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The evaluation of fibrin tissue adhesive for skin closure following eyelid surgery

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Abstract

The use of fibrin tissue adhesives in clinical practice has grown over the past 10 years, and there has been increased use of adhesives in different surgical subspecialties. Conventional suture closure of periorbital tissues is effective however may result in complications, which has led to the search for other techniques and innovations. Although tissue adhesives have been used in clinical practice there is a paucity of randomized controlled studies that have evaluated their advantages and disadvantage in surgical practice.

The goals of eyelid surgery include the restoration of tissue structure and function while causing minimal morbidity. The use of a medical product that induces physiological clotting and fibrin formation is appealing in both theory and clinical practice. However fibrin tissue adhesives present disadvantages and complications of their own. This thesis set out to evaluate the use of fibrin tissue adhesives in eyelid surgery and includes a 5-year randomized control study comparing fibrin tissue adhesives to suture closure of skin.

A challenge in the evaluation of eyelid surgery is the definition of a successful outcome. Surgical outcomes have traditionally been measured by surgical complications and the need for further redo surgery. Other relevant aspects of surgical outcome that have rarely been evaluated include surgical healing and scar formation, asymmetry that is present however not requiring further surgery, patient experience and satisfaction. This research set out to further define outcomes for eyelid surgery to enable a more comprehensive and objective evaluation of surgical outcome.

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Notations

ASGBI	Association of Surgeons of Great Britain and Ireland
BAAPS	British Association of Aesthetic Plastic Surgeons
BAPRAS	British Association of Plastic Reconstructive and Aesthetic Surgeons
BMA	British Medical Association
BOPSS	British Oculoplastic Surgery Society
CSF	Central Spinal Fluid
CT	Computerized Tomography
DOH	Department of Health
EBM	Evidence Based Medicine
FTA	Fibrin Tissue Adhesive
GMC	General Medical Council
HC	Healthcare Commission
LF	Levator Function
LREC	Local Research Ethics Committee
ML	Millilitre
MM	Millimetres
MPS	Medical Protection Society
MRD	Marginal Reflex Distance
MRI	Magnetic Resonance Imaging
MMCR	Müller's Muscle-Conjunctival Resection

NHS	National Health Service
NSAIDs	Non Steroidal Anti-Inflammatory Drugs
PA	Palpebral aperture
PROMS	Patient Reported Outcome Measures
RCT	Randomized Control Trial
RCOphth	Royal College of Ophthalmologists
SC	Skin Crease
WHO	World Health Organization

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1.0 Introduction

1.1 Background

The conventional use of sutures for closure of the skin following surgical procedures may be associated with suture related complications, increased patient morbidity and additional appointments for suture removal. Suture closure of the periorbital skin may lead to scarring, localized inflammation, hypertrophic scarring, asymmetry between the two sides and unhappy patients. These complications have led to the search for techniques that close the skin physiologically and improving healing (Nesi et al., 1987). Fibrin tissue adhesives (FTAs) were first made available in the 2nd World War for skin grafts although in a simplified form with low fibrinogen levels and limited effectiveness. Beginning in the 1980s, commercial adhesives have been developed which have offered advantages over conventional surgical techniques with improved surgical outcomes compared to conventional techniques (Piechotta and Flemming, 1983, Bruck, 1982, Bruck, 1978).

