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KAROLINSKA INSTITUTET, STOCKHOLM, SWEDEN

THE CUT AND PASTE TECHNIQUE
FIBRIN TISSUE ADHESIVE IN PTERYGIUM SURGERY

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Karolinska Institutet

Stockholm 2010

To my family with love

Published by Karolinska Institutet.

ISBN 978-91-7457-080-9

Printed by
REPROPRINT AB
Stockholm 2010
www.reproprint.se
Gårdsvägen 4, 169 70 Solna

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ACKNOWLEDGEMENTS

Many people have supported me in different ways during my work with this thesis, and I thank them all, especially the followings:

My tutor Eva Dafgård Kopp for her guidance, encouragement and support throughout this study.

Stefan Seregard for help with texts, statistics and general advices about what to do and what to avoid.

Ditte Artzén for her good spirit in learning the surgery and her immense work in judging my slides.

Thomas Wijk for his support during the study and the extra effort needed to investigate pterygium patients.

Bo Philipson for introducing me to the world of research and for help at my first AAO meeting.

Mats Örndahl for showing me the fibrin glue.

Björn Holmstedt and Ewa Krantz from Baxter Medical AB for their enthusiastic support with information and CD-records.

Per Montan who had to receive my complaints, doubts and who was always able to encourage me.

Sven Sahlin for allowing me to perform and improve the surgery at the Oculoplastic and Orbital Surgery Service at the St.Eriks Eye Hospital.

Nils O. Rehn for providing the “ancient” manuscript on pterygium surgery of J. G. Pipping.

Maud Leindahl who made and stored my countless slides.

Marielle Harris who organized and sifted through all those slides.

Carl Eric Oskarsson who made videos with unexpected qualities.

Linda Schenck for her excellent proofreading of this book.

Britt-Marie Karlheden and Ulla-Britt Schützler-Peterson who put up with my poor dealing with papers and documents, and always stayed calm and kind.

All nurses and staff in the operating theaters at St. Eriks Eye Hospital especially those at the Oculoplastic and Orbital Surgery Service for their understanding, patience and help during the development of the Cut and Paste method.

My colleagues and friends in Stockholm and Växjö, who listened to my problems, doubts and followed the development of this thesis.

I thank my wife Valeria for helping me through the final phase of this work and for providing a pleasant and peaceful environment at home.

I’m very proud and grateful to have such wonderful children, Jakob and Isa who give me so much cause for joy and thereby contributed to my sense of wellbeing during this work.

Finally, I thank my mother who always loved me, my father who believed in me and encouraged me, my brother Janos my sister Lisa for their support, and especially my sister Sussi who, by her own example, gave me the final push to bring this task to an completion.

ABSTRACT

Introduction. Pterygium has been a problematic disease throughout human history, owing its major tendency to recur after surgical removal. The factors causing primary pterygium and also those causing recurrence have been greatly investigated over the centuries. Many theories have been proposed along with countless surgical procedures aimed at preventing recurrence.
Material and Methods. In the 1990s simple excision and use of Mitomycin C (MMC) or free sutured conjunctival autografts were advocated as the best approach to managing pterygia. We compared these two methods in a randomized fashion at the St. Eriks Eye Hospital (Paper 1). All patients were operated on by a single surgeon (GK) and followed up in a regular, standardized manner. We followed our patients for four years in order to determine the method of choice for the future. Autografting turned out to be the best method and was chosen for use during the following years.
To shorten the surgery time, Tisseel Duo Quick, a fibrin-based tissue adhesive was tried instead of sutures to secure the autograft. We discovered that apart from the time for the procedure, postoperative patient discomfort had also been diminished. Therefore, a randomized controlled study was designed to compare suturing to gluing the conjunctival transplant (Paper 2). During the following years, the number and severity of recurrences also seemed to decrease. A retrospective study with long-term follow up was designed and performed, and we were able to confirm our discovery (Paper 3).
The Cut and Paste method has gained popularity in Sweden and elsewhere, and several ophthalmologists were guided by the inventor (GK). At the St. Eriks Eye Hospital two other ophthalmologists were also trained in the technique. In order to evaluate the learning curve, the rates of recurrence and complications when other ophthalmologists use the Cut and Paste method, the first 120 cases operated on by these surgeons were studied and compared with the results of GK (Paper 4).
Results. Autografting turned out to have the lowest recurrence rate and fewest complications. It was therefore chosen as the preferred procedure (Paper 1). We demonstrated that gluing the transplant was fast, safe and caused significantly less postoperative pain than sutures (Paper 2). In a long-term comparative study, we showed that recurrence rate and complications were lower when the autograft was glued rather than sutured (Paper 3). After other ophthalmologists were trained, there were only slight differences in recurrence rates and complications, and no significant learning curve was seen (Paper 4).
Conclusions. This thesis investigates the development and other aspects of the Cut and Paste method for surgery of primary pterygium. Conjunctival autografting was first shown to be superior to the technique of bare sclera with peroperative use of MMC. Then, the Cut and Paste method was shown to be even better, with less patient discomfort, shorter surgery time, and lower recurrence rate. Furthermore, we found it easy to teach and learn. This approach has also gained popularity and appreciation in Sweden and all over the world.
Hence, we propose Cut and Paste as the method of choice when operating on primary pterygium.

