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Laryngeal Soft Tissue Fixation Device

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Client: Dr. Seth Dailey, UW School of Medicine and Public Health

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Abstract

Damage or scarring to the vocal folds causes severe limitations to their pliability, inhibiting proper phonation. Previous treatments such as implants and injections have proved unsuccessful. Negative aspects of these procedures include extrusion, limited biocompatibility, and do not address lamina propria damage. A newly developed surgical procedure is to be utilized for this type of vocal fold repair. This procedure utilizes a local vascularized tissue flap for the augmentation of Reinke's space. Proposed designs to secure the tissue flap in place include an improved corkscrew, barbed nail, soft tissue glue, and gecko tape method. After evaluating these design options and client input, we have chosen to pursue the fibrin glue, Evicel. The use of biodegradable surgical glue will provide sufficient adhesion while avoiding damage to the soft tissue flap and tissue surrounding the vocal fold. Testing in cadaveric canine larynges has shown sufficient adhesive strength, while future testing will help develop the most effective and efficient method of glue application. Successful attachment of the soft tissue flap within the vocal fold will improve and possibly restore vocal function.

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MOTIVATION

Damage or scarring to the vocal folds causes severe limitations to their pliability, inhibiting proper phonation (Sulica 2011). More specifically, when the lamina propria, a histological layer of the vocal folds, becomes scarred or injured the freedom of tissue motion is impaired. Therefore the tissue becomes stiff, preventing oscillation (Gray 1999). Oscillation is also inhibited when fixation occurs between the lamina propria and the underlying tissues. In addition, asymmetric scarring of one vocal fold can cause inconsistencies between the vocal folds. For example, increased tension or a linear depression in one vocal fold can prevent the medial edge of the damaged vocal fold from meeting the opposite vocal fold (Schweinfurth 2010). Incomplete closure of the vocal folds often causes patients to have a breathy voice and vocal fatigue. Other symptoms of scarring include hoarseness, thin, high-pitched voice, and poor volume and projection (Schweinfurth 2010). Many of these symptoms have a significant effect on the daily lives of individuals with damaged vocal folds, providing a strong incentive for the creation of a method to correct for vocal fold damage and scarring.

ANATOMY

Anatomically, the vocal folds can be found within the larynx (figure 1). They are anteriorly connected to the thyroid cartilage and posteriorly attached to the arytenoid cartilage (figure 2). The neuromuscular control of the arytenoids causes the abduction (opening) and adduction (closing) of the vocal folds.

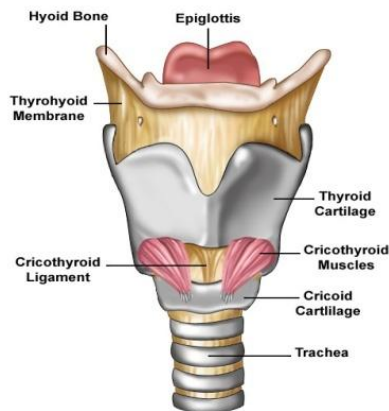


Figure 1. Anterior view of the larynx (Biology Corner 2011)

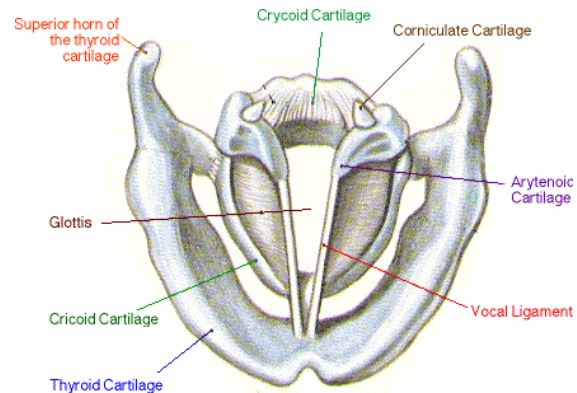


Figure 2. Transverse plane of the larynx viewed from above to show the anatomical location of the vocal folds (Singing voice 2011).