Conventional skin closure has been with sutures, and recognized complications include infection, granuloma formation, localized trauma, haemorrhage, discomfort, epithelial suture tracts, painful suture removal and scarring (Adams and Feurstein, 1986, Lowry and Bartley, 1994). Granulomas develop as a foreign body reaction to suture trimmings or other debris trapped in the wound during closure and present as nodular thickenings beneath the incision site (Bennett and Matas, 1982). In addition sutures provide point fixation that provides focal adhesion and not continuous adhesion of the wound surfaces that are optimal for vascularisation, reduced haematoma formation and postoperative scarring (Gibran et al., 2007). FTAs were proposed as an alternative method of skin closure that triggers a physiological clotting cascade with advantages over conventional sutures and staples (Greene et al., 1999, Mandel, 1992, Howell et al., 1995). FTAs are available as a two component system that contains highly concentrated fibrinogen and thrombin. The mixing of these agents immediately prior to use, promoted fibrin cross-linking resulting in physiological haemostasis and subsequent wound healing. The adhesive has been used in a number of surgical subspecialties including skin transplantations following burn injuries, neurosurgical closure of dura following central spinal fluid (CSF) leaks and the fixation of orbital implants. Studies have reported advantages including improved wound healing, reduced surgical time, complications and reduced pain compared to conventional sutures (Greene et al., 1999, Mandel, 1992, Howell et al., 1995). Anecdotally studies have reported improved healing with the use of FTAs although objective evidence and high quality research studies have been absent (Foster et al., 2006). There have been notable disadvantages that have included additional cost, risk of dehiscence and the potential risk of infection from the FTA product that is derived from human plasma. There have been few high quality studies evaluating the use of FTAs and no prospective randomized studies evaluating the technique following eyelid surgery.

Successful outcome following eyelid surgery has been frequently defined by surgical outcomes that highlight complications such as infection, delayed healing and the need for redo surgery. However these outcome measures often fail to account for important factors that impact surgical outcomes including facial symmetry, scarring and patient satisfaction. The proportion of redo cases are not representative of surgical failure as not all patients need or are prepared to undergo further surgery despite an unsatisfactory outcome. The importance of outcome measures has been highlighted by Darzi's report of "High Quality Care for All" (Darzi, 2007). The importance of Patient Reported Outcome Measures (PROMs) have been recognized as an essential component of measuring quality of care and for many surgical procedures including oculoplastic operations remain undeveloped (Block, 2006, Langley, 1998, Walburg, 2006). An objective of this study was to further define outcomes for eyelid surgery with particular focus in three specific areas; objective surgical measurements, patient satisfaction and the evaluation of standardized postoperative photographs.

1.2 Importance of Research

The healing response following eyelid surgery and resulting scar formation has marked implications to surgical outcomes and patient satisfaction. Conventional suture closure of the skin has been associated with complications related to the non-physiological constitution of the suture material. FTAs mechanism of action is to trigger the physiological clotting cascade and result in fibrinogen formation. There are very few randomized studies evaluating the use of FTAs and limitations of past studies include both confounding variables and subjective outcome measures. This study set out to evaluate the use of FTA in a randomized control study with a series of objective measures. This is the first randomly controlled study to evaluate the use of fibrin tissue adhesive skin closure for eyelid surgery.

The outcomes following eyelid surgery have traditionally evaluated measurements of the eyelids and re-operation rates, these outcomes provide an incomplete evaluation of surgical outcome. Patient satisfaction and the masked observation of standard photographs provide a more objective assessment of outcome. This study evaluated three patient outcomes following eyelid surgery with the objective of developing a benchmark for future eyelid surgery procedures.

1.3 Ptosis

Eyelid surgery was first described over 2000 years ago in the Susruta, an ancient Indian document written in Sanskrit (Kansupada and Sassani, 1997). Arabian surgeons are known to have cauterized excess upper eyelid skin to relieve eyelid droop as early as the tenth century (Dupuis and Rees, 1971), and the modern-day surgical technique is attributed to Costañares (Costañares, 1951, Rohrich et al., 2004).

1.3.1 Anatomy of the Eyelid

The upper eyelid is a mobile structure that protects the eye from injury and enables the even distribution of the tears on blinking. The eyelid consists of three principal layers: anterior lamellar (skin, subcutaneous tissue, orbicularis oculi muscle) middle lamellar (orbital septum) and the posterior lamellar (tarsal plates, smooth muscle and conjunctiva).

