A Light-Activated Surgical Adhesive Technique for Sutureless Ophthalmic Surgery

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Objective: To investigate a scaffold-enhanced, light-activated bioadhesive technique as a substitute for sutures in ophthalmic surgery.

Clinical Relevance: Suture use in ophthalmic surgery is technically demanding and time consuming and may be associated with serious complications such as inadvertent ocular penetration, which can result in retinal detachment and endophthalmitis. Bioadhesive surgery could eliminate many complications and limitations associated with the use of sutures.

Methods: The bioadhesive was composed of a poly(L-lactic-co-glycolic acid) (PLGA) porous scaffold doped with a protein solder mix composed of serum albumin and indocyanine green, which was activated with a diode laser. Extraocular rectus muscle-to-extraocular rectus muscle, sclera-to-sclera, and extraocular rectus muscle-to-sclera adhesions were created in freshly harvested tissue followed by tensile-strength testing of these surgical adhesions.

Results: Optimum tensile strength for muscle-to-muscle repair was achieved with 50% wt/vol bovine serum albumin and 0.5 mg/mL of indocyanine green saturated into a PLGA porous scaffold and activated with an 808-nm diode laser. The tensile strength was 81% of the native muscle's tensile strength (mean±SD, 433±70 g vs 494±73 g). Sclera-to-sclera adhesions achieved a mean±SD tensile strength of 295±38 g, whereas that for extraocular rectus muscle-to-sclera adhesions was 309±37 g.

Conclusion: Sutureless surgery using this bioadhesive technique for various ophthalmic procedures appears feasible and may result in reduced surgical complications and cost.

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The use of sutures is the mainstay of most forms of modern-day surgery. Until recently, virtually no ophthalmic surgery was possible without specialized sutures and needles. Strabismus correction, corneal transplantation, vitreoretinal surgery, trauma repair, oculoplastic procedures, glaucoma surgery, and extracapsular cataract removal all require precise suture placement through various fine structures of the eye and adnexa. Although microscopes, loupe magnification, and specialized illumination techniques have made it easier to perform ophthalmic surgery, suture placement is technically difficult and time consuming and may be associated with serious complications.

For example, strabismus surgery requires that a suture be inserted and advanced within the sclera at a depth of approximately half the scleral thickness. This is usually performed with the aid of loupe magnification. Perforation of the sclera during reattachment of an extraocular muscle may be associated with vision-threatening complications such as retinal detachment and endophthalmitis. It has recently been suggested that contaminated intrascleral sutures may produce endophthalmitis even in the absence of scleral perforation. Suture use in corneal transplantation may be associated with postoperative astigmatism and wound leakage. Traumatic stellate corneal lacerations can be difficult to close using sutures because of their complex, irregular geometry, whereas posterior scleral sutures required in the repair of a ruptured globe may be arduous to insert without putting excessive pressure on the eye.

Inherent complications and drawbacks of suture use are numerous. Suture placement can be time consuming. Sutures must be precisely placed to properly align the tissue. Often the tissue must be manually realigned before each pass of the suture’s needle. Imprecision placement of a suture may necessitate its removal and replacement; as a result, delicate ocular tissues may be damaged. Sutures frequently must be removed postoperatively. Not only is this process time consuming, but chil-
taching rabbit extraocular muscles to porous anophthal-
group, porcine eyes were obtained from a slaughterhouse ap-
saline for a maximum of 2 days at 4°C prior to use. In the third
obtained from an eye bank and stored in phosphate-buffered
line for a maximum of 4 hours at 4°C before they were prepared
vested approximately 45 minutes after euthanizing the ani-
experimental group, rabbit superior rectus muscles were har-
(3) extraocular rectus muscle to sclera (n=20). In the first
(4 subgroups of 10 specimens each); (2) sclera to sclera (n=20);
were placed together on a piece of parafilm. Four sets of ad-
ber 15; Bard-Parker, Franklin Lakes, NJ), and opposing ends
were 8.0±2.0 mm and 1.5±0.1 mm, respectively. A complete
The mean ± SD length and thickness of each muscle specimen
Group 1: Extraocular Rectus Muscle-to–Extraocular
Rectus Muscle Adhesion
The mean ± SD length and thickness of each muscle specimen
were 8.0 ± 2.0 mm and 1.5 ± 0.1 mm, respectively. A complete
transsection (n=40) was accomplished with a scalpel blade (num-
ber 13; Bard-Parker, Franklin Lakes, NJ), and opposing ends
were placed together on a piece of parafilm. Four sets of ad-
hesive fabrication parameters were studied. Each parameter set
differed in protein concentration and scaffold porosity.
(Table 1). The following groups were tested using a 2-factor,
2-level experimental design. Subset A received a 25% wt/vol
albumin solder with a scaffold pore size smaller than 106 µm.
Subset B had 25% wt/vol albumin with a scaffold pore size of
106 to 150 µm. Subset C received a 50% wt/vol albumin solder
with a scaffold pore size smaller than 106 µm; whereas subset
D had 50% wt/vol albumin with a scaffold pore size of 106
To the 150 µm. Before depositing the adhesive, the tissue surface
was blotted with cotton gauze to remove excess moisture. A
strip of adhesive with surface dimensions of 3.0 mm × 1.0 mm
was then placed over the transsection so that it bridged the ap-
posed tissue edges, and it was irradiated with a diode laser op-
erating at a wavelength of 808 nm (Optio Power Corp, Tucson,
Ariz). The laser light was coupled into a 660-µm-diameter silica
fiber bundle and focused onto the adhesive surface with an im-
aging handpiece connected at the end of the fiber. Because 808
nm is outside the visible spectrum, the laser included a low-
power aiming beam at 632 nm to assist the operator. Surgical
outcome was unaffected by the aiming beam as a result of its
low irradiance as well as the poor absorption of the chromo-
phore at this wavelength. The diode was operated in continu-
ous mode with a spot size at the adhesive surface of approxi-
mately 1 mm. An irradiance of 15.9 W/cm², as measured using

