2015

Penetrating keratoplasty: the search for a sutureless solution

https://hdl.handle.net/2144/16068

Boston University
BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

PENETRATING KERATOPLASTY:
THE SEARCH FOR A SUTURELESS SOLUTION

by

FAISAL AL BAHRANI
B.S., Case Western Reserve University, 2012

Submitted in partial fulfillment of the
requirements for the degree of
Master of Science
2015
Approved by

First Reader
Gwynneth Offner, Ph.D.
Associate Professor of Medicine

Second Reader
Samir Melki, M.D., Ph.D.
Assistant Clinical Professor of Ophthalmology
Harvard Medical School
ACKNOWLEDGMENTS

I would like to thank Dr. Samir Melki for inspiring me with the idea to pursue this topic. I would also like to thank Dr. Ali Fadlallah for his help in the editing process as well as his helpful comments and criticisms. Lastly, I would like to thank Dr. Offner for her continuous guidance.
PENETRATING KERATOPLASTY: THE SEARCH FOR A SUTURELESS SOLUTION

FAISAL AL BAHRANI

ABSTRACT

Specific Aim: Worldwide, there is a deficiency in the availability and the outcomes of corneal transplants procedures. The use of sutures in the various types of corneal transplant procedures increases the skill requirements for performing the procedure in addition to bringing about various suture-related complications. In order to avoid these complications and to make the procedure easier to perform, it is vital to review the properties and availability of various surgical adhesives in order to assess their potential as candidates for replacing suture use in corneal transplant procedures. The focus in this paper will be on the most prominent of these procedures: the penetrating keratoplasty procedure.

Recent Findings: Surgical adhesives that could potentially act as replacements or adjuncts to suture use in the penetrating keratoplasty procedure include homologous fibrin adhesives, polyethylene glycol sealants, cyanoacrylate glue, and poly [glycerol-sebacate-acrylate] (PGSA) glue. Polyethylene glycol sealants, when used as adjuncts to suture use in keratoplasty procedures lead to significant levels of wound dehiscence. Fibrin glues have been found to reduce the amount of sutures required in a “top hat” wound configuration penetrating keratoplasty when used as an adjunct to sutures in binding the donor button in place. Cyanoacrylate glues, although having higher levels of adhesive strength
than fibrin glue, lead to various unwanted side effects. Lastly, PGSA glue, given its recent development, remains an uncertainty due to the lack of research on it.

Summary: Overall, use of homologous fibrin glues is currently the most likely way to reduce the use of sutures in the penetrating keratoplasty procedure. Its use could lead to shorter operative times, fewer complications, reductions in cost, and higher availability for corneal transplant procedures. However, with further investigation, PGSA glue may prove to be a better candidate for the replacement of sutures than fibrin glues.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE</td>
<td>i</td>
</tr>
<tr>
<td>COPYRIGHT PAGE</td>
<td>ii</td>
</tr>
<tr>
<td>READER APPROVAL PAGE</td>
<td>iii</td>
</tr>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>iv</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>v</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>vii</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>ix</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>x</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>xi</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td><strong>Penetrating Keratoplasty</strong></td>
<td>3</td>
</tr>
<tr>
<td><strong>Deep Anterior Lamellar Keratoplasty</strong></td>
<td>5</td>
</tr>
<tr>
<td><strong>The Cons of Suture Use in Penetrating Keratoplasty</strong></td>
<td>7</td>
</tr>
<tr>
<td><strong>Ideal Characteristics of a Sutureless Alternative</strong></td>
<td>13</td>
</tr>
<tr>
<td>SPECIFIC AIMS</td>
<td>15</td>
</tr>
<tr>
<td>PUBLISHED STUDIES</td>
<td>16</td>
</tr>
<tr>
<td><strong>Fibrin Glues</strong></td>
<td>16</td>
</tr>
<tr>
<td><strong>Cyanoacrylate Glues</strong></td>
<td>26</td>
</tr>
</tbody>
</table>
## LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Advantages and Disadvantages of DALK Compared to Penetrating Keratoplasty</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>Summary of Results for Corneal Suture Insertion with Differing Grades of Surgeon Experience</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>Incidence and Timing of Suture Related Complications Following Penetrating Keratoplasty</td>
<td>13</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diagram of the Eye</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Example of a Penetrating Keratoplasty Post-Operative Eye</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Eye with Granular Dystrophy (Groenouw Type I).</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>Diagram of a Post DALK Cornea</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>Suture Removal Effect on Post Keratoplasty Astigmatism</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>Diagram of Fibrin Matrix Formation</td>
<td>18</td>
</tr>
<tr>
<td>7</td>
<td>Bonding Power of Fibrin Glues on Pig Skin</td>
<td>21</td>
</tr>
<tr>
<td>8</td>
<td>Post-Operative DALK Eye Set with Overlay Sutures and Fibrin Glue</td>
<td>24</td>
</tr>
<tr>
<td>9</td>
<td>Diagram of Various Wound Configurations for Penetrating Keratoplasty Procedures</td>
<td>26</td>
</tr>
<tr>
<td>10</td>
<td>Model of Cyanoacrylate Molecule</td>
<td>27</td>
</tr>
<tr>
<td>11</td>
<td>Magnitude of Adhesion of Various Adhesives to Epicardial Tissue</td>
<td>34</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS

D .......................................................................................................................... Diopters
DALK ............................................................. Deep Anterior Lamellar Keratoplasty
DMEK ............................................ Descemet Membrane Endothelial Keratoplasty
DSEK ................................................ Descemet Stripping Endothelial Keratoplasty
N ......................................................................................................................... Newton
PGSA ............................................................... Poly (Glycerol-Sebacate-Acrylate)
USP ................................................................. United States Pharmacopoeia
INTRODUCTION

Corneal transplantation is a well established form of treatment for various life-altering corneal pathologies including bullous keratopathy, dystrophies, keratoconus, trauma, and corneal scarring. To emphasize the impact of those pathologies, keratoconus, known to occur in up to 2.3% of the population in places such as India, is responsible for 5% of all cases of blindness (Arora et al., 2015). Corneal transplantations are carried out through one of a handful of different procedures including penetrating keratoplasty, deep anterior lamella keratoplasty (DALK), Descemet stripping endothelial keratoplasty (DSEK), and Descemet membrane endothelial keratoplasty (DMEK). The Eye Bank Association of America recently revealed that they distributed 88,227 corneal tissues in 2012 that were used in corneal transplants worldwide (Ple-Plakon & Shtein, 2014). Of those tissues, 36,716 were used for penetrating keratoplasty and 24,227 were used for lamellar keratoplasty.
Although the amount of corneal transplants performed across the globe each year is in the order of about one hundred thousand procedures, it has been estimated that approximately 10 million people worldwide would benefit from the procedures (Price et al., 2010). In addition to the problem of supply, the quality of corneal transplants in terms of outcomes in developing countries is significantly worse than those in more developed countries, leading to a high proportion of repeated surgeries (Garg et al., 2005). This lack in availability and quality can be attributed to a lack of skilled surgeons, less refined eye banking infrastructure, and less developed clinical facilities. To address these problems, changes can be made to the penetrating keratoplasty procedure to decrease the skill intensive nature of the procedure to allow more surgeons to perform the procedure. The problem can be alleviated by altering the painstaking and time consuming suturing step of the penetrating keratoplasty procedure to make it sutureless,
which would make the procedure quicker, easier to perform, and would potentially decrease the risk of certain complications. In this paper, the potential avenues for making the penetrating keratoplasty procedure sutureless will be noted and their respective advantages and drawbacks will be discussed with respect to penetrating keratoplasty performed with traditional 10-0 nylon sutures.

