

Novel Laser-Activated Solder for Sealing Corneal Wounds

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PURPOSE. To compare the effectiveness of a laser-activated biological tissue solder with that of standard sutures for sealing corneal incisions.

METHODS. Two keratome knives measuring either 3.0 mm or 2.85 mm were used to create a non-self-sealing peripheral oblique corneal wound (POCW) or a central perpendicular corneal wound (CPCW) in fresh rabbit cadaver eyes. Wounds were sealed with a solder strip (POCW; $n = 5$), a solder patch (CPCW; $n = 5$), or three interrupted nylon 10-0 sutures ($n = 5$). After the solder was placed on the wound, a diode laser was used to activate the solder, resulting in cross-linking to tissue. Wound stability was tested by a stepwise infusion of saline, and pressure changes were monitored with a digital manometer. Leaking pressure was recorded.

RESULTS. The pressurized mean baseline IOP in the intact globe was 131.13 mm Hg (SD, 4.66). Mean IOP after CPCW was 1.7 mm Hg (SD, 0.13); for PCW it was 3.62 mm Hg (SD, 3.09). For the CPCW group, the mean leaking pressure in the sutured eyes was 82.76 mm Hg (SD, 6.55), whereas in the solder patch it was 101.42 mm Hg (SD, 29.92; $P = 0.2222$). For the PCW group, the mean leaking pressure in the sutured eyes was 33.44 mm Hg (SD, 9.38), and the mean IOP achieved in the solder repaired eyes was 125.16 mm Hg (SD, 9.85; $P = 0.0079$).

CONCLUSIONS. The tested laser-activated solder was as effective as sutures when used as a patch and superior to sutures for clear corneal incisions in this animal ex vivo model. (*Invest Ophthalmol Vis Sci.* 2007;48:1038-1042) DOI:10.1167/iovs.06-0488

Sutures are the criterion standard for corneal incisions and wound repair because of the efficiency and strength of the closure but may not be the ideal method for wound closure, especially in the cornea. Therefore, many corneal surgeons recognize that sutures can be a source of potential problems. Suturing is usually labor intensive and may lead to infection,¹ induced astigmatism,² erosion,³ foreign body sensation, corneal neovascularization,⁴ and other abnormalities. In addition,

suture removal is required when a nonresorbable material is used, which increases the number of patient visits, extends the follow-up period, and results in higher cost and inconvenience to the patient.

Alternatives to the conventional closure methods have been investigated for many years⁵⁻⁹ and may be divided into four major groups: biological glues,⁹⁻¹¹ synthetic adhesives,⁹ chromophore-assisted laser welding,¹² and laser tissue welding.¹³ Several studies have reported the efficacy of light-activated solders to weld soft tissues.¹⁴⁻²⁰ Laser-activated tissue adhesives may be more appropriate in the apposition of wounds because the bonding mechanism is controlled by light exposure. This is especially important when a tridimensional shape must be preserved. Interest has become heightened in developing light-activated tissue solders and sealants as substitutes for conventional closure methods such as the fixation of grafts/implants and anastomoses. Advantages include speed of closure, reduced infection because of the elimination of foreign matter, evidence of accelerated wound healing, and ease of use in complex surgery, especially when watertight seals, limited access, or small repair size are important factors. Laser activation provides a directed energy source for precise placement of the weld and can amplify the mechanism for solder to tissue cross-linking. The strength of weld depends on reaching a precise temperature set by the choice of laser and solder composition to obtain protein reconstruction at the solder-tissue interface with minimal damage to adjacent tissue.¹⁹

The availability of a variety of laser output powers and of laser wavelengths that match the optical properties of tissue and the development of protein composites,¹⁸ layered solders,¹⁹ and solders modified with growth factors,²⁰ chromophores,¹⁵ or photochemicals²¹ have advanced solder technology. Reports indicate that some of these solders tend to undergo blood dilution during surgery, resulting in mechanical alteration that weakens the repair. The stronger solders are often brittle, inflexible, and not easily adapted to different tissue geometries.