All experiments were designed and carried out with appropri-
ate institutional review board and animal care committee ap-
proach. Three experimental groups were investigated: bond-
ing of (1) extraocular rectus muscle to extraocular rectus muscle
(4 subgroups of 10 specimens each); (2) sclera to sclera (n=20);
and (3) extraocular rectus muscle to sclera (n=20). In the first
experimental group, rabbit superior rectus muscles were har-
vested approximately 45 minutes after euthanizing the ani-
imals. Tissue specimens were stored in phosphate-buffered sa-
line for a maximum of 4 hours at 4°C before they were prepared
for the experiments. In the second group, human scleras were
obtained from an eye bank and stored in phosphate-buffered
saline for a maximum of 2 days at 4°C prior to use. In the third
group, porcine eyes were obtained from a slaughterhouse ap-

PREPARATION OF THE SURGICAL ADHESIVE
Porous synthetic polymer scaffolds were prepared from PLGA,
with a lactic acid–glycolic acid ratio of 85:15, using a solvent-
casting and particulate-leaching technique.11 The scaffolds were
cast by dissolving 200 mg of PLGA in 2 mL of dichlorometh-
ane. Sodium chloride (salt particle size: <106 µm or 106-150
µm) with 70% wt/wt was added to the polymer mix. The poly-
mer solution was then cast in a 60-mm Petri dish and left in a
fume hood for 24 hours to allow the dichloromethane to evapo-
rate. The salt was leached out of the polymer scaffolds by im-
ersion in filtered de-ionized water for 24 hours to create the
porous scaffolds. During this period, the water was changed 3
times at approximately 2-hour intervals. The scaffolds were
then air-dried and stored at room temperature until required.

Protein solder was prepared from either 25% wt/vol or 50%
wt/vol bovine serum albumin (BSA) (Cohn fraction V) and in-
docyanine green (ICG) dye at a concentration of 0.5 mg/mL
mixed in de-ionized water. The compounds were used with-
out further purification. The solder was stored in lightproof plas-
vials at 4°C until required. Solder not used within 1 week
was discarded.

The PLGA scaffolds were cut into rectangular pieces with the
desired dimensions. The scaffolds were left to soak for a
minimum of 2 hours in the protein solder mix before use. The
thickness of the solder-doped polymer scaffolds, determined
using scanning electron microscopy and measurement with pre-
cision calipers, was in the range of 200 to 205 µm.
a power meter (Fieldmaster G5; Coherent Scientific, Santa Clara, Calif) with a thermoprobe detector (LM100; Coherent Scientific), was used to denature the adhesive with a scan rate of approximately 0.5 mm/s. Breaking point tensile strength was measured within minutes of solder activation.