**Penetrating Keratoplasty**

Penetrating keratoplasty has been and has remained the most prominent form of corneal transplantation. Since its inception and after the first successful procedure in 1905, various advances to medicine have contributed to improved outcomes and surgical efficiency. The procedure itself is currently carried out through the use of a corneal trephine, a circular cutting device, or through a femtosecond laser, which make a deep, circular, cut in the cornea (Brightbill, 2009). The patient’s diseased circular disc of cornea is then removed and replaced with a similarly shaped, healthy, donor cornea. A radial pattern of sutures (see Figure 2), usually nylon and of the 10-0 USP designation, is then used to bind the donor cornea in place and to promote healing of the epithelial tissue. The first suture is placed at the 12 o’clock position, passed through the donor and host tissues, and tied with a triple knot followed by two single loops (the 3-1-1 knot) or a slipknot. The second suture is placed on the opposite side of the circular ring of donor cornea and tied in a similar manner. This suturing occurs at various angles radially until about 16, equally spaced, sutures are placed.
Figure 2. Example of a Penetrating Keratoplasty Post-Operative Eye. In this particular example, the surgeon used both 10-0 and 11-0 USP designation sutures (Taken from McGhee et al., 2013).

General indications for the surgery are various and include corneal pathologies such as trauma, keratoconus, repeat grafts from previous surgeries, infections, bullous keratopathies, and dystrophies (see Figure 3). Due to the immunological privilege of the eye, corneal transplant procedures are able to treat these pathologies at a success rate as high as 90% (Niederkorn, 2010). Despite the success rates, penetrating keratoplasty procedures require intensive follow up in order to address the various complications that occur. Known complications include induced astigmatism, graft rejections, wound leakage and dehiscence, secondary glaucoma, and ocular surface diseases (Ple-Plakon & Shtein, 2014). The induced astigmatism is due to the wound alignment of the donor cornea with the host in conjunction with the varying tightness of the
sutures that form a ring around the cornea and bind it in place. After the surgery, multiple follow-ups are required to manage the astigmatism through selective removal of tight sutures and through refractive lenses (Fares et al., 2012).

Figure 3. Eye with Granular Dystrophy (Groenouw Type I). Severe cases of granular dystrophy can be treated by corneal transplants (Taken from *Ophthalmology*, 2011).

**Deep Anterior Lamellar Keratoplasty**

Deep Anterior Lamellar Keratoplasty, or DALK, is a form of corneal transplantation which involves the selective removal of a partial, anterior, segment of the cornea (See Figure 4). Unlike penetrating keratoplasty, the partial segment that is removed does not include the underlying endothelium and Descemets membrane. The removal occurs in a similar fashion to the penetrating keratoplasty but also requires the injection of an air bubble to
separate the anterior cornea from the rest of the cornea (Anwar & Teichmann, 2002). Once the segment is cut out, it is replaced with a healthy donor’s anterior cornea and sown in place. Since DALK does not replace the endothelium, the primary indications are limited to those that only affect the anterior segment and include keratoconus and corneal scarring. Due to its less invasive nature and decreased graft rejection risk, DALK is generally preferred over penetrating keratoplasty in cases where the host has a healthy endothelium (Rajan, 2014).

**Figure 4. Diagram of a Post DALK Cornea.** The diagram portrays the partial segment of the anterior cornea that is replaced. The host retains their endothelium (Taken from “Kornea Nakli - DALK yöntemi,” n.d.).

The complications for DALK are less severe than those of penetrating keratoplasty. Since the host endothelium remains intact, there is minimal risk of endothelial graft rejection (Cassidy et al., 2013). However, DALK patients experience similar astigmatism rates from suture tightness and wound alignment, as well as also experience the risk of having their DALK procedures cause perforation of the Descemets membrane, which requires the DALK procedure to
be converted to a penetrating keratoplasty (Cassidy et al., 2013). The conversion rate has been observed to vary from 2.5% to 9.6% of the procedures (Ple-Plakon & Shtein, 2014). In addition to the conversion risk, DALK is generally considered to be more technically demanding than penetrating keratoplasty (See Table 1). Due to these limitations in both indications and technical requirements, the remainder of the paper will focus on the penetrating keratoplasty procedure as a means of increasing the availability of corneal transplants.

Table 1. Advantages and Disadvantages of DALK Compared to Penetrating Keratoplasty. (Taken from Cassidy et al., 2013).

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eliminates risk of endothelial graft rejection</td>
<td>More technically demanding</td>
</tr>
<tr>
<td>Reduced endothelial cell loss</td>
<td>Prolonged operative time</td>
</tr>
<tr>
<td>Improved graft survival (anticipated)</td>
<td>Astigmatism rates similar to PKP</td>
</tr>
<tr>
<td>Largely extraocular procedure</td>
<td>Risk of conversion to PKP</td>
</tr>
<tr>
<td>Simplified long-term management:</td>
<td></td>
</tr>
<tr>
<td>1. Less dependence on topical corticosteroids</td>
<td></td>
</tr>
<tr>
<td>2. Earlier suture removal</td>
<td></td>
</tr>
<tr>
<td>Cost effectiveness</td>
<td></td>
</tr>
</tbody>
</table>

The Cons of Suture Use in Penetrating Keratoplasty

The use of sutures in penetrating keratoplasty procedures is associated with a variety of disadvantages. The first of which is the skill intensive and time consuming nature of corneal suturing. As stated above, those properties add to the overall lack of availability of corneal transplants in the developing world since
it increases both the need for skilled surgeons to perform the surgery and could add to the poorer outcomes in those countries if the surgery is not performed adequately.

In the realm of corneal suturing, it has been shown that an experienced surgeon, when compared to novices or trainees, takes far less time performing a 3-1-1 knot with a 10-0 nylon suture through the cornea and with fewer, and shorter, movements (Saleh et al., 2006; See Table 2). As indicated in 2012 by a questionnaire sent to ophthalmic consultants identified by the Royal College of Ophthalmology, 10-0 nylon sutures used in a 3-1-1 knot is generally preferred for high risk penetrating keratoplasty cases (Lee et al., 2012). This fact, in addition to the fact that the 3-1-1 knot can withstand more force before failure than slipknots, makes the capacity to perform the 3-1-1 knot with ease more of a requirement for corneal transplant surgeons (Lutchman et al., 2014). Since the 3-1-1 knot has to be performed approximately sixteen times in a standard penetrating keratoplasty, the difference in time an expert surgeon would require compared to a novice or a trainee to perform a 3-1-1 knot would effectively be multiplied by sixteen for the total procedure, leading to a 40 minute mean difference between a novice and an expert surgeon and a 10 minute mean difference between a trainee and an expert to perform a penetrating keratoplasty based on the suturing step alone (Saleh et al., 2006). An example of how alternatives to suture use in ophthalmology can decrease operative time occurred in 2012, when a study was performed where pterygium excision procedures were performed with both
sutures and fibrin glues. The results indicated that glue use decreased the mean pterygium excision operative time by about 36% (Cha et al., 2012). In essence, surgical skill deficiency can manifest itself through the suturing step of the penetrating keratoplasty, which makes that step a viable target for reducing both the operative time and the skill requirement.