Key words: Pterygium, primary, fibrin glue, tissue adhesive, conjunctival autograft, Mitomycin C, learning curve.

LIST OF PUBLICATIONS

I

Intraoperative mitomycin C versus autologous conjunctival autograft in surgery of primary pterygium with four-year follow-up.
Koranyi G, Artzén D, Seregard S, Kopp ED.
Acta Ophthalmol. 2010 May 28. [Epub ahead of print]

II

Cut and paste: a no suture, small incision approach to pterygium surgery.
Koranyi G, Seregard S, Kopp ED.
Br J Ophthalmol. 2004 Jul;88(7):911-4.

III

The cut-and-paste method for primary pterygium surgery: long-term follow-up.
Koranyi G, Seregard S, Kopp ED.
Acta Ophthalmol Scand. 2005 Jun;83(3):298-301.

IV

Learning curve in the Cut and Paste method for surgery of primary pterygium
Gabor Koranyi MD, Ditte Artzén MD, Tomas Wijk MD.
Submitted.

LIST OF ABBREVIATIONS

AAO	American Academy of Ophthalmology
GK	Gabor Koranyi
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HSV	Herpes Simplex Virus
MMC	Mitomycin C
UV-A	Ultraviolet radiation with wavelength of 400-315 nm
UV-B	Ultraviolet radiation with wavelength of 315-280 nm
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor

AIMS OF THE THESIS

The purpose of this thesis was to present a new surgical technique for managing primary pterygium. Our aim was to find a more effective method than the one previously in use.
We wanted to demonstrate and prove that we found such a technique, the Cut and Paste method, and that it has low recurrence rates, minimal postoperative pain and requires short surgery time.
In addition, it is a procedure which is easy to learn and teach.
Finally, we wanted to show how much it has become appreciated and used all over the world.

INTRODUCTION

Definition and description of pterygium

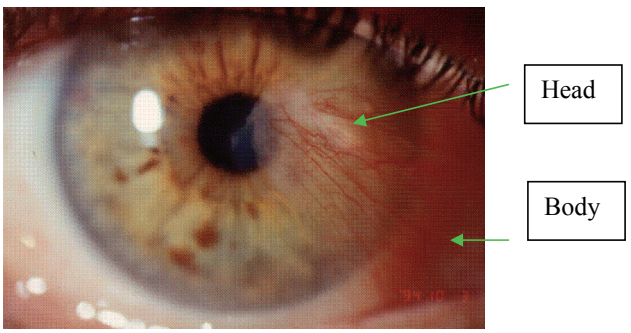
The term pterygium comes from the ancient Greek πτερυξ (pteryx) = wing and πτερυγιον (pterygion) = fin. Pterygium is characterized by a triangular portion of the bulbar conjunctiva encroaching onto the cornea[1], usually within the intrapalpebral fissure and most often from the nasal side.

Pterygium is most common in the so-called "pterygium area", which is defined by a geographical latitude of 40° north and south of the equator[1]. In this area, prevalence of up to 22% has been reported[2,3]. In countries outside of this area reported prevalence rates usually do not exceed 2% of the general population, and the lesion affects mostly patients with an extensive exposure to sunlight[4,5].

Source: the World Wide Web

Pterygium seldom presents before 12 years of age. It evolves slowly over the years, growing from the limbus towards the center of the cornea. Sometimes, in about 1-2% it appears on both the nasal and the temporal sides. Classifications have been created based on size, rate of growth, fleshiness and visual impairment[6]. Typically, both eyes are affected, often with the lesion in the dominant eye preceding that in the other.

Anatomically, pterygia can be subdivided into the head and the body aspects.

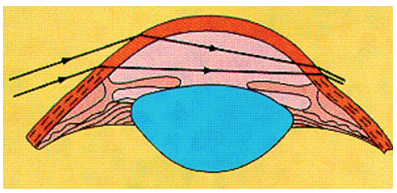


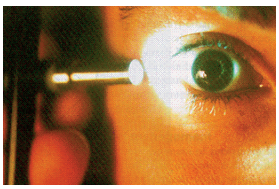
Histopathologically, elastotic degeneration of the conjunctival stroma is considered to be pathognomonic[7], although, excessive fibroproliferative reaction in the stroma has long been recognized[8]. Epithelial changes such as hyperkeratosis, parakerathosis and akanthosis have also been described[9].

Symptoms associated with pterygium development include chronic ocular surface inflammation and tearing, eventually astigmatism and blurred vision attributable to optical axis involvement[1]. The natural history of the condition is variable, prolonged static periods do exist. However, progressive growth characterizes the majority of cases of pterygia, especially those affecting younger individuals, often necessitating surgical removal.
This acquired condition occurs around the world. Its cause and proper treatment have long been uncertain[10] and still surprisingly little is known about this common disorder.