In the present study, we compared the adhesive strength of a novel tissue solder based on a laser-activated, purified, chemically modified collagen solder with that of standard suture methods. The purpose of the study was to detect maximum intraocular pressure (IOP) resistance before wound leakage in rabbit eyes to evaluate the adhesive properties of the solder that was applied as a film strip or as a patch to the repair site.

MATERIALS AND METHODS

Solder Preparation

Purified, telopeptide-poor, type I collagen was prepared from porcine or bovine dermis and subsequently chemically modified with glutaric anhydride. The anhydride reacts with free amines, substituting a carboxyl group for active hydrogen and making the composition anionic. The degree of chemical modification or substitution was selected so that the modified collagen would remain soluble at physiological pH. Chemical modification was performed by adjusting the pH of the soluble collagen (5 mg/mL) to 9.0 and adding solid anhydride to the

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collagen (wt/wt). The pH was reduced to 4.5 to allow precipitation of the modified collagen. The precipitate was recovered by centrifugation and dissolved in 5 mM phosphate buffer at a final concentration of 5 mg/mL, and the solution was freeze dried.

Solder films were prepared from the lyophilized stock collagen. Lyophilized sheets were cut into small pieces and homogenized in a tissue mill. The desired collagen solid concentration was obtained by exposing the dispersions to a controlled-temperature water bath. As the collagen powder dissolved, more was added until the target concentration was achieved (wt/vol). Once the desired concentration was obtained, the viscous solution was centrifuged and poured into warm 12-mm-diameter round molds. Solder thickness ranged between 100 and 200 μm . After cooling for 3 minutes, the clear, transparent discs were removed from the mold, vacuum packaged, labeled, and stored at 4°C until use.

Chemical modification and collagen concentration were controlled so that the resultant solder exhibited a thermal transition in the 40°C to 45°C temperature range when exposed to the laser but had sufficient pendant carboxyl group concentrations for enhancing cross-linking to tissue. Collagen solders used in this study had a 30% degree of chemical modification, with collagen concentrations in the 55% to 60% range.

Laser Activation

A custom-designed diode laser was used to melt and denature the solder in these experiments. The laser system was composed of a fiber-coupled diode laser array with an operating wavelength at 1.45 μm in a continuous wave (CW) mode, a feedback temperature controller, and a handpiece. The laser was coupled to a 1-mm diameter, low OH⁻ fused silica fiber. The temperature controller consisted of a non-contact IR detector (model KT22; Wintronics, Millington, NJ) that sensed thermal radiation from the weld site and output a signal relative to the temperature at the site. Circuitry conditioned the detector signal, and a computer was programmed with algorithms to compute the weld site temperature as a comparison to a set temperature and to monitor the laser input control signal that ultimately drove the laser output. This control loop (i.e., temperature sensing, set temperature comparison, and output to control the laser to increase or decrease power output) continuously monitored the temperature and modulated the laser output to approach and maintain the set temperature. Two optical fibers (one to collect and transmit thermal radiation in the 7- to 15- μm range to the detector and the other to transmit laser energy to the weld site) were aligned and secured in a delivery device held by the surgeon. The handpiece was geometrically configured to ensure that the detector fiber collected radiation within the heated area. Lenses were combined with the laser delivery fiber to expand and focus the laser beam to a 4-mm spot size at a working distance of 1.29 to 3.79 cm. For this study, the laser parameters were set to a maximum CW output of 1.0 W, with a set temperature of 40°C. The solder was continuously exposed to the laser while the beam was moved slowly over the entire surface area to achieve uniform melting of the solder.