**Table 2. Summary of Results for Corneal Suture Insertion with Differing Grades of Surgeon Experience.** (Taken from Saleh et al., 2006).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Novice Surgeons* (n = 10)</th>
<th>Trainee Surgeons* (n = 10)</th>
<th>Expert Surgeons* (n = 10)</th>
<th>Kruskal-Wallis P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Path length, median (interquartile range), mm</td>
<td>366 (107-3968)</td>
<td>1255 (450-2164)</td>
<td>316 (172-402)</td>
<td>.002</td>
</tr>
<tr>
<td>Hand movements, median (interquartile range), No.</td>
<td>125 (108-211)</td>
<td>81 (43-98)</td>
<td>40 (24-59)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time, median (interquartile range), s</td>
<td>264 (231-270)</td>
<td>140 (106-164)</td>
<td>105 (83-107)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Novice surgeons were those who had previously performed fewer than 5 corneal sutures; trainee surgeons, 5 to 100 corneal sutures; and expert surgeons, more than 100 corneal sutures.

The next issue that arises from suture use in penetrating keratoplasty is that of the induced astigmatism that arises via the varying tightness of the sutures binding the graft in place and the extensive post-operative suture removal. Suture tension and suture removal have been noted along with the instability of keratoplasty wounds as the predominant causes of keratoplasty induced astigmatism (Hoppenreijs et al., 1993). The suture tension tugs and alters the keratometry of the cornea, which can lead to the development of a significant astigmatism. This astigmatism causes post-operative patients to experience poor uncorrected vision and require prescription lenses to correct for
the astigmatism. Since the follow-up visits for the keratoplasty procedure require gradual removal of the stitches, the astigmatism will begin to change for every suture removed. This adds further complications to the correction of the patients’ vision and makes maintenance of properly corrected vision via lenses less practical and costly. The high astigmatism can lead to other problems as well. Premature suture removal performed with the intent of decreasing astigmatism has been shown to be a lead cause in post-operative wound gaps and dehiscence (Fujii et al., 2014).
Figure 5. Suture Removal Effect on Post Keratoplasty Astigmatism.
A, C, and E are progressive corneal topographies. B, D, and E are eye images that correspond, respectively, to the A, C, and E topographies. The arrows indicate where sutures were removed. Changes in the magnitude and axis of astigmatism can be noted. (Taken from Sarhan et al., 2010)

Preliminary studies have indicated that alteration of the suturing step of the penetrating keratoplasty procedure may solve the astigmatism-based complications. In 2013, a study was performed in which lamellar keratoplasty procedures were performed on multiple groups of rabbits, of which some had the
donor corneas attached with 8 bite sutures and others through synthetic glues (Cho et al., 2013). The group that had their grafts sutured with 8 bite sutures experienced significant differences in keratometry while the synthetic glue group experienced no significant changes in keratometry. This indicates the possibility that replacing the use of sutures with glues or other alternatives could be an efficient way to reduce penetrating keratoplasty induced astigmatism in addition to decreasing the required suture removal follow-up visits and astigmatism related complications. Synthetic glues as alternatives to sutures in penetrating keratoplasty procedures will be discussed in further detail later.

Lastly, suture use can lead to a variety of additional physical complications in keratoplasty procedures such as loose sutures, wound leakage, infection, wound dehiscence, ulcerations, and even graft rejection. It has been shown that up to 34% of keratoplasty cases can show these complications (Christo et al., 2001). The most common symptom is that of epithelial erosion, causing discomfort, mild pain, and the foreign body sensation for the patients. The most severe series of complications, however, results from spontaneous loose sutures. These sutures require removal followed by repair of the graft by means of resuturing. Approximately 13% of those loose suture scenarios resulted in a graft reaction, followed by complete graft failure. The data approximating the incidence of these complications as well as their timing can be found below.
Table 3. Incidence and Timing of Suture Related Complications Following Penetrating Keratoplasty. Taken from (Christo et al., 2001)

<table>
<thead>
<tr>
<th>Complication</th>
<th>No.</th>
<th>%</th>
<th>Average time (months)</th>
<th>Range (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erosions</td>
<td>39</td>
<td>10.8</td>
<td>14.1 ± 13.9</td>
<td>0–60</td>
</tr>
<tr>
<td>Sterile infiltrates</td>
<td>34</td>
<td>9.4</td>
<td>19.9 ± 16.9</td>
<td>0–62</td>
</tr>
<tr>
<td>Infectious keratitis</td>
<td>12</td>
<td>3.3</td>
<td>30.8 ± 23.5</td>
<td>1–65</td>
</tr>
<tr>
<td>Spont. loose sutures in need for repair</td>
<td>30</td>
<td>8.3</td>
<td>10.1 ± 11.1</td>
<td>1–28</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>9</td>
<td>2.4</td>
<td>10.6 ± 14.1</td>
<td>1–30</td>
</tr>
</tbody>
</table>

Ideal Characteristics of a Sutureless Alternative

In order to assess the potential of a sutureless alternative, the qualities of interest must be defined. First and foremost, an alternative to sutures in penetrating keratoplasty procedures must be able to generate the required amount of tensile strength to hold the donor cornea in place. This tensile strength must be maintained for a long enough duration that so that healing is promoted. Additionally, adequate tensile strength would prevent wound dehiscence, wound leakage, and other similar complications that are known to occur with suture use. The required forces needed to break and unravel a 10-0 nylon suture 3-1-1 knot are .71 N and .48 N respectively (Lutchman et al., 2014). If an alternative is able to withstand similar forces without breaking, then it can act as a full replacement when it comes to this criterion.
Second, the ideal alternative should not obstruct or alter vision in any way. This includes significant alterations to keratometry and astigmatism. Additionally, the alternative should not cause opacification of the cornea or lead to any opaque materials existing within the humour.

Inflammation, irritation, and pain should be kept to a minimum. In order to minimize the level of irritation and inflammation a patient experiences, the alternatives should have a high degree of biocompatibility with human corneal tissue. High levels of biocompatibility would also minimize discomfort and foreign body sensation.

The ideal alternative should also be safe and easy to use as compared to 10-0 nylon sutures. This would improve the operative time and reduce the need for highly skilled surgeons and increase overall availability of corneal transplants. Additionally, the alternative should be biodegradable or easily removable within the six to nine month post-operative period. This characteristic would minimize the required follow-up visits when compared to the extended amount of follow-ups required for suture removal.