PATHOGENESIS OF PTERYGIUM

There are several theories on the etiology of pterygium. Both internal and external factors have been suggested.
Pterygium has long been believed to be an environmental disease. There is regional variation of pterygium distribution in the world, with higher occurrence closer to the Equator[1] suggesting the impact of UV light. The effects of UV-A and UV-B (280-400 nm) are considered particularly detrimental[11]. Prevalence differences may also be explained by differences in lifestyle[12]. People working and living outdoors have shown be more affected. Multivariate logistic analysis in an Australian population has identified risk factors including hazel-green eye color, red hair, skin burns, time spent outdoors and use of sunglasses[13].
Periorbital architecture, including the presence of eyebrows and nasal prominence imply that the eyes are well protected from direct light exposure from above. On the other hand, the eyes are relatively unprotected from light scattered laterally and from below (the albedoeffect of the snow, water and sand). The possible impact of this scattered UV light, which could cause death of the corneal epithelial stem cells on the nasal limbus, has been shown by Coroneo et al[14,15].





Courtesy of Prof. Minas Coroneo, Chairman of the Department of Ophthalmology, University of NSW, Australia.
The temporally incident light is focused at the nasal limbus where pterygia usually are formed.

It was suggested that the scattered light might follow a transcameral optical pathway, hitting and altering the nasally positioned limbal epithelial stem cells.
Genetically defective or injured limbal stem cells with altered matrix metalloproteinases have shown to play an important role in the etiology of pterygium[16,17].
Focal limbal failure is a key feature. Conjunctivalisation of the cornea occurs, with tissue characterized by extensive chronic-inflammation, cellular proliferation, connective tissue remodeling, and angiogenesis. This theory has gained popularity in recent years.
Viral etiology from HSV and HPV has been suggested by some authors[18]. Other studies have found abnormal p53 tumour suppressor gene expression in pterygium, suggesting a possible relation[19] owing to oxidative stress. Hereditary factors have also been considered[2,20] and shown[21]. However, it was not possible to verify whether the pterygium itself is inherited as an independent trait or if the affected individuals shared increased susceptibility to the oculodermal effects of sunlight. To date, no specific genetic locus has been associated with pterygium development.

SURGICAL INTERVENTION

Pterygium surgery may lead to further clinical manifestations, including conjunctival scars affecting ocular motility, corneal clouding, delayed epithelial healing. Postoperative recurrence rates could have been up to 50% of the cases. The basic goals of good pterygium surgery are to cleanly remove pterygium tissue from the ocular surface and to prevent recurrence. Today, satisfactory cosmetic results are also a concern[22].

Pterygium and its treatment have been described since ancient India by Susruta in approximately 1000 BC: "… the pterygium is loosened … with the patient looking laterally. A sharp hook is used to secure the growth … the pterygium is gotten rid of by scratching it with a sharp, round topped instrument …". "The condition disturbs both the patient, because of its appearance, and the surgeon because of the tendency to recur in a matter of weeks or months". In order to avoid recurrence, pterygia have been "incised, removed, split, transplanted, excised, cauterized, grafted, inverted, galvanized, heated, dissected, rotated, coagulated, repositioned and irradiated"[23].

Pterygium was also mentioned by Hippocrates around 400 B.C.[24] He treated it with eye drops made of lead, zinc, copper, iron, bile juices, urine and maternal milk. Celsus (25 BC) and Galenus (129 AD) also advocated complex topical solutions. Avicenna (1000 AD) proposed cutting the pterygium with scissors[23].

Historically, there has been a common understanding that surgery is the only way to cure the disease. Medical treatments, chemical cauterization and laser therapies have all been used and abandoned. However, recently anti-VEGF therapy[25] has been tried with some success. Many different methods of pterygium surgery have been advocated and used, some with unpredictable and poor results, due to the propensity to recur[23].

Proper reconstructive surgery began in the nineteenth century with Scarpa, Arlt (use of conjunctival graft), Desmarres and Knapp. Elschnig (1926) performed advanced conjunctival plastic surgery. β-irradiation[26] began to be used in the 1950s and the use of MMC as adjunct therapy[27] began in Japan in the 1960s. Amniotic membrane to substitute the conjunctiva[28] was used as early as in 1946 but the idea was developed and popularized by Tseng[29] in the 1990s. Pterygium surgery today still varies from the simplest procedure of bare sclera excision to complex surgery such as sclerokeratoplasty[30] and amniotic membrane transplantation with or without tissue adhesive[31].

Simple excision and suturing of the conjunctiva to the sclera (bare sclera technique) gives a high percentage of recurrences[32,33]. The rationale for the bare sclera technique was that the area left uncovered would be epithelialized by epithelial cells from the anchored conjunctival rim, which could then act as a barrier against pterygium regrowth. However, up to 50% recurrence rates have been reported[32] with this technique. Therefore, adjunct therapies such as beta-irradiation[34] and chemotherapeutics such as MMC[35] have been tried. Unfortunately, there were not only low recurrence rates but also reports of serious side effects[36,37]. These adjunctive medical therapies are still in use: β-irradiation[38] with Strontium 90, topical Thiotepa[39] and topical MMC[40] in spite of the documented risk of adverse effects such as delayed healing, keratitis, scleral and corneal melting, and endophthalmitis[41].

Understanding the important role of normal conjunctiva in blocking recurrence was the basis for surgical modifications of the initial technique. These include different conjunctival flaps attached to the pterygium bed[42].

Kenyon et al. published the use of a free conjunctival autograft in 1985[43]. This was shown to result in great improvements[44]. The method was first discouraged for use in primary pterygia because it was time consuming and difficult to master, but it has slowly emerged to be the golden standard thanks to the good results and the fear of the serious complications with the other procedures.