FUNCTION

The primary function of the vocal folds is to protect the airways (Reeve 2011). During respiration the vocal folds are open, allowing for air to pass into and out of the body. The ability

of the vocal folds to constrict the airway leads to phonation. Phonation begins as the positive air pressure from the lungs forces the vocal folds open momentarily. The high velocity air causes a decrease in pressure by the Bernoulli effect, bringing the vocal folds back together again (Reeve 2011). Subglottic pressures increases again and the process continues. The air compressions and refractions caused by the vocal folds create sound. Pitch is determined by the rate at which vocal folds come together and separate over a period of time. The exact number of repetitions is known as the frequency. Higher frequencies are perceived as higher pitched while lower frequencies result in a lower perceived pitch (Reeve 2011).

The vibrating frequency of the vocal folds relies heavily on the integrity of the underlying layers of tissue, specifically the superficial layer of the lamina propria (Sulica 2011). The histology of the vocal fold contains five layers with the superficial layer of the lamina propria being the closest layer to the epithelium at the free end of the vocal fold (figure 3)(Balasubramanian 2011). The superficial layer of the lamina propria is often referred to as Reinke’s space. A thin layer of epithelial cells acts as a supportive and protective boundary between the lamina propria and the airway. Below the superficial layer lie the intermediate and deep layers of the lamina propria.

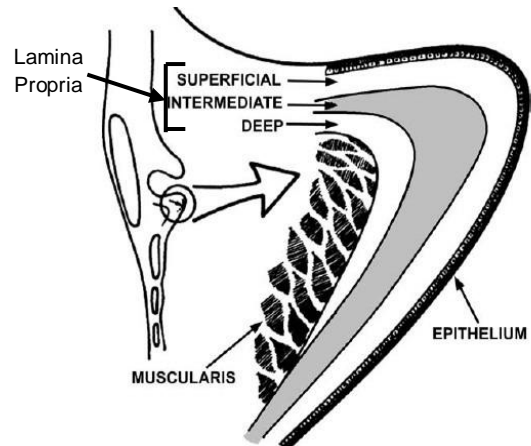


Figure 3. Histological layers of a vocal fold (Balasubramanian 2011)

Finally, the vocalis muscle lies underneath the lamina propria. The superficial layer of the lamina propria is composed of loosely packed fibers offering minimal resistance to vibration (Balasubramanian 2011). This layer contains a negligible amount of elastic and collagenous fibers whereas the intermediate layer has a higher concentration of connective tissue and the deep layer has a dense collection of elastic and collagenous fibers. The composition of the intermediate and deep layers of the lamina propria serves to provide protection to the vocal folds from mechanical damage (Balasubramanian 2011).

SURGICAL PROCEDURE

The proposed method for the treatment of scarred vocal folds uses a local vascularized flap for the augmentation of Reinke’s space (Dailey 2011). The soft tissue flap used in this procedure is known as the composite thyroid ala perichondrium flap (CTAP). A thin layer of tissue is removed from the anterior surface of the thyroid cartilage. The tissue was perforated along the contralateral oblique line, allowing for the removal of only half of the tissue found on the anterior face of the thyroid cartilage. The flap is left attached to only the inferior edge of the thyroid cartilage. In addition to the perichondrial tissue, adjacent adipose tissue was left attached to the distal end of the flap (figure 4). The adipose tissue was removed from the anteromedial pre-epiglottic space. The adipose tissue is the desired tissue to be inserted into Reinke’s space, while the perichondrial tissue functions as the vascular tissue for the adipose

tissue. By inserting the adipose tissue into the lamina propria, it serves to restore function to the damaged or scarred vocal folds. This is possible due to the similar viscoelastic properties of the lamina propria and adipose tissue. Viscosity determines the amount of energy required for tissue oscillation. As damage and scarring occur to the vocal folds, tissue viscosity increases, which consequently increases the amount of energy required for oscillation (Gray 1999). By inserting adipose tissue into the damaged Reinke's space, the original properties of the region can be restored.