Lastly, the ideal alternative would be cost effective, transportable, and widely producible. This characteristic would enable effective globalization of the technique for improved overall global availability. In the next section, the potential alternatives to sutures for the penetrating keratoplasty procedure will be highlighted and later compared to 10-0 nylon sutures with respect to these criteria.
SPECIFIC AIMS

The specific aim of this paper is to assess the properties, availability, cost, and current research on various potential alternatives to suture use for the penetrating keratoplasty procedure. The alternatives will be assessed based upon the ideal characteristics of a suture replacement above. It is the author’s intent to find a replacement for sutures that will maximize the global availability, the ease, and the efficacy of the penetrating keratoplasty procedure while minimizing surgical and post-operative complications, operative time, and patient discomfort. Given the unique physiology of the eyes and the cornea, only experimental papers involving use of those alternatives on the eye and cornea will be considered.
Sutures have been a cornerstone in surgery as a means of binding tissue and as promoters of healing. Over time, other mechanisms been developed and refined to accomplish similar goes. Examples include surgical staplers, adhesives, patches, and welding lasers. Tissue adhesives, especially, have seen wide use due to the ease of their application. Tissue adhesives have been localized to two primary categories: synthetic glues and biological glues. For the cornea, the main synthetic and biological glues that have seen extensive use are cyanoacrylate derivatives and fibrin based adhesives, respectively (Sinha et al., 2009). New adhesives available for potential ophthalmic surgical use include polyethylene glycol adhesives and poly (glycerol-sebacate-acrylate) glue (Panda et al., 2009; Lang et al., 2014). Below, each of these suture alternatives will be highlighted with regard to relevant publications that reveal their potential worth as replacements and adjuncts to suture use in penetrating keratoplasty procedures. Afterwards, these alternatives will be discussed with respect to the criteria of an ideal replacement in order to identify the best possible alternatives.

**Fibrin Glues**

*Properties*

Fibrin sealants act in a way that mimics the later parts of the natural coagulation pathway. The sealants are derived from plasma coagulation proteins, fibrinogens and thrombin. These two components are loaded into two syringes
that have a common port. Upon injection, the enzyme, thrombin, reacts with the fibrinogens to form fibrin monomers that create a gel matrix (See Figure 6). Factor XIII, which is present in the fibrinogen, acts to cross-link and stabilize the monomers. The concentration of thrombin determines the reaction rate and, thus, can be altered so that the rate of formation of the fibrin matrix can be tailored to specific uses (Atrah, 1994). For example, use of thrombin 500, a highly concentrated thrombin, would lead to a 10 second clot formation, whereas use of thrombin 4, a dilute thrombin, would require 60 seconds for clot formation. This variability in clot formation can be beneficial in keratoplasty procedures since time is required to properly align the donor tissue with the host’s tissue and clean excess glue. Although a delayed setting time is likely to be preferred, a surgeon’s particular preference and skill level can also play a role in which thrombin concentration is ideal.
An additional advantage to the use of fibrin glues with respect to sutures is the inherent biocompatibility and biodegradability of the mixture. They do not produce inflammation, necrosis, fibrosis, or foreign body reactions (Radosevich et al., 1997). The fibrin clot, itself, is broken down during the natural healing process. The process can take time ranging from days to weeks to completely break down, a variable based upon the concentration of the sealant and the

Figure 6. Diagram of Fibrin Matrix Formation. Taken from (Chernysh et al., 2012).
proteolytic activity of the treated area. During this time period, the fibrin sealant promotes tissue growth, healing, and angiogenesis (Matras, 1985).

The first drawback to the use of fibrin based adhesives is that the effective tensile strength of fibrin glues has not been adequately quantified. This is due to the variable nature of the glue composition and the tensile strength’s inherent dependence on external factors such as the tissue composition and the surface area of the target of adhesive application. Another example of tissue based limitations of fibrin sealant use, fibrin glues have been shown to work at peak effectiveness in primarily dry settings (Spotnitz, 2014). Since the penetrating keratoplasty procedure involves fluid exposure from both the humour of the eye and from topical anesthetics, fibrin glues are likely to be more viable for use in lamellar procedures since the endothelium prevents humour exposure. In addition, since the host maintains their endothelium, the graft-host interface has more surface area for glue adhesion in lamellar procedures than penetrating keratoplasty procedures, further increasing the viability disparity between the two types of corneal transplantation.

In order for fibrin glues to adequately replace sutures in penetrating keratoplasty procedure, it is preferable that they reduce the operative times and the inherent skill requirement of the procedure. Studies have also shown that the effectiveness of fibrin glues in surgical procedures is in part determined by the surgeons previous experience with fibrin sealants (Wang et al., 2003). This
indicates that fibrin glue use does have a learning curve and may require significant practice for maximum efficacy.

Additional drawbacks to fibrin glue use have been due to the method of fibrin adhesive preparation methods. Since the adhesive is derived from coagulation proteins, there exists a risk of transmitting diseases from the blood donors to the fibrin adhesive recipients (P A Everts, 2006). Additionally, the capacity to produce mass quantities of fibrin glue has been limited by its cost ineffective nature as a plasma based product. However, in 2008, Aizawa et al. presented a method of preparing large batches of thrombin, in the order of thousands of liters, from blood plasma through a series of separation techniques (Aizawa et al., 2008). They achieved a thrombin purity of 75%, sufficient for the production of fibrin adhesives. Additionally, the processed batches were run through various viral activity reduction techniques. The overall product was found to have a high degree of virus safety due to these steps. Lastly, the process was highly cost effective since it was produced from the waste fraction of the commercial production of Factor IX, a protease required in the treatment of Christmas disease. Through the technique presented by Aizawa et al., mass production of thrombin can increase the overall supply of fibrin glues and decrease their cost to make fibrin a more viable replacement to sutures.

In terms of efficacy, fibrin glues have been found to have a wide range of effective bond strengths, preparation times, cost effectiveness, and safety levels. As it stands, the safest fibrin glues are autologous fibrin adhesives, those derived
from a patient's own blood, since the patient is not at risk of any foreign infectious contaminants (Siedentop et al., 2001). The primary drawbacks for those autologous fibrin adhesives are that they require time for preparation, facilities capable of producing the sealant, and also have significantly lower bonding power than homologous fibrin adhesives (See Figure 7). The preparation time required for the production of autologous fibrin adhesives is not necessarily a detriment to penetrating keratoplasty procedures, since the procedure is not generally performed as an emergency. However, the decreased bonding strength could lead to wound dehiscence.

![Figure 7. Bonding Power of Fibrin Glues on Pig Skin.](image)

Autologous fibrin tissue adhesives (AFTA) A, C, and E display significantly lower bonding power, in grams, than ViGuard and Tisseel, homologous fibrin tissue adhesives. Taken from (Siedentop et al., 2001)
Availability

Currently, only three topical fibrin sealants are approved by the FDA ("Fractionated Plasma Products - Fibrin," n.d.). Tisseel (Baxter Healthcare Corp) was the first fibrin glue approved by the FDA in 1998. It is now joined by ARTISS (Baxter Healthcare Corp) and Evicel (OMRIS Biopharmaceuticals Ltd). In terms of the indications of use, fibrin sealants are currently only approved for use on skin graft and facial flap attachment procedures. Tisseel, Evicel, and ARTISS were found to have the high bonding strengths required for surgical use and are generally considered to be safe for use in humans. Tisseel comes in a syringe fully mixed (fibrinogen and thrombin), needs to be frozen for storage, and requires only five minutes or so for thawing (Spotnitz, 2014). Evicel also comes mixed in a syringe, can be preemptively thawed, and stored by means of refrigeration for up to a month. Given that keratoplasty procedures are not performed in emergency settings, the thawing and frozen storage aspects should not act as detriments to its use. These sealants are available for purchase at a cost of about $50 per milliliter (Spotnitz, 2012).