Group 2: Sclera-to-Sclera Adhesion

Using a 50% wt/vol BSA solder with 0.5 mg/mL of ICG in a PLGA scaffold (pore size, 106-150 µm), uniform 4.0 mm, samples of human sclera, which had been previously prepared by transecting the sclera with a scalpel blade, were joined together (n=20). Two segments were positioned adjacent to each other on parafilm. Scaffolds saturated with the solder were trimmed to a size of 3.0 mm × 1.0 mm, placed over the transection so that they bridged the apposed scleral tissue edges, and irradiated with a diode laser operating at a wavelength of 808 nm. The same repair procedure used for group 1 was applied, but only the optimal adhesive parameters determined in group 1 were tested (subset D). Tensile strength was measured within minutes of solder activation.

Group 3: Extraocular Rectus Muscle–to–Sclera Adhesion

A 360° conjunctival peritomy was performed on the globes, exposing the sites of extraocular muscle attachment. The superior rectus muscle was carefully dissected from the globe using scissors. The muscle was reapproximated to the sclera using a pair of forceps so that the end of the muscle was located adjacent to but not overlying the original site of insertion. Excess moisture was blotted away. A piece of adhesive with surface dimensions of 3.0 mm × 1.0 mm was then applied across the top of the tissue in a Band-Aid–like fashion and irradiated with the 808-nm laser. The point of attachment was the superior aspect of the muscle before failing. Two-way analysis of variance demonstrated that tensile strength was significantly greater at the higher level of BSA concentration (P=.001) and pore size (<.001) without significant interaction between these variables (P=.79). A 50% wt/vol BSA mixture with 0.5 mg/mL of ICG and a PLGA scaffold with a pore size from 106 to 150 µm produced the greatest tensile strength (Table 2). This provided a mean±SD breaking load of 433 ±70 g or 88% of the inherent tissue strength. The rabbit extraocular rectus muscle had an intrinsic mean±SD breaking load of 494±73 g.

Table 3 shows the distribution of tensile strengths of the soldered sclera-to-sclera bonds. The mean±SD breaking load for these sutureless reattachments of the sclera was 295±38 g. Table 4 lists the range of breaking strengths for the repairs of the soldered extraocular rectus muscle–to–sclera adhesions. The mean±SD tensile strength of these sutureless bonds was 309±37 g.

TENSILE-STRENGTH ANALYSIS

Tensile-strength analysis of the repairs was performed using a calibrated material strength–testing machine (858 Table Top System; MTS, Eden Prairie, Minn) interfaced with a computer. The repaired tissue specimens were clamped to the tensiometer with pneumatic grips attached to a 100-N load cell and pulled apart along an axis within the plane of adhesion between the tissue and adhesive, at a rate of 1 gravitational force per second, until the repair failed. Failure was defined as complete separation of the tissue edges. The maximal load in grams was recorded at the breaking point. The tissue specimens were kept moist during this procedure to avoid the false elevations in repair strength associated with drying.14 A 2-way analysis of variance was used to analyze and test for mean differences in tensile strength due to BSA and pore size as well as for eventual interaction between these 2 factors.
size of the suture and needle. Serious complications such as ocular penetration may cause endophthalmitis or retinal detachment. The manipulation of fine needles may also place operating room personnel and physicians at risk for needlestick injuries and transmission of serious diseases. Many surgical specialties have substituted bioadhesives to replace or aid suture techniques in various procedures, including vascular surgery, skin closure (particularly in pediatrics), and orthopedic procedures.15-19

The evolution of laser tissue soldering has occurred during the past 15 years. Laser tissue soldering is a bonding technique in which protein solder is applied to the tissue surfaces to be joined and laser energy is used to bond the solder to the tissue surfaces. The efficacy of diode laser tissue soldering using ICG-doped albumin protein solders has been demonstrated in a wide range of tissues including the blood vessels, genitourinary tract, gastrointestinal tract, liver, nerves, dura mater, skin, trachea, and cartilage, with promising results.20,21 Recent success has been demonstrated with a new light-activated surgical adhesive used to achieve vascular anastomoses.22,23 This surgical adhesive is composed of a polymer scaffold doped with serum albumin and a chromophoric dye. A copolymer of glycolic acid and lactic acid, PLGA, is degraded in vivo with hydrolysis of the ester bonds to produce nontoxic metabolic by-products.24 In addition to current use in biodegradable sutures, these materials have been evaluated as potential drug delivery systems. The in vivo degradation rate and consequently the drug delivery rate can be modified by altering the composition of the polymer.25,26 Thin films of PLGA of various thickness are easily fabricated in the laboratory using a solvent-casting technique. When doped with serum albumin, the scaffolds provide better flexibility and improved repair strength compared with previously published results using albumin protein solders alone.26 The chromophoric dye, ICG, provides for selective absorption of the laser irradiation. The end result is a new surgical adhesive that can be light activated and used to join tissues together.