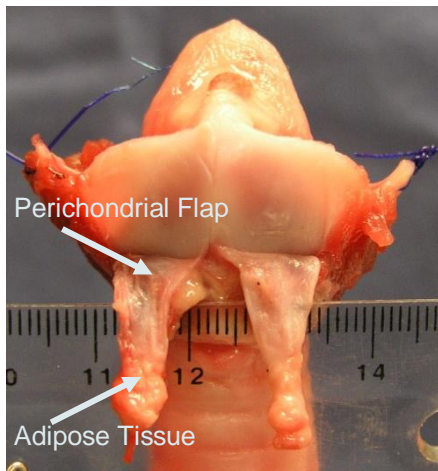


Figure 4. Removal of the perichondrial flap with attached adipose tissue from the surface of the thyroid cartilage (Dailey 2011)

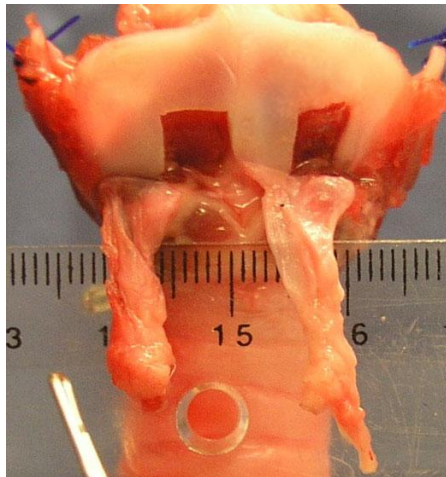


Figure 5. Minithyrotomy, the procedure used to gain access to Reinke's space by creating a window through the thyroid cartilage (Dailey 2011)

Once the tissue flap is removed, access to Reinke's space is achieved through a minithyrotomy, as described by Gray. Entrance to the lamina propria is achieved by creating a 4 mm window in the thyroid cartilage, slightly off the midline along the inferior edge (figure 5). This procedure lines up the direction of dissection in the anterior-to-posterior orientation, avoids incisions through the epithelial layer of the vocal folds, and provides access for microscopic instruments with the surgeon's hand in close proximity to the tissue of interest (Gray 1999). It is especially important to note the advantage of leaving the epithelial layer intact as the larynx is subject to a plethora of bacteria that passes through the esophagus. When the epithelial layer in the larynx is severed, severe and even lethal infections can occur at the incision site. Therefore, a minithyrotomy is an advantageous approach to the insertion of the tissue flap used for the augmentation of Reinke's space.

Once access has been gained to Reinke's space, dilation of the space needs to occur to allow for insertion of the soft tissue flap. This process is achieved with the use of a set of titanium dilators of various diameters (figure 6). Dilators are inserted through the window created by the minithrotomy, starting with the smallest diameter and progressively growing to the dilator with the largest diameter. This method is used to expand the tissues in the lamina propria in order to create an adequate amount of space for the insertion of the flap and the materials required for the appropriate fixation of the flap. Once the tunnel through the superficial layer of the lamina propria has been created, the soft tissue flap is inserted into the tunnel with the distal end of the flap extended to the posterior end of the tunnel (figure 7).

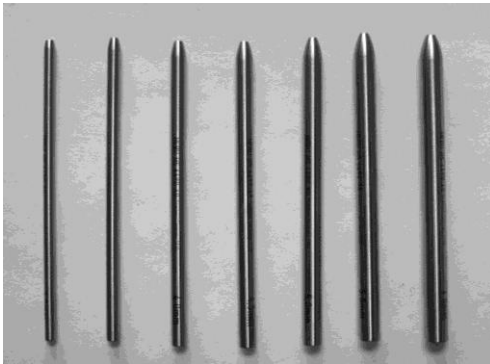


Figure 6. Dilators used for the insertion and fixation of the soft tissue flap in Reinke's space (Dailey 2011).

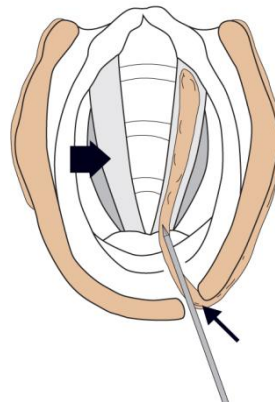


Figure 7. Insertion of the soft tissue flap (thin arrow) into the lamina propria (bold arrow) (Dailey 2011).

CLIENT INFORMATION

The design project that we are challenged with this semester has been proposed by Dr. Seth Dailey, an otolaryngologist for the University of Wisconsin, Department of Surgery. Dr. Dailey specializes in voice, airway and swallowing disorders. He is also interested in designing and testing novel surgical strategies for reconstruction of the impaired or injured larynx.