Experimental Ophthalmic Surgeries Using Fibrin

Although the true tensile strength of fibrin glues has been difficult to quantify, fibrin glues have seen use in experimental keratoplasty procedures that has allowed comparison of their effectiveness to 10-0 nylon sutures. The first attempted introduction of fibrin glue to corneal transplants was performed by Katzin et al. in 1946 when penetrating keratoplasty procedures were performed
on rabbits with the help of fibrin adhesives (Katzin, 1946). The penetrating keratoplasty procedures were performed without sutures and with fibrinogen and applied thrombin as acting sealants. The grafts were retained with an 86% success rate. However, Katzin reported that the risk of wound dehiscence was too great to attempt the procedure on humans. Following this study, a multitude of other studies arose to better approach fibrin as an alternative and potential replacement for sutures in keratoplasty procedures. In 1975, Rosenthal et al. used a fibrinogen and thrombin mixture as a corneal adhesive in a sutureless lamellar keratoplasty in rabbits. They demonstrated a 50% sutureless graft retention rate (Rosenthal, Harbury, Egbert, & Rubenstein, 1975). In 1978, Rosenthal et al. repeated the experimental use of fibrinogen and thrombin as replacements for sutures but for penetrating keratoplasty instead of lamellar (Rosenthal et al., 1978). For this experiment, a 75% graft retention rate was achieved. The authors noted that the material was easy to apply and did not cause inflammation or lid irritation.

Since then, both surgical technique and fibrin glue preparation methods have progressed in quality. In 2007, Narendran et al. performed a novel DALK procedure on a 21 year old patient with keratitis (Narendran et al., 2007). Rather than using the standard radial sutures, they used Tisseel fibrin glue and overlay sutures to secure the donor tissue onto the host bed (See Figure 8). The glue was applied at the base of the donor button as pressure was applied with forceps
until the glue set. They found that this technique was time efficient and reduced suture related complications since the sutures were removed early.

Figure 8. Post-Operative DALK Eye Set with Overlay Sutures and Fibrin Glue. The top image is of the eye a week after surgery and the bottom image is an image from four months after surgery. Taken from Narendran et al., 2007.

Also in 2007, Bahar et al. performed a series of penetrating keratoplasty procedures on human rims containing both cornea and sclera placed upon an artificial anterior chamber (Bahar et al., 2007). Of the twenty rims, 8 underwent
traditional penetrating keratoplasty, 6 underwent a “Top hat” penetrating keratoplasty, and the remainder underwent a “top hat” penetrating keratoplasty with fibrin glue (Tisseel) used on opposing wound edges. The results indicated that a “top hat” keratoplasty performed with the fibrin glue withstood more intraocular pressure before wound leakage and wound bursting occurred, when compared to traditional penetrating keratoplasty and “top hat” keratoplasty with sutures only. The results also indicated that the induced astigmatism in the “top hat” keratoplasty with fibrin group was only 2.5 D when compared to the traditional keratoplasty and the “top hat” keratoplasty, which induced an astigmatism of 3.1D each.

The “top hat”, mentioned in the study above, refers to an alternative wound cutting method that alters the shape of the donor-host interface (Bahar et al., 2008). The “top hat” wound cut is produced by a cylindrical cut followed by a wider, ring shaped cut, forming the shape of a top hat (See Figure 9). The “top hat” configuration has been found to be the most effective configuration, when compared to the traditional, “mushroom”, “Christmas tree”, and “zig-zag” configurations in terms of the intraocular pressure required to cause wound leakage and wound bursting in penetrating keratoplasty post-operative eyes. This wound configuration not only provides mechanical support for prevention of wound leakage, but also increases the surface area on the donor-host interface to maximize the total tensile strength of the glues applied on those surfaces. Use of this wound configuration could increase the efficacy of any potential adhesive
used as a suture replacement through mechanical stabilization and surface area enhancement.

Figure 9. Diagram of Various Wound Configurations for Penetrating Keratoplasty Procedures. Each of the images represent different cuts through the host and donor corneas. A) Traditional penetrating keratoplasty. B) “Top Hat” configuration. C) “Mushroom” configuration. D) “Zig-zag configuration”. E) “Christmas Tree” configuration. Taken from Buzzonetti et al., 2012.

Cyanoacrylate Glues

Properties

Cyanoacrylate glues are a group of industrial, synthetic, glues that are known for their quick exothermic polymerization. The cyanoacrylate glue group
includes ethyl-2-cyanoacrylate, know commonly as super glue, n-butyl
cyanoacrylate, methyl 2-cyanoacrylate, and 2-octyl cyanoacrylate. The structure
of cyanoacrylate glues contains an ethylene group, a cyano group, and a variable
length alkyl group, which determines the name of the glues (see Figure 10).

Figure 10. Model of Cyanoacrylate Molecule. For cyanoacrylate glues,
the $R^2$ group would be a hydrogen and the $R^1$ group corresponds to the variable
alkyl group. Potential $R^1$ variable groups include: a methyl group, an ethyl group,
and an octyl group.

Their use has generally been limited to the skin and external wounds due
to inflammation that they induce (Panda et al., 2009). The inflammatory nature of
these glues is due to their alkyl chains which, when broken down, generate
cyanoacetate and formaldehyde. These products are difficult to metabolize, build
up, and cause the inflammatory effects (García Cerdá et al., 2014). The length of
the alkyl chains also determines the rate at which the glue fixates. The short alkyl
chain glues react and fixate very quickly, and release heat upon reacting. This makes short-chain cyanoacrylate glues, such as methyl 2-cyanoacrylate glue, unsuitable for use on human tissue (Matsumoto et al., 1967). Additionally, short alkyl chain cyanoacrylate glues generate formaldehyde and cyanoacetate faster than longer alkyl chain cyanoacrylate glues. This leads to build up of the inflammatory materials.

The cyanoacrylate glues, when coming into contact with basic fluids and substances, polymerize and form long chains (Hollander & Singer, 1998). In terms of adhesive strength, comparative studies in rat models have shown that N-butyl-2-cyanoacrylate use for wound closure produced similar results to nylon suture use in terms of the healing process of the abdominal walls, but the cyanoacrylate group showed a higher tensile strength in wound closure 14 days into the healing process (Batista et al., 2008). Most studies, however, have suggested that sutures and tacks provide more overall tensile strength than cyanoacrylate adhesives (Ladurner et al., 2011).

**Availability**

Histoacryl Blue (Braun), an N-butyl-2-cyanoacrylate adhesive was the first commercially available. Additional commercially produced medical cyanoacrylate glues include Dermabond (Closure Medical Corporation), an octyl-2-cyanoacrylate, and Indermil (Vygon), an n-butyl-2-cyanoacrylate. If kept refrigerated, cyanoacrylate glues have a shelf life of about one year (Burchardt &
The cost of cyanoacrylate glues is approximated to be about $5 per milliliter.