In cases with large conjunctival defects created following pterygium excision, preserved human amniotic membrane can be used, as was first suggested by Tseng and coworkers[29].
The first known Swedish paper on pterygium surgery was written by Prof. J G Pipping in 1799, where two patients and bare sclera surgery were described[45]. Since then, the surgery technique in Sweden seems to have followed the practice elsewhere in the world. At the St. Eriks Eye Hospital in the early 1990s suturing of sliding conjunctival flaps was the common procedure for primary pterygium[46], with moderately high recurrence rates, in line with other reports in the literature[47]. Conjunctival autografts were used mainly for recurrent pterygia as recommended by Kenyon et al[48]. After having tried the bare sclera with intraoperative MMC and sutured autoconjunctival transplants, the Cut and Paste technique was introduced in 1999 (Paper 2).

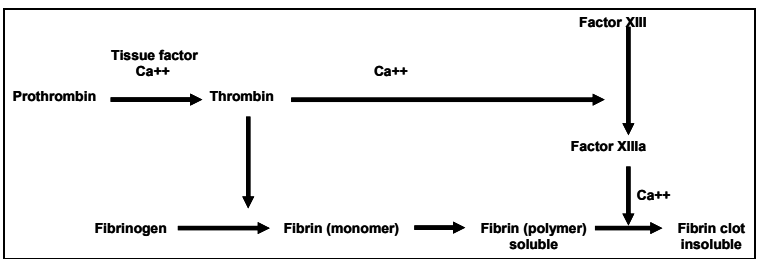
MATERIALS AND METHODS

Patients
During the study period almost all pterygium patients in Stockholm were operated on at the St. Eriks Eye Hospital; thus a cross-section of the entire population living there. Since the area has many immigrants, only about 50% of our patients were from Northern Europe. 18% were from the Middle East 18% Northern Africa of Latin origin and the rest from the Far East. The gender distribution was even. The mean age was 48.5 years (range 18-97). Dropouts were less than 10%, and follow up times were between 6 months and 4 years.

Mitomycin C
The mitomycins are a family of natural products isolated from Streptomyces species. One of these, mitomycin C, from streptomyces caesiptosus is an antibiotic, capable of alkylating the DNA double helix and blocking both transcription and translation[49]. Thus, MMC is also a potent inhibitor of cancer cells. MMC has been given intravenously as well as topically. Given systemically it causes bone marrow damage, lung fibrosis and renal damage. Topical use for mucosal cancer as bladder instillation has been widespread. Its use and side effects in eye surgery, particularly pterygium surgery were described[50] as early as in the 1960s and many times since. Both trabeculectomy and pterygium surgery gained great benefits from its use, however delayed epithelialisation, corneal and scleral melting, fungal keratitis and even endophthalmitis have also been reported[51,52]. In pterygium surgery, MMC is often used intraoperatively in concentrations of 0.2-0.4 mg/ml episclerally or subconjunctivally for 2-3 minutes. Therapy as postoperative eye drops has also been tried[35].
In our study (Paper 1) we used 0.4mg/ml MMC preoperatively for 3 minutes on the scleral bed.

Sutures
In our studies 7/0 Vicryl Rapide sutures were used to secure the free conjunctival graft in order to achieve quick resolution of the suture. The suture characteristics provided rapid strength loss and softening/dissolving of the suture material. Thus, there was no need for suture removal. All this meant less discomfort for the patient.

Tisseel Duo Quick
Since ancient times, people have dreamt of gluing together parts of the body. There are tales from the classical Greeks about using resin to improve wound healing. In 1905, Morawitz showed that calcium ions transformed pro-thrombin to thrombin in the blood, which turned fibrinogen to fibrin[53].



During the 1940s, blood plasma was used in animal studies to glue peripheral nerve fibers, and human skin transplantation was also tried. The strength of the glue was unsatisfactory until the 1970s, when Matras published the results of his studies with different fibrin preparations[54] which led to registration of Tisseel, a fibrin adhesive.

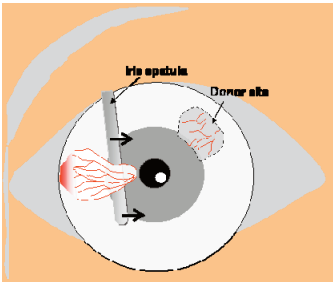
Tisseel consists of 2 components:

a) mixture of fibrinogen, fibronectin, factor XIII, plasminogen and aprotinin
b) thrombin with calcium chloride solution.

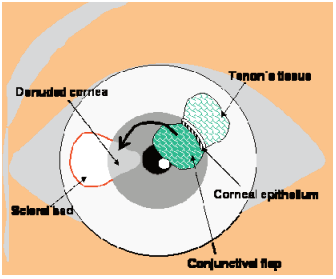
Mixing a) and b) initiates a coagulation cascade and a relatively strong tissue adhesive is formed. The reaction time can be controlled by varying the concentration of the thrombin (4 IU/ml or 500 IU/ml). The strength of the fibrin sealant reaches 70% at 3-5 minutes and 100% in 2 hours. Degradation takes about two weeks according to the manufacturer, but in our clinical ophthalmologic practice we have seen it disappear within a few days. Tisseel is mainly manufactured from human plasma checked for various antigens such as HIV, Hepatitis A, B and C. Aprotinin, however, is of bovine origin and could cause allergic/anaphylactic reactions when used repeatedly in heart surgery, mastectomy and nasal mucosa haemostasis[55,56,57,58] which has been a concern, although this adverse reaction has never been observed or described in eye surgery.

