because the endothelium pumps fluid out of the cornea, dehydrating the stroma and creating a swelling pressure that holds the tissues together as long as the flap–graft neither becomes overhydrated nor develops a large epithelial defect that permits rapid fluid ingress. In the case of lamellar grafts, even if increased tensile strength from wound healing develops slowly, the fluid pump should hold the cornea together, as it does in LASIK, as soon as epithelial integrity is re-established. In this study, we demonstrated that the fibrin adhesive maintains the bond between the graft and the cornea during the early

postsurgical period until the graft is re-epithelialized; all eyes were completely epithelialized when the bandage lens was removed 1 week after surgery.

We arbitrarily chose the depth of the microkeratome cut to use a 200-μm plate on both the donor and recipient corneas from which the epithelium had been removed. Because the human corneal epithelium is approximately 50 μm thick and we removed it before making the microkeratome cut, the residual cornea was between 250 and 275 μm thick, sufficient that tensile strength from the flap would not be required to prevent keratectasia.

The need for lamellar grafts in the treatment of stromal scars persists. Superficial stromal scars, in particular recurrent erosions and basement membrane dystrophies such as Reis-Bückler's dystrophy, can be treated with phototherapeutic keratectomy. However, when the lesion is deeper in the stroma, the laser tends to ablate the scar unevenly, resulting in clinically significant irregular astigmatism. Furthermore, phototherapeutic keratectomy can cause a considerable hyperopic shift, and healing may be associated with visually significant haze. Thus, phototherapeutic keratectomy probably should be limited to excision of those scars that are extremely superficial. For deeper scars, lamellar keratoplasty can provide perfect clarity without a risk of rejection even when the donor stromal tissue is nonviable, in that donor stromal keratocytes can readily be replaced by recipient keratocytes. The procedure described in this report presents a technique that can be used with donor stromal tissue that has been refrigerated or frozen for a prolonged time with no need for sutures and a greatly diminished risk of epithelial ingrowth owing to the sealing effect of the adhesive around the circumference of the wound.

The experience gained with these 6 patients indicates that this commercially available adhesive, Tisseel, is satisfactory for the attachment of lamellar corneal grafts and amniotic membrane patches, suggesting that it would be useful where large shear forces are not expected to be applied to the tissue. Although fibrin adhesives have been used in the past, some required polymerization with a laser and others may not have been standardized to the same degree as Tisseel and may not have contained aprotinin, which is present in Tisseel to prevent the rapid lysis of the fibrin adhesion. We think it is very likely that an adhesive such as Tisseel would be ideal for those clear cornea cataract wounds where postoperative leakage is a possibility, the adhesion of amnion to cornea and sclera, the adhesion of conjunctiva in surgery such as pterygium removal and conjunctival flaps, and many other uses. It also may be especially useful after LASIK enhancements that result in large epithelial defects or flap elevation for removal of epithelial ingrowth.

Nevertheless, several properties make this adhesive somewhat less than ideal. First, it is of human origin, and there is the theoretical worry, despite Food and Drug Administration approval and precautions to the contrary, that human viruses may be carried in the material. Second, it is costly and comes in relatively large quantities for ocular use, leading to wastage. Also, the hardware that comes with the kit (bulky double-barrel syringe with large-bore cannula) is not well adapted for ophthalmic use. Third, mixing and preparing the ingredients, which must be carried out in the operating room, requires a substantial amount of time (a minimum of approximately 20 minutes) and

requires a water bath. Finally, the working time is short (as this study demonstrates, not too short, but still short enough to require careful planning). Newer fibrin adhesives that are prepared more rapidly are being developed, but will require further testing.

These deficiencies are compensated for by the brevity and expedience of the surgical procedure. We perform the procedure as one may perform LASIK. The donor graft must neither be placed in fluid nor have fluid applied after it is cut. A bandage soft contact lens is placed on the eye. No sutures are used and no special care is needed. The bandage lens is removed after 1 week. The only anesthetic is a drop of local anesthetic, as is used with LASIK, and the patient is under the microscope for approximately 10 minutes. It may be that more precise matching of the donor cornea and recipient bed would give even better results and firmer long-term adhesion, and we will test this in the future.

Although we report our experience with only a small number of patients, follow-up is not extensive, and one patient with an ammonia burn required a subsequent tarsorrhaphy to promote adequate epithelialization. In general, this procedure has been satisfactory and there have been no major complications. We suggest this technique would be of use for removing corneal scars easily and for approximating other tissues. It avoids the need for sutures, which are time consuming to place, can distort optics, are associated with their own set of complications, and typically require a second procedure for removal.

Microkeratome-cut lamellar keratoplasties with the “free-cap” donors held in place with a commercially available human fibrin adhesive may provide a superior way to remove corneal scars with minimal risk or morbidity and may avoid the need for sutures. Also, this adhesive apparently is useful for the attachment of tissue such as amnion. Further studies may demonstrate its usefulness in sealing clear corneal wounds, in sealing LASIK wounds where epithelial defects or epithelial ingrowth occur, and for adhering conjunctiva and other tissues. Until a superior adhesive is developed, Tisseel VH, which is commercially available, may be a useful adjunct to many types of ocular surgery.

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