PROBLEM STATEMENT

Dr. Seth Dailey has requested the development of a device to affix a soft tissue flap within the lamina propria during vocal fold reconstruction. The implanted fat tissue of the flap will match the viscoelasticity of the lamina propria and, therefore, allow enhanced oscillation of the scarred or damaged vocal fold. This fixation procedure should allow typical laryngeal movements that may otherwise dislodge the soft tissue flap, such as coughing, sneezing and swallowing.

COMPETITION

Pre-existing methods for the treatment of vocal fold scarring include implants and injections. One successful procedure for the correction of large glottic defects is a type I thyroplasty as modernized by Isshiki. In this procedure an implant is placed in the vocal folds intending to improve the medial displacement of the vocal fold. However, implants are usually exogenous, costly, can extrude, require an external incision, and do not automatically correct lamina propria alterations (Dailey 2011).

Similarly, injections are used as an additional method for the treatment of vocal fold scarring. Injection agents such as collagen and Radiesse™ are widely available, effective, safe, and easily delivered into the paraglottic space. Drawbacks to the injection treatment include variable durabilities, rejection or migration of the injection and a difficulty in revising the injection (Dailey 2011). The fact that pre-existing methods merely address the symptoms instead of the defects in the lamina propria provides a strong motivation for improved techniques for the treatment of scarred vocal folds. Furthermore, because autologous tissue implants have already been proven effective at treating vocal fold scarring in the short term, providing vasculature for these implants would provide a significant improvement, as proposed in the local vascularized flaps for augmentation of Reinke's space.

PREVIOUS DESIGNS

Several designs for attaching the tissue flap to the arytenoid have been tried before our team's involvement with this project. Many of the devices (figure 8) would use a screw or other device to provide an anchor in the arytenoid cartilage. Suture thread would be attached to this anchor and the distal end of the flap, allowing the flap to be pulled into the vocal fold canal. Because of the nature of the minithyrotomy procedure a length of suture would be inaccessible and remain in the vocal fold. Because of this a single device providing anchorage to the arytenoid cartilage and the flap's distal end would be preferred over a device which relies on sutures to attach the flap to the anchor.

The most recent design is a micro-corkscrew which has achieved moderate success (figure 9). The screw is approximately 1.5mm long and 0.5mm wide. To attach to flap to the arytenoid, first the screw is embedded in the adipose tissue at the distal end of the flap. Next the flap is placed in a cannula and inserted through the vocal fold until it reaches the arytenoid. The screw is twisted three times into the cartilage and the cannula removed. To avoid any torsion on the flap it is counter-rotated prior to insertion. Drawbacks of using this device include counter-rotation of the flap and difficulty fixing the screw in the desired location on the arytenoid cartilage. Furthermore devices that do not disrupt the arytenoid cartilage and instead attach the flap to surrounding soft tissues should also be pursued.

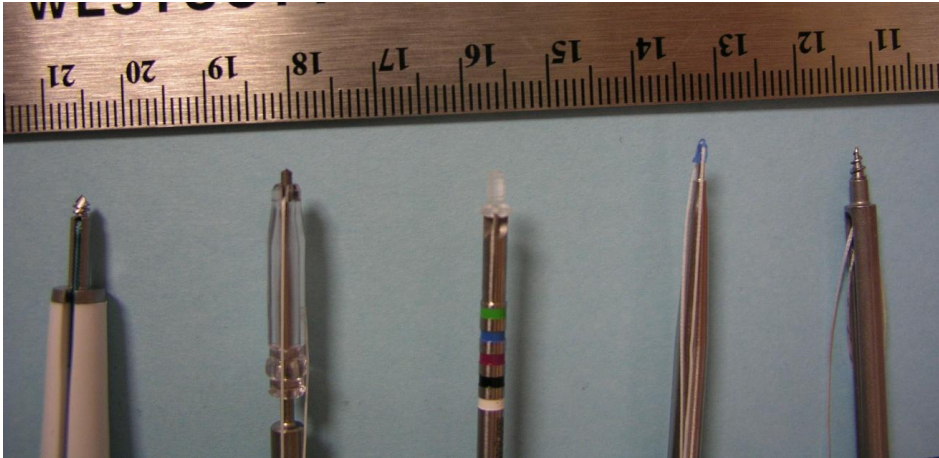


Figure 8 (left). Several previously designed devices.

Figure 9 (below). Micro corkscrew with delivery cannula.