THE CUT AND PASTE TECHNIQUE

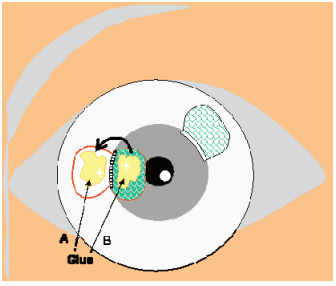
The use of fibrin sealant in eye surgery was first described in 1978 for corneal surgery[59] and for conjunctiva in 1984 by Buschman et al[60]. By 1999, about 50 more papers regarding fibrin glue had been published, but only one on pterygium surgery[61].
In 2000 we presented our first Cut and Paste study[62] and since then more than 100 manuscripts containing use of fibrin sealant in the human eye have been published, mostly on conjunctival and pterygium surgery.
The surgery is mainly done under local anesthesia. In the beginning, subconjunctival or subtenonal injections were used. This evolved to only topical oxybuprocain 0.4% (Chauvin Pharmaceuticals Ltd. London, UK) and tetracain 1% (Chauvin Pharmaceuticals Ltd. London, UK) eye drops. Today, we use lidocain 2% gel (Xylocain, Astra Zeneca AB, Södertälje, Sweden). A tunnel is created between the sclera and the pterygium neck at the limbus, using scissors. Blunt avulsion of the pterygium head follows. This can be done for example with an iris spatula. The exposed cornea is scraped clean with a crescent formed knife to achieve a smooth and even surface. Gentle diathermy of the bleeding vessels follows. Then the free limbal conjunctival graft is prepared as free from Tenon's tissue as possible. Subconjunctival injection of saline can be helpful. The size of the graft should be somewhat larger than the uncovered sclera. Before cutting off the limbus, the conjunctival flap lies with its epithelial side on the cornea. It is then separated from the limbus and is slid nasally to a position opposing the scleral site. One drop of each of the two components of the fibrin glue is placed onto the sclera and onto the graft respectively. The graft is then flipped over, smoothed out and pressed onto the scleral bed for 20-30 seconds.



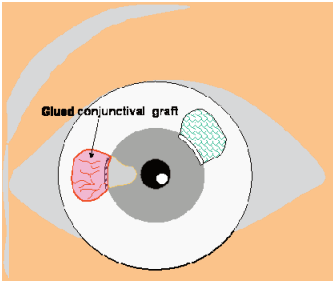
The head of the pterygium is separated from the cornea by blunt dissection



The body of the pterygium is excised. A conjunctival flap is created superiorly



The 2 components of the fibrin glue are placed onto the backside of the free flap and the bare sclera



The free graft is flipped over and glued onto the sclera

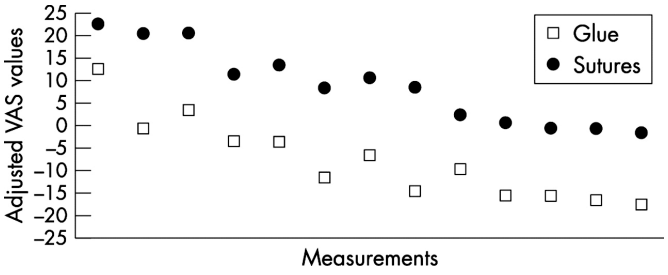
Postoperatively rimexolone eye drops (Vexol, Alcon Laboratories, Hempstead, UK) 6 times daily and fucidic acid ointment (Fucithalmic, Leo Pharma, Malmö, Sweden) 2 times daily are given for the first week, thereafter the fucidic acid is discontinued and the rimexolone tapered weekly for 5 additional weeks.

GUIDANCE

During the years a large number of ophthalmologists have been trained in this method in Sweden (at 13 eye clinics) and abroad (Bergen, Norway; Budapest, Hungary; Mumbai, India) according to the following program:
5-6 patients with nasal primary pterygium were gathered. The first patient of the day was operated on by GK assisted by the trainee instead of a scrub nurse. The next patient was operated on by the trainee with assistance of GK. Then we discussed the difficulties and GK did the next surgery, again showing the details of the technique. The remaining patients were operated on by the trainee. Surgeons at the St. Erik's Eye Hospital could, if necessary, ask for assistance during the following days but others were left to develop their surgery on their own. One example of the result of this teaching is a paper published 2007 in Hungary[63], where the recurrence rate was 5.9%, another is the paper of Ayala from Örebro in 2008[64] with a recurrence rate of 4.5%.