Experimental Setting

Ten adult New Zealand White rabbit heads (20 eyes) were obtained from a local farm and were used for the study. Heads were transported in a cool, moist chamber (4°C) before the eyes were enucleated. Globes were surgically removed approximately 2 hours after death of the animals, leaving a sufficient conjunctival skirt as an aid for fixation. Each globe was mounted on a metal base supporting a receptacle filled with polystyrene foam, and the remaining conjunctiva was secured in all four quadrants with pins. A 27-gauge needle (BD Biosciences, Franklin Lakes, NJ) connected to an infusion system with a BSS bag (Abbott Laboratories, Abbott Park, IL) was inserted at the 3 o'clock position relative to the surgeon's view and parallel to the iris plane. A second 27-gauge needle attached to a digital manometer (Digimano 1000; Netech Corp., Hicksville, NY) was introduced into the anterior chamber 180° away from the first needle. BSS bag height was adjusted

by means of a pulley system. IOP was subsequently increased by raising the infusion bag at its maximum height to determine the highest IOP achievable with the experimental setup before any incisions were made. Just before incisions were made, the BSS bag height was adjusted to maintain an IOP of 18 to 22 mm Hg, similar to physiological measurements.²² Under microscopic visualization (Möller Ophthalmic 900; Haag-Streit AG, Wedel, Germany), a 3.0-mm-wide uniplanar non-self-sealing peripheral oblique corneal wound (POCW) was made parallel to the iris with a disposable 45° angle keratome (Beaver; BD Surgical System, Franklin Lakes, NJ) in 10 rabbit eyes. Incision was performed 90° away from the needle ports and was designed to leak spontaneously. In another group of globes ($n = 10$), a straight keratome, 2.85-mm wide, rounded-tip crescent knife (Beaver; BD Surgical System) was used to create a central perpendicular corneal wound (CPCW). Immediately after the incisions were made, leaking pressures obtained from the digital manometer were recorded in all eyes.

Experimental Groups

Both incision groups were subdivided in two ($n = 5$) for each type of sealing method used in this trial. The methods were laser-activated solder and three interrupted nylon 10-0 sutures. For the 3.0-mm-wide uniplanar non-self-sealing PCW, the solder was sized, cut into strips, and inserted along and in the wound to cover the incisions (Fig. 1). For the 2.85-mm-wide CPCW, a patch of solder was placed on the wound with care taken to completely cover it while leaving approximately 0.5-mm excess around the wound edges (Fig. 2).

After the solder strip was inserted in the PCW or placed on the CPCW as a patch, the diode laser was applied for 5 to 7 seconds to completely melt the solder. Then the solder was allowed to cure for 5 minutes before IOP leakage tests were begun. Eyes in the control groups for both wound types ($n = 5$ each) were sutured with 3 interrupted nylon 10-0 sutures at approximately 90% of stromal depth.

Wound Stability Tests

Wound stability was tested by means of slowly increasing the IOP. Wounds were closely monitored in all groups through the operating microscope at 12 \times magnification during the IOP increase to accurately determine the onset of leakage. Maximum pressure resisted before leakage was displayed on the digital manometer connected to the anterior chamber.

Statistical Analysis

Comparisons between groups were performed with statistical software (StatsDirect 2.4.1; Windows, Cheshire, UK). Comparisons between

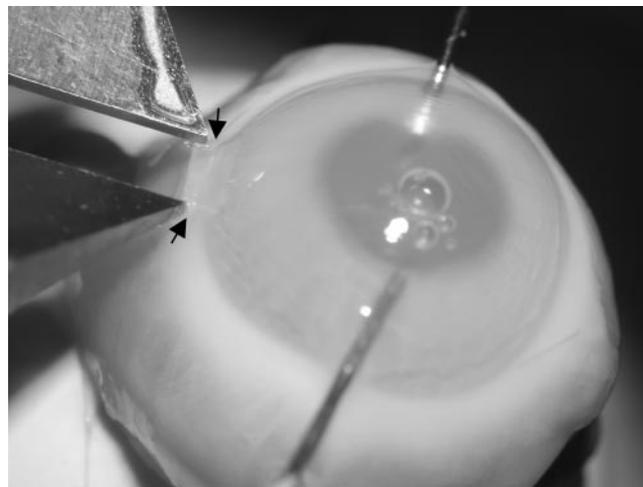


FIGURE 1. Insertion of adhesive film through the 3-mm-wide PCW in one of the study group eyes (arrows). Film was measured by a digital ruler.