**Experimental Ophthalmic Surgeries Using Cyanoacrylate Glues**

It has been indicated that, when used in situ, cyanoacrylate glues tend to form an impermeable mass. These masses can form crusting, and in the case of use on the cornea, has been shown to lead to giant papillary conjunctivitis (Carlson & Wilhelmus, 1987). This, in addition to the inflammatory nature of formaldehyde as breakdown product, can lead to significant discomfort if used on a patient’s eyes.

Studies have enabled comparison of cyanoacrylate glues to fibrin glues in a corneal setting. In 2003, Sharma et al. treated 41 patients with 3 mm corneal perforations. One group was treated with fibrin glue and the other with N-butyl-2-cyanoacrylate. The results indicated that both glues successfully sealed the corneal perforation. The results also indicated that the fibrin adhesives provided quicker healing, but took longer to set, requiring a few minutes to set compared to the few seconds required for cyanoacrylate (Sharma et al., 2003).

Additionally, in 2013, another study was performed to evaluate the effectiveness of tissue adhesives on corneal trauma cases. Corneal incisions in 8 rabbits were sealed with either cyanoacrylate or fibrin glues. The results indicated that the fibrin glue polymerized at a slower rate when compared to cyanoacrylate glues, which gave surgeons time to manipulate the wound. Additionally, due to the quick polymerization of the cyanoacrylate glue, surgeons
were limited in their ability to manipulate the wound. The excess glue from cyanoacrylate use was also shown to cause the rabbits irritation (Papadopoulou et al., 2013).

**Polyethylene Glycol Glues**

*Properties*

Polyethylene glycol sealants are formed through a combination of two polyethylene glycol polyethers that are able to cross link with the proteins found in the target tissues (Cosgrove et al., 2007). The polymerization results in a clear hydrogel that breaks down within 8 weeks. The products of breakdown are generally filtered by the kidneys when applied in areas within that time period with sufficient vascular access. The glues are synthetically produced and thus do not have a risk of transferring infectious agents. Additionally, the glue polymerizes in 5 seconds and reaches its maximum mechanical strength in approximately 60 seconds (Garcia-Morales et al., 2014).

The most notable disadvantageous property of polyethylene glycol glues, with respect to the aim of this paper, is that the adhesive can swell up to 4 times the volume of application within 24 hours (Garcia-Morales et al., 2014). If placed on the rim of the donor-cornea interface in penetrating keratoplasty procedures, it is likely that this change in volume will have detrimental effects to the patient’s vision or the healing of the cornea.
**Availability**

Available FDA approved polyethylene glycol sealants include DuraSeal (Covidien), ProGEL (NeoMend, Inc), and CoSeal (Baxter Healthcare Corporation). Approved indications for use include dura matter surgery, sealing lung tissue to prevent air leaks, and sealing blood vessels and arteries (Health, n.d.-a; Health, n.d.-b; Health, n.d.-c). The sealants can be stored at room temperature, but require about 1 to 2 minutes to mix the preparation, after which it must be used within two hours (Cosgrove et al., 2007). The cost of polyethylene glycol glues is approximated to be $56 per milliliter (Pocius, 2002).

**Experimental Ophthalmic Surgeries Using Polyethylene Glycol Glues**

In 2003, Kalayci et al. attempted to seal 1-5 mm incisions on the cornea of rabbit eyes through the use of polyethylene glycol sealants. The experimental group was compared to the use of 10-0 nylon sutures. For all incision sizes, the results indicated that the intraocular pressure required to cause wound leakage was significantly higher in the group sealed by the polyethylene glycol glue (Kalayci et al., 2003).

Comparison of polyethylene glue efficacy in comparison to fibrin glues and sutures was made possible in 2013. Cho et al. conducted a study comparing the changes caused by sutures, fibrin glues, and polyethylene glues to the keratometry of rabbit eyes after lamellar keratoplasty. The rabbit grafts were set with eight sutures alone in one group, fibrin glue and four sutures in another, and polyethylene glue and four sutures in the last. The fibrin glue group showed no
hint of histological toxicity or inflammation. Polyethylene glycol showed moderate inflammation in the groups and limited wound repair when compared to sutures and fibrin glue. The authors concluded, based upon the results, that fibrin was a sufficient replacement for sutures in lamellar keratoplasty grafts, and that polyethylene glycol glues were not sufficient (Cho et al., 2013).

**Poly [Glycerol-Sebacate-Acrylate] Glue**

*Properties*

Poly [Glycerol-Sebacate-Acrylate] (PGSA) is composed of 2 naturally occurring monomers and one synthetic monomer. Glycerol exists in the body as a substrate in reactions leading to the synthesis of lipids. Sebacate exists in the body as an intermediate of fatty acid reactions.

The glue itself was developed in 2014 by Lang et al. for the purpose of repairing blood vessels and heart defects. The glue exists as a combination of a PGSA prepolymer and a light-reactive initiator. When exposed to ultra violet light, via a curing pen light, the adhesive forms cross-links and begins to set (Lang et al., 2014). The adhesive reaches its maximal tensile strength after 5 seconds of exposure to a .38 W/cm² intensity ultra violet light. This controlled setting time could provide a significant advantage when compared to other adhesives if used in corneal transplant procedures. In giving the surgeon the choice of when to activate and set the adhesive, ample time would be provided to adjust the positioning of the donor button and to remove excess glue.
The bonding strength of PGSA light-activated glue, when used on epicardial tissue, is about three times stronger than fibrin glue and about half as strong as cyanoacrylate glues (See Figure 11). Since the experiments presented earlier by Bahar et al. indicated that fibrin glue can function well as an adjunct to sutures in penetrating keratoplasty through the use of a “top hat” wound cut, PGSA light-activated glue could provide similar, if not better, results considering its higher bonding strength.

In terms of biocompatibility and inflammation, the glue exhibited similar inflammatory reaction patterns to fibrin glue and better biocompatibility than cyanoacrylate glues. The synthetic nature of the glue also removes the risk of transfer of infectious factors. The breakdown products of the glue, sebacic acid, glycerol, and the photoinitiator components exhibited biodegradable properties. The glue also had significant adhesive properties even when exposed to blood when compared to cyanoacrylate due to its hydrophobic qualities (Lang et al., 2014).
Figure 11. Magnitude of Adhesion of Various Adhesives to Epicardial Tissue. Cyanoacrylate glue (CA), fibrin glues, and PGSA hydrophobic light-activated adhesive (HLAA) are compared in terms of their adhesive strength through a pull-off test. The various time increments shown are the ultra violet light exposure times required to activate the PGSA glue. PGSA HLAA reaches its maximal adhesion after about 5 seconds of exposure to ultra violet light. Taken from (Lang et al., 2014).
**Availability**

The PGSA light activated glue was developed within the past year and, thus, robust logistics data for cost of production and storage are not readily available.