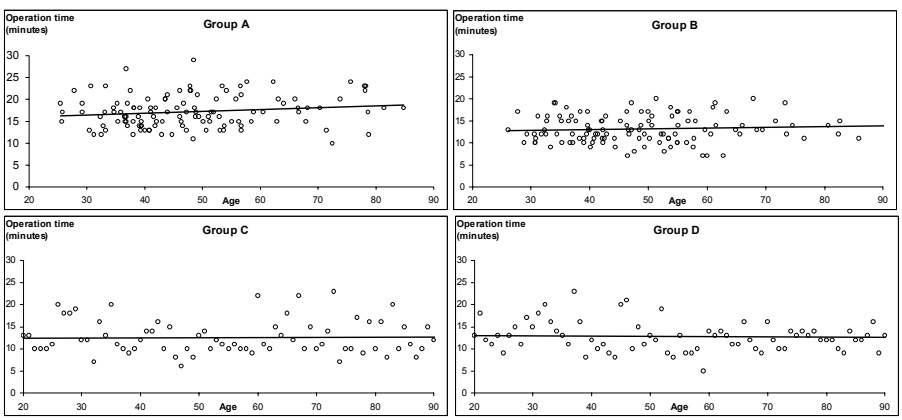
RESULTS

The recurrence rates with bare sclera excision and MMC was 38% compared to 15% that with conjunctival autografting with sutures ($p<0.05$). The reoperation rates were 53% and 29% respectively. Average surgery time was 13 minutes and 28 minutes. There were no significant changes in visual acuity or in astigmatism. The results showed that apart from the time of the procedure, conjunctival autografting was superior to surgery with bare sclera and intraoperative use of MMC.
Operating with fibrin glue instead of sutures lowered the average pain measured with VAS significantly ($p<0.05$). That was true both for the initial pain on the operating day and every day during the first postoperative week.



Postoperative pain measured twice daily by VAS, adjusted to preoperative pain threshold.

Average time for the surgery was significantly shorter, 9.7 minutes and 18.5 minutes respectively ($p<0.001$).
Recurrence rates were 5.3% and 13.5% ($p<0.01$) and reoperation rates were 1.2% and 3.3% ($p<0.05$) respectively in the long-term study. Complications occurred equally in both groups.
When training other ophthalmologists (A and B) at St. Eriks Eye Hospital mean surgery time was 17 minutes and 13 minutes respectively compared to 13 minutes for GK. There was a slight learning curve slope for surgeon A but not for surgeon B.



Temporal distribution of operation times for surgeon A, B and GK (C beginner, D experienced).

Recurrence rates were 8.9% and 6.8% respectively, not significantly different from that of GK (5%). The temporal distribution of recurrences did not show any learning curve.

THE CUT AND PASTE METHOD IN SWEDEN AND INTERNATIONALLY

A questionnaire was sent to all 42 ophthalmology clinics in Sweden.
The questions were:
1. Which method do you use when performing primary pterygium surgery?
2. What is your recurrence rate?
3. Are you satisfied with your results?
4. If applicable, when did you start using the "Cut and Paste" technique and how did you learn it?
5. If applicable, how did the change of method alter the indications for surgery?

The Medline database was also searched for pterygium surgery using autologous conjunctival transplantation with fibrin adhesive.

Results
34 (81%) answers to the questionnaire were obtained. Of these 34 Swedish ophthalmology clinics, 7 did not performed pterygium surgery at all. Twenty-two (81%) of the remaining 27 used the Cut and Paste method and all of them were satisfied with the results. Thirteen of these 27 had been trained personally by GK. Some started using the technique in 2001, some as late as in 2010. Ten of the 22 (45%) using the Cut and Paste method answered that the change of method had resulted in wider indications and earlier surgery.
Five (19%) clinics applied different techniques: bare sclera, MacReynolds, bare sclera with MMC and suturing of the conjunctiva and two used only suturing. 4 of these clinics were satisfied with their results.
None of the clinics had reliable statistics of the recurrence rates, 16 did not know at all, 7 reported <1% assumed recurrence rate and the rest approximately 5%.

Medline search with the words "pterygium, conjunctival, fibrin" resulted in 35 hits. Our papers were referenced in 17 of these articles. After excluding the review articles and our papers 14 relevant original articles were found. All reported less postoperative discomfort and fewer complications with fibrin glue than with sutures. The average number of patients was 34 (total 474, range 9-92) and the average recurrence rate was 3.1% (range 0%-9%). The authors were working in different countries including India, Singapore, New Zeeland, Australia, Brazil, UK, USA, Canada, Korea, China and others, which indicates widespread use of the method.

DISCUSSION

We found that pterygium excision with sutured conjunctival autograft results in a statistically significant lower recurrence rate than the bare sclera method combined with intraoperatively 0.04% MMC. There is a considerable variation of the recurrence rates in the literature[65]. We think that relatively small sample sizes are an important factor causing differences in the reports. Our results are in line with other reports on this method[66,65]. Kenyon emphasized the method of using free autologous conjunctival grafts in pterygium surgery early[48]. This technique is considered safe, but surgically more demanding and time-consuming. In our study the average surgery time in this group was 26 min, twice as long as the average surgery time in the MMC group. The greatest advantage of our first study is its long follow-up period of 4 years. All recurrences after pterygium surgery appeared within a year which is consistent with earlier findings: Hirst and co-workers showed that there is a 50% chance for a recurrence after pterygium surgery to occur within 4 months and a 97% chance within 1 year[67]. In another article on recurrence time[68] it is shown that 1-year follow-up is optimal, which also coincides with our results.

The cut and paste method was the first surgical method developed to address patient discomfort, especially postoperative pain and surgical time. In addition, postoperative patching, healing time and restrictions in normal life after surgery were of concern. Evaluating pain is not easy because patients report different sensitivity for the same stimulus. In addition, they have different capacity to withstand the pain. Furthermore, they have different ability to report their experience.