DESIGN SPECIFICATIONS

The requirements specified by our client cover a range of topics, including size, ease of delivery, strength, biocompatibility, cost, and minimizing tissue damage. Our design must be simple, easy to manufacture, and cost-effective. It also must be biocompatible while still providing a strong method of fixation for the tissue flap inside of the lamina propria. On top of all that, it must be easy to use and easy to integrate into the surgical procedure. To achieve a device to satisfy these needs, we investigated four possible designs.

DESIGN ALTERNATIVES

IMPROVED CORKSCREW

The corkscrew design has been proven to provide a strong anchor to the arytenoid and is the basis of the first design. For a corkscrew design to be successful modifications must be made to increase the ease of delivery into the cartilage and to avoid counter-rotation of the flap. A two part screw which allows the screw to rotate independently from the tissue attachment point was proposed. However this design was set aside because of the difficulty of producing complex parts on such a small scale. Next a design which combines a pin and a single twist corkscrew was investigated (figure 10). The pin would help accurately place the screw in the cartilage. This design would still need the flap to be pre-rotated once. Various prototypes of this design were made from 0.38 mm high carbon content steel. Several improved corkscrew prototypes were fabricated by feeding the wire through a 20-gauge needle acting as a spacer. The wire was then folded over the terminal end of the needle and tightly rotated down and around the length of the needle. Next, the needle was removed and the ends of the wire were trimmed to the appropriate length. Limitations of this design include twisting of the tissue flap,

difficulty achieving precise and consistent placement and a lack of an appropriate delivery device.

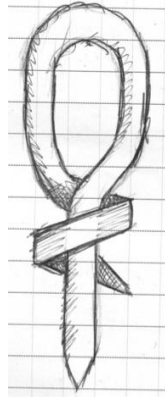


Figure 10. Sketch of improved corkscrew design with side and top view.

BARBED NAIL

A previous barbed design utilizing the suture anchor technique did not provide an adequate anchor into the arytenoid. This design failed because the barbs that deployed were inadequate and pulled out of the cartilage. However we feel that a modified device with redesigned barbs would have more success. A thin nail would be outfitted with barbs on one end and a cap on the other. The nail would be pinned through the tissue flap and inserted into the arytenoid. When tension is applied to the barbs pivot outwards and embed into the arytenoid cartilage, holding the anchor in place. This design simplifies the fixing process and does not require counter-rotation of the flap. In addition the nail has the possibility to be made from bioabsorbable materials. Drawbacks to this design include difficulties designing the barbs on a micro scale and disruption of the arytenoid.

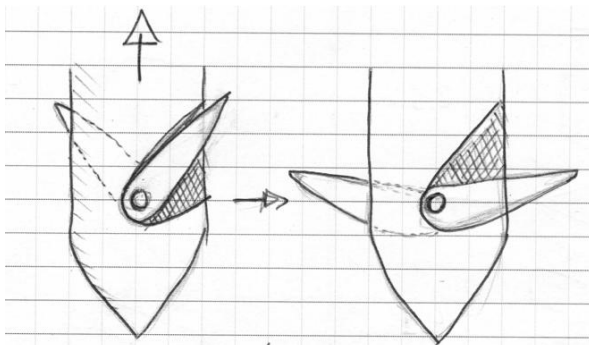


Figure 11. Sketch of barbed nail design. Pivoting barbs can be seen before and after the barbs are engaged in the arytenoid.

SOFT TISSUE GLUE

As an alternative to the mechanical solutions, the third design uses a tissue glue to attach the flap to the surrounding soft tissue in the vocal fold. Various types of soft tissue glues are

currently on the market including the two most commonly used cyanoacrylate ‘super’ glues and fibrin sealants. Cyanoacrylates were not considered, as they would remain in the vocal fold for an extended period of time. Furthermore, degradation components of cyanoacrylates are often harmful. Further emphasis and consideration was given to fibrin glues. Fibrin tissue adhesives are composed of fibrinogen and thrombin. When the two components are combined, thrombin acts to convert fibrinogen to fibrin. Fibrin is a fibrous protein that serves as a clotting factor or an adhesive. Advantages to using a fibrin glue for fixation of the tissue flap include simplicity and ease of application, biocompatibility as fibrin glues can be composed entirely of human products and minimal damage to the integrity of the tissue flap. One concern of placing glue into the vocal fold is that the glue may alter the viscoelastic properties of the lamina propria, preventing proper phonation.