**Experimental Ophthalmic Surgeries Using PGSA Glue**

There have yet to be trials or experiments using PGSA glue in ophthalmic surgeries given its recent development. Given the unique physiology of the eye and cornea, tensile strength comparisons in a corneal setting would be necessary in determining its potential efficacy as an adjunct or replacement to sutures in penetrating keratoplasty procedures. Additionally, since studies have previously shown that ultra violet light can be associated with keratopathies, keratitis, pterygium, and other eye-related malignancies, it would be beneficial to have data on whether the particular ultra violet light wavelengths and intensities for PGSA glue fixation are harmful to humans in the 5 seconds time intervals required for curing (Yam & Kwok, 2014).
DISCUSSION

The first property to consider in this search for an alternative to sutures for penetrating keratoplasty procedures is whether or not these alternatives can successfully bind the donor button in place and promote healing without significant risk of wound dehiscence. If the alternative cannot meet these criteria, even when used as an adjunct to sutures as opposed to being used as a replacement to sutures, then there would be no room to consider it as an alternative. According to the results presented by Cho et al., polyethylene glycol glues, when applied as an adjunct to sutures in lamellar keratoplasty procedures in rabbits, lead to significant amounts of wound dehiscence. Lamellar keratoplasty procedures provide more surface area for glue adhesion at the donor button and host tissue interface. Consequently, although the results applied only to lamellar keratoplasty procedures, the results hint that polyethylene glycol’s potential as an alternative to suture use in penetrating keratoplasty procedures may be limited. The authors proposed that the glue’s inherent change in volume within the first 24 hours after application was the true culprit for the unsatisfactory performance. They proposed that this factor lead to decreased epithelial healing and, thus, the dehiscence. It is for the reasons stated above, in conjunction with its high relative cost per milliliter, that polyethylene glycol glues will not be considered any further as either replacements or adjuncts to sutures in penetrating keratoplasty procedures.
To continue on the assessment of each glue’s adhesive potential, through the experiments run by Bahar et al., it has been illustrated that fibrin glue can function well as an adjunct to suture use in “top hat” penetrating keratoplasty procedures. Its use resulted in fewer sutures being needed for a penetrating keratoplasty with 2.5 D of induced astigmatism when compared to the 3.1 D induced by the traditional keratoplasty and the “top hat” penetrating keratoplasty with no adhesive use (Bahar et al., 2008). The “top hat” wound configuration acted to increase the surface area for adhesion to occur as well as act as a mechanical support, making wound leakage and bursting occur at higher intraocular pressures than those necessary to occur after a standard keratoplasty. In the study, the investigators only used the fibrin glue Tisseel, a homologous fibrin glue, which have been shown to have stronger bonding strength than autologous glues. Overall, the study indicates a strong potential for biocompatible adhesives as adjuncts and perhaps eventual replacements to sutures in penetrating keratoplasty. However, further testing would be essential to determine if any adhesives currently available have the capacity to replace sutures entirely.

Given that both cyanoacrylate and PGSA glue have displayed higher adhesive strength per square centimeter than fibrin glue in certain tissues, it is likely that cyanoacrylate and PGSA glue can provide equal or greater tensile strength if also tested under various wound configurations (Lang et al., 2014). Consequently, when considering tensile strength alone, PGSA, cyanoacrylate,
and fibrin glues are very likely to see success, at the very least, as adjuncts to suture use, if not as replacements.

One of the criteria mentioned earlier for the ideal replacement for sutures in penetrating keratoplasty procedures was that the alternatives did not opacify or occlude vision in any way. According to the published studies considered above, none of the adhesives still in consideration, which includes fibrin, PGSA, and cyanoacrylate glues, were reported to cause any sort of opacification or obstruction of vision.

The next criteria to consider is that of the ease of use of each alternative in a surgical setting. If the alternatives are able to provide sufficient tensile strength to, at the very minimum, reduce the amount of sutures required for the procedure, they will be able to decrease operative time significantly. As stated earlier, the amount of time and skill required to place all 16 of the sutures required in a traditional keratoplasty can be very daunting, requiring an average of about four minutes per suture for novice surgeons. All of the glues, barring polyethylene glycol glues, should be able to provide the tensile strength required to reduce the amount of sutures necessary which indicates that all of the glues remaining have the capacity to reduce operative time.

For ease of use, in addition to reduction of operative time, it is very important to consider the time each glue takes to set. The time a glue takes to set determines the time a surgeon has to adjust the donor cornea button with respect to the host’s tissue. This time is also useful for removal of excess glue.
For the fibrin glues, this variable can be controlled by the thrombin enzyme concentration, which determine the reaction rate, and, for the cyanoacrylate glues, this can be somewhat controlled by which alkyl group the cyanoacrylate glue contains. Both of these glues begin to set somewhat quickly though, and once placed on the tissues, the control out of the surgeon’s hands. There is an alternative solution for fibrin glues however. Fibrin glues usually come in dual syringes that mix the thrombin and fibrinogen upon ejection of the glue from the syringe, causing the setting process to begin. The alternative solution is to manually mix the two components at a time of convenience. This requires that the fibrinogen be placed first and then thrombin can be applied when the surgeon ready.

The tissue adhesive that seems to best fulfill surgical requirements is the PGSA glue. In having absolute control of when the glue sets, by means of deciding when to begin the curing light exposure, the surgeon can control the exact moments at which the polymer crosslinking occurs and when the glue sets. This enables skilled surgeons to cause the glue to set quickly after the donor button is properly positioned and less experienced surgeons to cause the glue to set as their individual pace requires.

The next criteria to consider is that of side effects and complications associated with the use of the use of each of the adhesive alternatives. Fibrin glues have the unfortunate capacity to transmit infectious factors due to their synthesis from plasma. Although this factor can lead to terrible consequences,
modern anti-viral preparatory methods can reduce the risk of transfer significantly (Aizawa et al., 2008). Aside from the risk of transferring infectious diseases, fibrin glue is safe due to its natural biocompatibility as represented by the published studies discussed above. Cyanoacrylate glues, on the other hand have shown numerous inflammatory and irritating side effects when used on the eyes including side effects such as giant pupillary conjunctivitis, irritation from excess glue, and inflammation from the formaldehyde breakdown products. These side-effects severely limit cyanoacrylate’s viability as an alternative to sutures since its use may lead to more risks than rewards. Lastly, PGSA glue has been reported to have similar biocompatibility profile as fibrin glues and higher biocompatibility than cyanoacrylate glues.

As, discussed above, sutures have been shown to induce histologically identifiably inflammation. Inflamed tissue around sutures can lead to loose sutures, which can lead to premature suture removal, wound dehiscence, and perhaps even graft rejection. In having a high biocompatibility, low immune and inflammatory responses, and reducing the amount of required sutures, use of fibrin and PGSA glues could significantly improve overall penetrating keratoplasty outcomes. Overall, fibrin glues are likely to be the best choice when it comes to limiting the inflammatory reactions given the extensive and robust nature of the studies available that highlight these properties. On the other hand, future studies on the use of PGSA glue on the cornea in comparison to fibrin would help in
evaluating their relative biocompatibility in the eye and perhaps reveal significant differences which could help determine the better suture alternative.

Sutures techniques for corneal transplants requires extensive amount of follow-ups and testing, such as corneal topographies, in order to identify and remove the appropriate sutures. From the published studies considered, it has been shown that both fibrin adhesives and PGSA adhesives both breakdown into products that are naturally found in the body. For fibrin glue specifically, this breakdown occurs naturally as the cornea heals and overall breakdown is complete within the early post-operative months. Since this breakdown is handled by the body, there is no need to schedule appointments to address the glue removal. Additionally, in acting as an adjunct to suture use and reducing the amount of sutures required to bind the donor button in place, fibrin glue has been shown to reduce the initial induced astigmatism. This can also reduce the follow up appointments required by reducing the need of selectively removing the sutures in order to reduce the induced astigmatism. The reduction in astigmatism can also prevent or limit the risk of removing sutures prematurely for reducing astigmatism, which has historically shown to increase the risk of graft rejection.