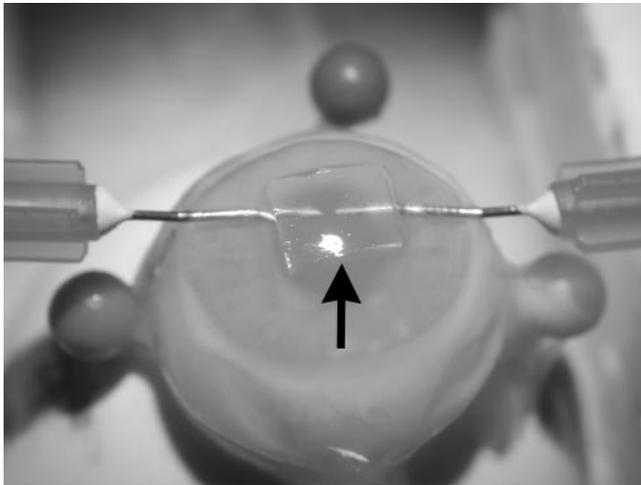


FIGURE 2. Adhesive patch placement over the 2.85-mm-wide CPCW in one of the study group eyes (arrow).

maximum resisted IOPs before leakage were performed with the nonparametric Mann-Whitney *U* test.

RESULTS

Strength Testing in Corneal Incisions

Mean baseline IOP in the intact globes (before incisions were created) was 131.13 mm Hg (SD, 4.66; range, 123–140.2 mm Hg) at a height of 200 cm above the level of the globe fixture. This pressure and height were considered sufficient to achieve a watertight sealing effect of the tissue adhesive for corneal wounds.

3.0-mm-wide POCW Group

Mean nonsealed incision IOP was 3.62 mm Hg (SD, 3.09; range, 0–9.1 mm Hg). Mean leaking pressure in eyes in which sutures were placed was 33.44 mm Hg (SD, 9.38; range, 25–45 mm Hg). Mean maximum IOP resisted in eyes that received the solder film was 125.16 mm Hg (SD, 9.85; range, 113.5–135 mm Hg). None of the eyes that received the glue showed leakage at the maximum pressure allowed by our system. The difference between the maximum resisted IOP was significant between these two groups ($P = 0.0079$).

2.85-mm-wide CPCW Group

Mean nonsealed incision IOP was 1.7 mm Hg (SD, 0.13; range, 0.1–4.8 mm Hg). Mean leaking pressure in eyes in which sutures were placed was 82.76 mm Hg (SD, 6.55; range, 76–93 mm Hg). Mean maximum IOP resisted in eyes that received the solder patch was 101.42 mm Hg (SD, 29.92; range, 60–138 mm Hg). In the solder patch group, two of the eyes showed leakage at the maximum pressure allowed by our system. The difference between the maximum resisted IOP was not significant between these two groups ($P = 0.2222$).

DISCUSSION

The aims of corneal wound repair are to restore the integrity of the ocular globe, to stabilize the intraocular contents, and ultimately to preserve vision. Wound edges must be evenly apposed to promote healing. The use of adhesives in ocular surgery was proposed in 1963²³ and first reported for the

management of corneal perforations in 1968.^{24,25} Tissue adhesives have been used in ophthalmology as a structural filler or as support in the replacement of donor tissue.^{26,27} Cyanoacrylate-based glues are far from ideal for cornea repair because they can be toxic, which can cause inflammatory reactions, and because they are nonbiodegradable.²⁸ Fibrin-based adhesives are not particularly effective because they usually form bonds of insufficient strength,^{10,29} present the possibility of viral infection if prepared from pooled human plasma, and may inhibit wound healing.³⁰ Even with these disadvantages, fibrin glue is used extensively in ophthalmic surgery, including surgery for corneal perforation and corneal thinning, pterygium, and glaucoma.^{31–36} Cyanoacrylates have also been used in the management of corneal perforations and severe thinning.^{9,37}