GECKO TAPE

The final design alternative used a developing technology known as “Gecko” tissue tape to attach the flap to surrounding soft tissues. The tape is made of biodegradable polymers and adheres to wet tissues by mimicking the fibrous nano-architecture of the gecko footpad. This is accomplished by nano molding a PGSA polymer into the desired pillar shape. A thin layer of oxidized dextran is applied to the film which provides aldehyde functionalities to promote covalent cross-linking with tissue (Mahdavi 2008). At this time gecko tissue tape is still under development at MIT and Northwestern laboratories and not available for market.

DESIGN MATRIX

Our client has requested that we continue with more than one design for the project since no design would be proven effective until it was used in a live surgical procedure. To fulfill the requirement we decided to weigh our proposed designs and continue with the best two. In order to help determine which final design was the best to pursue, the design matrix below was constructed.

Table 1. Design Matrix

	Weight (%)	Fibrin Glue	Improved Corkscrew	Barbed Nail	Gecko Tape
Size	15	5	2	3	4
Ease of Delivery	25	3	2	4	2
Strength	15	3	5	3	3
Biocompatibility	20	2	3	3	4
Minimize Tissue Damage	20	4	2	3	4
Cost	5	2	4	4	0
Total	100	3.25	2.75	3.3	3.15

Our designs were evaluated based on the categories listed: size, ease of delivery, strength, biocompatibility, minimizing tissue damage, and cost. After weighing each category based on its importance to the overall product we rated each design. Ease of delivery was the most important category due to our client's need to keep the surgical process simple and quick. Biocompatibility and minimizing tissue damage were the next most important aspects. The design must be biocompatible, not to lead to infection or unwanted swelling. The aforementioned could cause discomfort in the patient or prolonged healing time. Our device must also minimize the damage to the lamina propria, arytenoid cartilage, and surrounding tissues. Damaged tissue could lead to further scarring and possibly permanent damage in the vocal folds. For this reason we weighted the category with second-highest priority. The categories with the next highest priorities were size and strength. These are both important categories, but are weighted less because they are not directly related to the healing of the tissue and strength may not be a significant issue considering the device will likely experience limited stress. The lowest ranked category was cost. Cost received the lowest weight since we were not given a specific budget.

After our mid-semester conclusions, we were encouraged by our client to reevaluate the barbed nail. The design contained moving parts and would be extremely difficult to manufacture on a micro scale. In addition, the procedure for placing the flap with this device would be problematic due to the pyramid-like geometry of the arytenoid cartilage. Furthermore, the nail could cause damage to or pull out of the arytenoid cartilage resulting in inflammation or infection. Therefore we chose to abandon the barbed nail design and continue solely with the fibrin glue and improved corkscrew. After creating prototypes of the improved corkscrew, our client decided not to continue with this option and focus our efforts on a fibrin glue. The improved corkscrew was eliminated as a design alternative due to requirements for a delivery device and the potential harm that it may cause to the flap.

FINAL DESIGN

We have chosen to use a fibrin glue, Evicel, manufactured by Ethicon. The glue is a mixture of human-derived fibrinogen (BAC2 55-85 mg/mL) and thrombin (800-1200 IU/mL). Upon mixing the components, an adhesive fibrin clot is formed. Because Evicel is derived from human compounds, the glue is degraded and absorbed within the body in 1-2 weeks (Evicel 2009). Although fibrin sealants are most commonly used for hemostasis, we have found Evicel to serve as an effective adhesive to fix the tissue flap within the vocal fold while maintaining the integrity of the flap.



Figure 12. The application syringe for Evicel alongside the packaged thrombin and fibrinogen (Evicel 2009).

begins instantly and is fully formed within two minutes, allowing for a quick procedure. The benefits of this design are the ease of application, the minimization of damage to the tissue flap and arytenoid cartilage, and the biodegradable characteristic of the glue.

Evicel's two components, fibrinogen and thrombin, are loaded to a double barreled syringe for delivery(Figure 12). Once added to the syringe, the glue remains viable for up to 24 hours. For our application method we will use only a few drops of a 50/50 mix of fibrinogen to thrombin. Clot formation

TESTING

Initial testing of the fibrin glue was done to quantify the bond strength and observe the oscillation behavior of vocal folds injected with the fibrin sealant. It was important to determine if the glue could hold with an adequate force, and if the inclusion of the fibrin glue in the vocal cord would adversely affect its ability to oscillate. All tests were done with cadaverous canine larynges.