Prospective series in the literature report recurrence rates of 2–39% after pterygium surgery using sutured conjunctival autografts[69,32] . Wide excision of the nasal Tenon's tissue, better quality of the graft or different suture techniques might possibly explain the low numbers of recurrences in some other studies. The recurrence rates in our hands when using sutures (13.8%) is in accordance with these results. We expected the long-term recurrence rate for glued grafts to be similar to that of sutured grafts, but it turned out to be only 5.4%.

There is always some reparative inflammation following surgery. Since the glue components form pure human fibrin, it does not give rise to additional inflammation. In contrast to glue, the presence of sutures causes significantly more postoperative pain[70]. This may be caused by an up-regulated inflammatory process around the sutures during degradation[71]. Both silk and nylon sutures placed in the conjunctiva can cause inflammation, and migration of Langerhans' cells to the cornea[72]. More severe inflammation may cause higher recurrence rates[73].

Conjunctival autografting has been considered to be difficult and time consuming and was first advocated only for recurrent pterygia[48,74,75]. Despite of this, pterygium surgery is often seen as a trivial procedure and delegated to less experienced surgeons[32,47,73,76].

The authors propose a learning curve effect, change of surgery technique, better education and supervising. We could not find any reference on learning curve analysis in pterygium surgery, thus, our paper could be the first attempt. We do not see pterygium surgery as a trivial procedure and residents do not perform this surgery. Instead, ophthalmologists are educated in this task. We think that the differences in average operation time rather mirror the personal character of a surgeon than the difficulty of the surgical method.

Our impression has been that performing more pterygium procedures the same day promoted the skills and confidence of both surgeons and nurses and shortened the surgery time.

Adequate follow up, small number of drop out cases and the fact that all surgeries were done in a similar fashion are strength of our study. We have also analysed a large number of pterygium surgeries for each surgeon, more than in earlier studies on learning effects in eye surgery[42,73,76].

CONCLUSIONS

Pterygium surgery with sutured free autologous conjunctival grafting was associated with fewer recurrences, fewer reoperations and fewer complications than the bare sclera technique together with a single intraoperative dose of MMC.
The Cut and Paste technique in pterygium surgery resulted in significantly less postoperative pain and shorter surgery times than using sutures. Furthermore, this surgery resulted in a significantly lower recurrence rate and fewer complications.
Our study also indicates that the Cut and Paste technique is easy to learn and master.
We suggest that Cut and Paste surgery should be considered as the first method of choice for primary pterygia. The surgery should be performed by “large volume surgeons” and concentrated to sessions of 5-10 procedures.

SHORT PRESENTATION OF THE ORIGINAL PAPERS

Paper 1.
At St. Eriks Eye Hospital it was decided in 1993 that all pterygia should be operated on by a single surgeon (GK). In order to improve the recurrence rates, literature research was done. This revealed that bare sclera surgery with postoperative MMC eye drops had low recurrence rates, but owing to the fear of the side effects also intraoperative use of MMC was taken into consideration. Transplantation of conjunctival autograft was considered the best methods in the literature but difficult surgery and prolonged surgery time were concerns.
Therefore, a study was planned to compare the results of intraoperative MMC with the results of the conjunctival autograft technique in a prospective, randomized trial with very long-term follow up. Conjunctival autotransplantation appeared to be significantly more effective in terms of recurrence rates than bare sclera with a single intraoperative dose of MMC. With the modified technique developed by Shaw, the surgery times of autografting was only about 25 minutes. The recurrences after MMC were more aggressive and demanded additional surgery at higher rates. Complications also appeared to be more frequent in the latter group.
Therefore, we decided to use the conjunctival autograft when operating all cases of pterygia as the preferred technique. In addition, since not any late onset recurrences appeared, we suggested that 12 months of follow up would be satisfactory for future studies of pterygium surgery.
During the following years, almost all cases of pterygia in Stockholm were directed to our hospital owing to our good postoperative results. A vast amount of experience in this type of surgery was thus developed.

Paper 2.
In 1999 our researchers were searching for modulators when performing phototherapeutic keratectomy in order to correct irregular corneas. One of the investigated substances was a fibrin adhesive, Tisseel Duo Quick. Since the author of the present thesis (GK) was involved, the thought of attaching the conjunctival autograft in pterygium surgery with this glue instead of sutures arose. The goal was to shorten the surgery time.
The idea was tried out and we discovered that along with the shorter and easier operation, patient discomfort and postoperative complaints also diminished. A study was designed to compare surgery time and postoperative pain when securing the autograft with glue vis-à-vis sutures. The postoperative pain was measured on the standardized Visual Analogue Scale. The surgery time was measured in minutes from the subconjunctival anesthesia until the draping was removed.
The results confirmed the initial impression and the study was first presented at AAO 2000 in Dallas, Texas. According to these results, the surgery indications were changed to involve subjective symptoms together with pterygium size and visual impairment. This resulted in a larger number of operations and a great deal of experience being gained. The method was spread, taught in different courses and on site in certain hospitals in Sweden and abroad (Bergen, Norway 2001) as well as in live surgery at ophthalmologic meetings (Bombay, India 2004, Budapest, Hungary 2007).