If the adhesives are to act as replacements or adjuncts to suture use, they need to have costs comparable to those of the sutures. Ophthalmic sutures are generally very fine monofilament sutures, such as the 10-0 USP designation nylon suture. A box of 12 of these sutures can cost approximately $300 to $400, equating to about $30 per suture. The price per milliliter of fibrin glue is
approximately $50 and the price per milliliter of cyanoacrylate is approximately $5. Given that the milliliter is equivalent to one cubic centimeter and that the average cornea has a diameter of 11.5 mm and a thickness of about .6 mm, about two milliliters of glue should suffice for use in a keratoplasty surgery. The cost of production data is not available for PGSA hydrophobic light activated adhesive. Also, the cost of producing fibrin glue can be reduced even further by adopting the high volume thrombin production techniques described by Aizawa et al. This could bring the overall cost of producing fibrin glue to well below $50 per milliliter. Overall, this indicates that the cost of performing the surgery could be reduced if the adhesives reduce enough of the number of required stitches to cover their cost.

The last criterion to consider is that of preparation and storage of each of the materials. The fibrin glues usually come in dual syringes that allow for instantaneous mixing. Fibrin glues require frozen storage and need to be thawed before a procedure. The thawing takes about five minutes. Cyanoacrylate glues can be stored through simple refrigeration. No information about PGSA glue regarding its storage is available, however the glue does require mixing before application, which can take a few minutes.

Conclusion

Overall, from the studies currently available, completely replacing sutures for the penetrating keratoplasty procedure with adhesives would require a significant amount of additional studies and experiments. At this point in time,
using fibrin glues as an adjunct to suture use in a “top hat” penetrating keratoplasty is the most likely way to effectively achieve a reduction in the sutures required for the procedure. This would reduce the numerous suture based complications, inflammation, wound bursting and dehiscence, operative time, the skill requirements of the procedure, the follow up appointments, and even the overall cost of the procedure.

Polyethylene glycol glues had the unfortunate downside of increasing in volume after polymerization. Cyanoacrylate glues, although inexpensive and highly adhesive, form crusts, cause inflammation, and potentially cause giant pupillary conjunctivitis. Lastly PGSA glue could prove a better fit than fibrin glue as an adjunct or replacement to sutures. PGSA glue displayed higher adhesive strength per square centimeter on pericardial tissue, can be manually cured by ultraviolet light at any point of the surgeon’s choosing, displayed a similar biocompatibility profile to fibrin glues, and is a hydrophobic glue, making it less affected by the aqueous nature of the fluids within the corneal environment. The primary downside to PGSA glue is that it was developed recently and there is still a distinct lack of information regarding production logistics, how it interacts with eye tissue, whether its adhesive strength is different when applied on the cornea as opposed to the heart. Upon further investigation, PGSA glue could prove to be a formidable replacement to suture use in the penetrating keratoplasty procedure.
Future Directions

In order to better understand whether or not adhesives can completely replace sutures for penetrating keratoplasty procedures, studies can be performed to test the adhesion of each glue on corneal tissue. In addition, tests and experiments with the aim of maximizing the surface area of the donor button and host interface by means of variable wound configurations would also be insightful. This testing, in conjunction with the knowledge of the adhesive strength per square centimeter of each glue, would indicate each glue’s maximum potential total tensile strength for each wound configuration. With this knowledge it would be easier to predict if sutures would still be necessary with different wound configurations, and, if they are, how many sutures are still required.

In addition to those tests for tensile strength, further testing on the PGSA glue would be very helpful. Since it was developed recently, and since the preliminary data showed very promising results, it may prove to be a great boon towards the advancement of sutureless penetrating keratoplasty procedures. Points of interest for study would be comparisons of the biocompatibility, tensile strength, and cost of PGSA glue with respect to the same properties of fibrin glue when used on the human cornea. Another point of interest is whether or not the ultraviolet light used to cure the adhesive induces unexpected side effects. These tests should indicate whether PGSA glue is a better candidate as an adjunct or a replacement to sutures than fibrin glue. PGSA glue may reduce the required
amount of sutures in a penetrating keratoplasty procedure by more than fibrin glue, or remove the need for them all together.

The adhesives and technologies currently available enable the possibility to, at the very least, reduce the amount of sutures required for the penetrating keratoplasty procedure. Upon further study, modifications can be implemented to improve the procedure’s effectiveness, have less suture related complications and side-effects, induce less astigmatism, and potentially cost less. This would increase the overall appeal and availability of corneal transplantation and hopefully make it more accessible to who need it most.
REFERENCES

http://doi.org/10.1016/j.thromres.2007.12.027


http://doi.org/10.4103/0301-4738.151468

http://doi.org/10.1136/bmj.308.6934.933

http://doi.org/10.1097/ICO.0b013e31815b7d50

http://doi.org/10.1097/ICO.0b013e318151f8e8

46


http://doi.org/10.1038/srep00879


http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm12787.htm


http://doi.org/10.1007/BF01268097


http://doi.org/10.1097/ICO.0000000000000063


http://doi.org/10.1016/j.clae.2007.02.007


http://link.springer.com.ezproxy.bu.edu/chapter/10.1007/978-3-540-85544-6_1


http://doi.org/10.1007/s10792-013-9791-x
CURRICULUM VITAE

Faisal Al Bahrani
30600 Summit Lane; Pepper Pike, Ohio 44124
Phone: 216-509-3962
fmb10@case.edu; fmb10@bu.edu

Personal Data:
Year of Birth: 1991
Place of Birth: Baghdad, Iraq

Education:
B.S., Systems Biology, Case Western Reserve University, May 2012
M.S, Medical Sciences, Boston University, Expected May 2015

Laboratory Experience:
Research Assistant, Department of Radiology Imaging Research, Case Western Reserve University, University Hospitals Case Medical Center
Under Ann Marie Broome, Ph.D., May 2010 – May 2012

Laboratory Skills:
Tissue Culture
Immunohistochemistry
Fluorescent and bright field Microscopy

Teaching Experience:
Laboratory Teaching Assistant, Department of Biology, Case Western Reserve University
Under Professor Barbara Kumerle, Ph.D. January 2011 – May 2011

Biochemistry Tutor, Department of Graduate Medical Sciences, Boston University
Under Gwynneth Offner, Ph.D. September 2014 – December 2014
Memberships:
Case Western Board Games Club, Founder/President. 2010-2012
Case Western Role-Playing Games Club, Treasurer/Member. 2008-2012

Volunteering Experience:
*Boston Living Center, 2014- present, 15 hours.*
- Prepared and served meals to victims of HIV and AIDS.

*Habitat for Humanity, 2011, 80 hours.*
- Cleaned and transported donated furniture.

*Cleveland Botanical Gardens, 2008, 100 hours.*
- Answered questions about the flora and fauna of the two glasshouse biomes.

Hobbies:
Computer Science and programming.
Science Fiction and Fantasy novels.
Board games.