To begin strength testing a CTAP flap was prepared as outlined previously with the inclusion of a suture attached at the proximal end of the flap. One to two drops of the fibrin glue were applied to the distal end of the flap, and the flap was inserted into the vocal fold. After waiting five minutes to insure the glue had fully set up, the proximal tissue flap attachment was cut leaving the glue solely responsible for holding the flap within the vocal cord. Next the proximally attached suture was threaded over a pulley and tension was increased by addition of 2 g weights to the suture. Weights were added until the glue failed and the flap was pulled out of the vocal fold. This failure point was then recorded. In six trials the maximum weight held was 42 g, with an average of 17.3 g (figure 13).

To test oscillation behavior a pair of CTAP flaps were prepared and inserted into the vocal folds, and the cavities were filled with the fibrin glue until oozing out. After approximately thirty minutes the larynx was set up on a machine, which could create a laminar airflow through the trachea. Vocal fold oscillations were observed with a mounted camera zoomed in on the oscillating cords. At a 30 mmHg pressure differential normal symmetric waves of oscillation could be viewed leading us to conclude that the inclusion of the glue would not significantly alter the viscoelastic properties of the lamina propria.

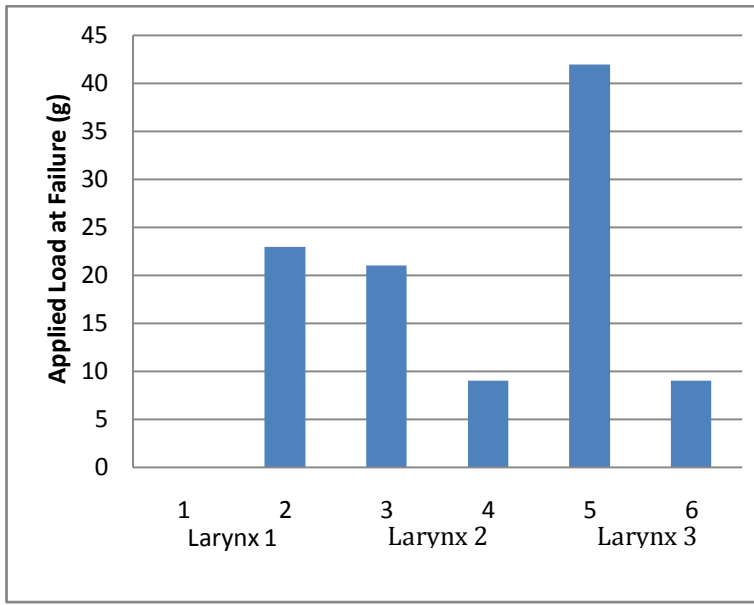


Figure 13. Results of applied loads during testing in deceased canine larynges to determine the fixation strength of Evicel glue.

FUTURE WORK

The focus of future work on this design will be on determining the most effective and efficient method of glue application for tissue flap adhesion. To develop the most successful procedure, additional testing will be performed to evaluate many procedural variables. The general adhesion properties of Evicel will be evaluated through testing in cadaveric canine tissue. By using this type of tissue and not larynges, we are able to generalize about the properties of Evicel adhesion and apply this knowledge to more specific testing on canine larynges. Since the adhesive properties of Evicel may depend on the types of tissues being connected, we will test the strength of adhesion between different connection types including: perichondrium to muscle, perichondrium to lamina propria, adipose to muscle, and adipose to lamina propria. Evaluating the adhesion strength of the different connection types will provide insight into the best method of glue delivery. Next, the effect of glue set time on adhesion strength will be tested. Strength testing will be performed on adhered tissue at different time points after initial contact. This factor will be important if we find that the flap must be held in place after insertion into the lamina propria.