Paper 3.
We were very pleased with our results and also noted that the recurrences were fewer and smaller. This led to the next project, a comparison of recurrence rates.
All pterygium surgery were still performed by the same surgeon (GK) and was followed up like the previous sutured transplants. This produced a database that could be compared with that from the earlier method. We confirmed our impression, which we presented at ARVO 2001. The retrospective comparative study with a large number of patients and a long follow up time revealed that the recurrence rate of the sutured transplants was 3 times higher than that of the

glued ones. The recurrences of the pterygia operated on with fibrin adhesive were also smaller, less troublesome and required reoperation less frequently.
Other authors began to publish their results with the same technique, confirming our results.

Paper 4.
To diminish the workload on the single surgeon and to increase the availability of the surgery, other surgeons were also involved; Wijk T 2002 and Artzén D 2003. They were taught to perform the surgery in the same manner and used the same postoperative regimen and follow up.
When analysing their outcome, we did not find a significant learning curve regarding surgery time, recurrences or complications. We think that reported success rates may depend on patient factors, surgeon factors and lesion characteristics. We also believe that general surgeon qualities and devotion, more than the learning curve for the method affects surgery time, complications and recurrence rates. It is important that trainees get adequate instructions and support from qualified consultants. In this context we were interested in whether the Cut and Paste method was easy to learn and what happened in terms of complications and recurrences. Others have reported that inexperienced surgeons had worse results than senior ophthalmologists when learning to suture conjunctival autografts. It turned out that at our hospital this did not apply, the two surgeons had almost the same results and almost no learning curve with the Cut and Paste technique.

SAMMANFATTNING PÅ SVENSKA

Pterygium är en triangulär bindhinneduplikatur som växer över hornhinnan. Genom tusentals år i mänsklighetens historia har det varit en besvärlig sjukdom, som ofta orsakat lidande och t.o.m. blindhet. Det kunde inte botas med mediciner och nästan alltid recidiverade efter kirurgiska ingrepp. Man har länge sökt dess orsak och varför det återkommer efter dess avlägsnande. Många teorier har föreslagits och ännu fler kirurgiska metoder har testats med mer eller mindre bra resultat. Gemensamt för dessa var att pterygiumhuvudet och en del av bindehinnan över senhinnan skulle avlägsnas.

På 1990-talet ansågs enkel excision av pterygiet med tillägg av Mitomycin C vara en bra operationsmetod. Svårare fall eller recidiv opererades med suturering av fri bindhinnelambå över den blottade senhinnan. På S:t Eriks Ögonsjukhus i Stockholm jämförde vi dessa tekniker på slumpmässigt utvalda patienter (Paper 1). Alla opererades och följdes upp av samma kirurg (GK). Vi kontrollerade patienterna i 4 år. Operation med bindhinnelambå visade sig vara överlägsen, recidivfrekvensen var 15% mot 38% i MMC-gruppen och den valdes som vår standardmetod. Vi kunde också visa att recidiv uppträder under det första postoperativa året, alltså 1 års uppföljning i framtida studier kommer att räcka vid beräkning av recidivfrekvensen.

1999 testade vi att ersätta suturerna med ett välkänt fibrinlim, Tisseel Duo Quick, för att kunna förkorta operationstiden. Våra förväntningar infriades och vi upptäckte dessutom att patienterna upplevde klart mindre obehag postoperativt. Vi utformade och genomförde då den första jämförande studien (Paper 2) som övertygande bevisade våra intryck. Smärtupplevelsen enligt VAS-skalan var signifikant lägre ($p<0.05$) och operationstiden blev också signifikant kortare 9.7 mot 19.5 minuter ($p<0.01$). Vi kallade den nya operationsmetoden för Cut and Paste (klippa och klistra).

Under följande år användes endast denna teknik och med tiden såg vi att antalet recidiv var färre än förväntat. Vi utförde då en retrospektiv jämförande studie av dessa två metoder (Paper 3). Utfallet blev 5.3% resp. 13.5% ($p<0.01$). Reoperationsfrekvensen var också lägre, 1.2% resp. 3.3% ($p<0.05$).

Metoden började få gott rykte och ögonläkare vid andra svenska och utländska kliniker ville också lära sig den. Vid St. Eriks Ögonsjukhus fanns det behov av fler operatörer och två ögonläkare (A och B) utan tidigare erfarenhet av pterygiumkirurgi blev introducerade. Vi passade på att undersöka hur svårt det var att lära sig och bemästra denna operationsteknik. Vi opererade flera fall av primära pterygier under samma dag så att GK och eleven opererade varannan patient. Vi utvärderade sedan resultaten efter de första 120 operationerna av vardera kirurg och jämförde det med GK-s resultat (Paper 4). Medelvärdet för operationstiden var 17 resp 13 minuter för A och B, och 13 minuter för GK. Recidivfrekvensen var 8.9% resp 6.8% som inte skiljde sig signifikant från GK-s (5%). Varken operationstiderna eller recidivfrekvensen visade någon signifikant ökning under studieperioden.

Med en enkätundersökning bland svenska ögonkliniker och genom litteratursökning har vi sett att Cut and Paste metoden har blivit populär både i Sverige och i stora delar av världen samt att våra resultat har upprepats och bekräftats av andra.

Vi föreslår den som första val vid operation av primära pterygier.

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