In contrast, tissue repair with the aid of laser-activated biodegradable solders is a unique approach that eliminates the problems associated with sutured closures. Although a diode laser (808 nm) in combination with an albumin-based tissue solder has been reported to seal scleral tunnels,³⁸ the deep penetration of the laser light can cause damage to other ocular tissues. The operating laser wavelength used in this study is considered safe because it is efficiently absorbed by the water content in the cornea before it reaches other sensitive structures of the eye.³⁹

Native tissues are welded with lasers because of loosening or collapse of the collagen triple helix. With quenching, interaction can occur between the polypeptide strands, creating adhesive bonds.^{40–42} A major disadvantage is the precise temperature control required to promote tissue bonding while avoiding tissue shrinkage.⁴³ The chemically modified collagen solder evaluated in this study is considered a bridging material that exhibits a thermal transition at 40°C, absorbing most of the incident laser energy to activate linkages that preferentially bond to underlying tissue. Furthermore, thermocoupled measurements (model 91100 to 50 Dual Thermocouple Thermometer using type K thermocouples; Digi-Sense, Laudium, South Africa) determined that the temperature measured at the solder-tissue interface was adequate for melting the solder collagen but remained well below that required for irreversible protein denaturation in the cornea.⁴⁴

Rabbit corneas are thinner than human corneas, making it difficult to create a valved, self-sealing incision. To test the sealing capacity of the collagen solder for this animal model, a wound was created that would leak continuously or seal spontaneously. This study showed that laser solder enabled significantly higher IOP than sutures in the POCW group and similar IOP in the CPCW group. Control corneas resisted a higher bursting pressure in the CPCW group, possibly because the size of the wounds was smaller in these corneas.

The conventional suture approach used routinely for POCW and CPCW involves additional tissue injury and possibly a foreign body response that can lead to increased inflammation, scarring, and neovascularization. Laser-assisted tissue welding may reduce wound slippage and render the wound impermeable to microorganisms. The ideal solder material should be strong, effective, nontoxic, biodegradable, and available in a sterile preparation. Collagen was chosen because of its long history as a safe, biocompatible biomaterial and its ability to be chemically functional in a base formulation with unique cohesive and adhesive characteristics. The high-concentration preparations formulated for this study are capable of being cast into films for subsequent sectioning into strips or patches for application to a repair site.

Previous experience with collagen shields for the cornea shows dissolution of these devices within hours of implantation in the surface of the eye.⁴⁵ We may expect a similar behavior of these solder patches in vivo, though exposure to the laser and cross-linking may delay the effects of tear colla-

genes and prolong the dissolution of the solder. Similarly, reepithelialization over the patch surface may protect the solder from collagenolytic enzymes in the tear film. However, these concerns can only be addressed after wound healing behavior is observed in an experimental animal model in vivo.

The collagen solder permitted bonding between the solder and corneal tissue without the use of sutures. In addition, this technique might provide additional clinical benefit by sealing the wound, preventing bacteria and particulate matter from migrating to the open wound.⁴⁶ It remains to be investigated what effect this procedure would have on visual acuity.

Although it may not be appropriate to compare our results with those in other experimental models because testing methodology is not always standardized,⁴⁷ we were able to demonstrate a superior sealing effect of the biological adhesive compared with standard suturing. This may represent a significant improvement in corneal surgery if other aspects of safety and toxicity of this adhesive are found to be compatible with the living eye.

Wound sealing using a laser-activated process may be an alternative to traditional closure. Although this approach was efficacious in this ex vivo model, significant work must be carried out before any clinical application can be considered. This should include testing the laser-activated solder in animal wound models in vivo.

The ex vivo rabbit model is probably not the ideal one in which to simulate conditions that may occur in human eyes because the rabbit's corneal thickness, size, and biomechanical properties are very different from those of humans. However, it is a simple model that has been used extensively and that may serve as a reference for further in vivo experiments to test for biocompatibility, wound integration, and, again, adhesive strength through bursting pressure measurements.

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