After initial testing of cadaveric tissue, we will perform more specific testing glue application to cadaveric larynges based on our preliminary findings. The method of glue application will be investigated through strength testing of different methods. Application methods that will be tested include 1) application of Evicel to the tissue flap, then insertion of flap into lamina propria, 2) insertion of the flap into the lamina propria, then application of Evicel into the lamina propria, and 3) application of one component of Evicel to the flap, then insertion of the flap, and finally application of the second component of Evicel into the lamina propria. For this testing, consistent amounts of Evicel will be used to ensure comparable results. Furthermore, the effect of the amount of Evicel on adhesion will be tested. An infusion pump will be used to standardize the amount of Evicel delivered to the soft tissue flap. We expect that

a small amount of Evicel, such as one or two drops, will provide sufficient adhesion strength for our purposes.

Finally, once our glue application method is fully developed, it will be integrated into the overall surgical procedure for vocal fold repair. By preparing a standard protocol for this repair, there will be a base for future variations and improvements. With this biocompatible, efficient, and effective method of tissue flap fixation, many individuals will benefit from improvements in phonation.

CONCLUSIONS

Using Evicel glue as an adhesive to secure the tissue flap is an effective means to ensure the permanent fixation of the flap into the lamina propria of the scarred vocal fold. Although long term success of Evicel is yet to be determined in living tissue, it is expected that results of a prospective study would only show an increased level of success as the living tissue will simultaneously create additional points of fixation, further strengthening the bond. Additional advantages of using Evicel, a fibrin sealant, in conjunction with the designed minithyrotomy include ease of delivery, limited damage to the vasculature of the flap and unaltered viscoelastic properties of the lamina propria. Therefore, the tissue will remain healthy and intact for a greater duration postoperatively. With the vascularized tissue flap secured in place, vocal fold function will be improved and may be permanently restored.

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APPENDIX A. PROJECT DESIGN SPECIFICATIONS

#36- Fixation device for laryngeal soft tissue flap for vocal fold reconstruction

May 4, 2011

Team: Ross Comer, Bryan Jepson, Christa Wille, William Zuleger

Client: Seth Dailey, MD

Advisor: John Webster

Function:

The device will secure a perichondrial tissue flap into the lamina propria layer of the vocal folds. Insertion of this flap into the vocal fold will benefit individuals with scarred and damaged vocal folds. This fixation device should endure typical laryngeal movements that may otherwise dislodge the soft tissue flap.

Client Requirements:

- Surgical procedure should involve limited rotation of the tissue flap
- Fixation must be held for one to two weeks
- Device must be able to be inserted via minithyrotomy
- Insertion must not perforate the epithelial layer of vocal folds
- Insertion must maintain vasculature of the tissue flap
- Device must cause minimal damage to surrounding tissue

Design Specifications:

1) Physical and Operational Characteristics

a) Performance requirements

- i. Must effectively secure soft tissue flap and withstand typical laryngeal movements
- ii. Must remain sterile before implantation
- iii. Must maintain fixation for 1-2 weeks

b) Safety

- i. No negative biological effect

- ii. Degradation products should be biocompatible
 - c) *Accuracy and Reliability*
 - i. Must accurately attach to desired location inside the lamina propria
 - d) *Life in Service*
 - i. Minimum of one week for attachment to ensure tissue regrowth
 - e) *Shelf Life*
 - i. Evicel can be refrigerated for up to 30 days or frozen for extended life
 - ii. Once vials are opened, glue must be used within 24 hours
 - f) *Operating Environment*
 - i. Within the superficial layer of the lamina propria of the vocal fold
 - g) *Ergonomics*
 - i. Glue must be easily applied via glue applicator
 - h) *Size*
 - i. Applicator must be less than 2 mm in diameter
 - i) *Weight*
 - i. Weight of 1-2 drops of Evicel is negligible
 - j) *Materials*
 - i. Composed of human fibrinogen and thrombin
 - ii. Fibrin glue and its degradation products are biocompatible
 - k) *Aesthetics*
 - i. N/A
- 2) Production Characteristics
- a) *Quantity*
 - i. 1-2 drops per procedure
 - ii. Multiple procedures can be performed with one vial if done within 24 hours
 - b) *Target Product Cost*
 - i. \$150
- 3) Miscellaneous
- a) *Standards and Specifications*
 - i. FDA approval required for glue application
 - ii. IRB approval required for human testing
 - b) *Customer*
 - i. Medical schools
 - ii. Hospitals
 - c) *Patient-related concerns*
 - i. Biocompatibility
 - ii. Immune response
 - d) *Competition*
 - i. Injections or implants
 - ii. Previous screw prototypes