In our experiments, a scaffold-enhanced, light-activated protein solder was used to replace sutures in ocular tissues commonly joined by suturing. The breaking point of the extraocular rectus muscle–to-sclera bond using our repair technique was beyond that of the actively developed horizontal fixation force measured in vivo in humans and suggests that this procedure may be applicable for eye muscle surgery. Collins et al27 found a mean active fixation force at 50° extreme gaze of 74.8 g for the medial rectus muscle and 59.1 g for the lateral rectus muscle with a range of 48 g to 103 g for all individuals measured, much less than that created by the scaffold-enhanced, light-activated protein solder bond.

An ideal bioadhesive should have several critical properties. It must possess sufficient tensile strength to maintain wound integrity until the healing processes have restored sufficient tensile strength to resist failure in normal circumstances. It must be easily applied in a precisely controlled fashion. Nonviscous liquids are difficult to control and spread beyond the desired area of application. Excessively viscous adhesives may be difficult to apply uniformly or denature evenly throughout the entire area of application. The ideal adhesive must set quickly but only when desired. Although newer cyanoacrylates are strong and produce little inflammation, they have the disadvantage of difficult application and rapid hardening before the tissues can be properly aligned. Light-activated solders are ideal: activation is rapid, controlled, and limited to the area of precise absorption of the laser irradiation. Our repair technique is advantageous because the solder remains contained in a porous scaffold. The scaffold can be made in any shape or size and custom-cut if desired. This facilitates alignment, quick and precise solder activation, and enhanced tensile strength. In addition, the scaffold can conceivably act as a temporary reservoir for the release of drugs.

**Table 3. Maximum Tensile Strength of Scaffold-Enhanced, Light-Activated Soldering of Sclera to Sclera**

<table>
<thead>
<tr>
<th>Specimen No.</th>
<th>Breaking Load, g</th>
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<tbody>
<tr>
<td>1</td>
<td>284</td>
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<tr>
<td>2</td>
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<tr>
<td>20</td>
<td>366</td>
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<tr>
<td>Mean ± SD</td>
<td>295 ± 38</td>
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</table>

**Table 4. Maximum Tensile Strength of Scaffold-Enhanced, Light-Activated Soldering of Extraocular Muscle to Sclera**

<table>
<thead>
<tr>
<th>Specimen No.</th>
<th>Breaking Load, g</th>
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<td>372</td>
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<tr>
<td>Mean ± SD</td>
<td>309 ± 37</td>
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such as steroids, antibiotics, growth factors, or growth factor inhibitors.\textsuperscript{28} Finally, an ideal adhesive must be nontoxic, must be available in a sterile preparation, and cannot produce excessive inflammation beyond that occurring in secondary-intention wound healing or conventional sutures used in a particular technique. Serum albumin sizers have been used in vivo and do not produce excessive inflammation.\textsuperscript{22-29,30} We have used 2-octyl-cyanoacrylate in conjunction with the scaffold described in this article to recess extraocular rectus muscles in a rabbit model.\textsuperscript{31} Clinical observations during a 2-week period revealed no excessive ocular inflammation, and histologic analysis 2 weeks after surgery revealed no discernable inflammation in the area of application or reattachment.

The scaffold-enhanced, light-activated solder described in our experiments can easily be used as a suture substitute in selected ophthalmic surgical procedures. It also has advantages compared with other adhesives. First and foremost, the scaffold facilitates fine control of adhesive placement and tissue alignment. It provides an additional reinforcement for tensile strength and can act as a slow-release drug delivery system following surgery. The ability to activate the solder with a specific wavelength of light permits long or large wounds to be closed quickly and precisely. Besides the potential cost savings in suture products, operating room time may be reduced, especially in a resident teaching situation. Also, the time required to precisely align sutures under a microscope can be minimized. These savings are in addition to the ultimate goal of increasing the safety and efficacy of surgery for both the patient and personnel performing the procedures.

In summary, we have demonstrated that the immediate tensile strengths achieved with scaffold-enhanced, light-activated solders are greater than those physiologically required for strabismus surgery and likely for the closure of scleral, corneal, and conjunctival incisions. In addition to tensile strength, further work is currently being performed by our group to assess the in vivo degradation rate of both the solder and scaffold in strabismus surgery, corneal wound repair, scleral wound closure, and conjunctival incisions. If the reduction of solder strength is sufficiently slow to allow inherent wound tensile strength to return to physiologic requirements, this technique may become widely used in ophthalmic surgery.

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\textbf{REFERENCES}