Eyelids

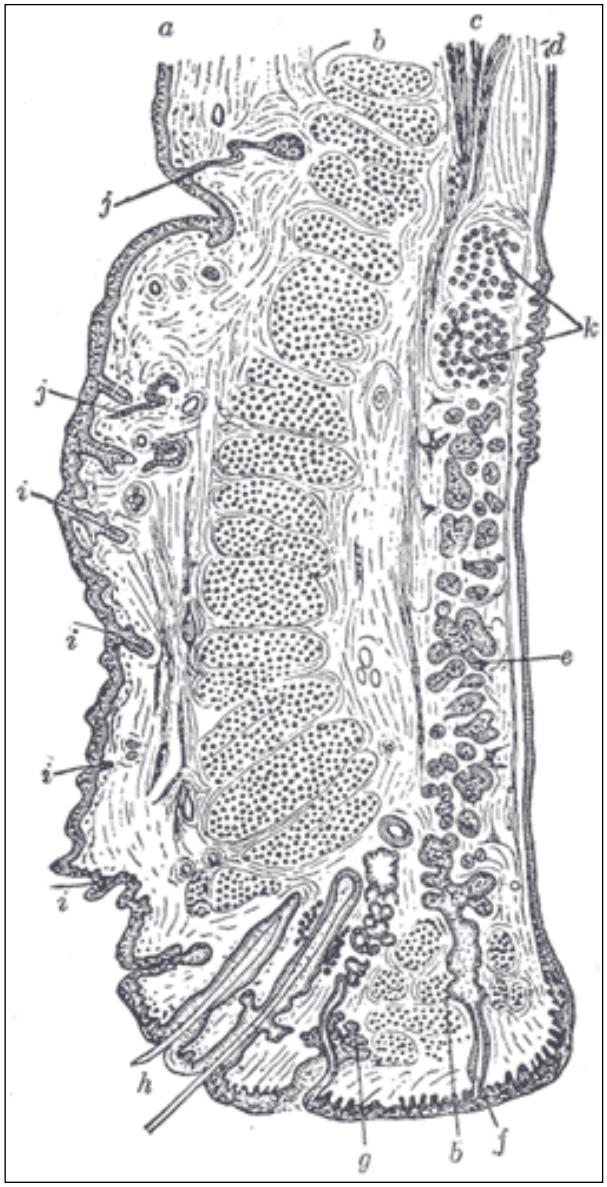
The skin of the upper eyelid is thin and divided by a horizontal furrow termed the superior palpebral sulcus or "skin crease", and is formed by insertion of the levator palpebral aponeurosis insertion in the skin of the upper eyelid (Fengzhi et al., 2009). In general the skin crease is approximately eight to twelve mm in Caucasian and Afro-Caribbean patients. The upper eyelid meets the lower eyelid at the medal and lateral canthal angles that when open form an angle of approximately sixty degrees. The lateral canthus is approximately two millimetres (mm) higher than the medical canthus in Caucasian and Afro-Caribbean patients (Snell and Lemp, 1998). The normal position of the upper eyelid, when the eye is open and looking straight ahead, covers the top 2-3mm of the superior cornea. The position of the lower eyelid is independent of the upper eyelid and usually lies at the edge of the cornea termed the limbus.

The margin of the upper eyelid is approximately thirty mm in length and two mm in thickness. At approximately five mm from the medial angle there is a small elevation termed the papilla lacrimalis, this is the entry to canaliculus lacrimalis and the lacrimal drainage channel. The eyelashes are short hairs at the margin of the eyelids that curve in an anterior direction, and are arranged in two to three rows. A sagittal cross-section of the upper eyelids is show in Figure 1.

In Asian patients there is often an absence of the eyelid skin crease, although the most common cosmetic procedure in Southeast Asia is the creation of an upper eyelid skin crease. Anatomical studies have identified a lack of the fibrous connection between the aponeurosis and the skin in the Asian double eyelid. Together with the lower positioned orbital septum, prominent pre-aponeurotic fat and thick orbicularis oculi result in the distinctive eyelid characteristics that are different to the Caucasian eyelid (Fengzhi et al., 2009).

The motor nerve supply to the orbicularis muscle in the upper eyelids is from the buccal, zygomatic and frontal branches of the facial nerve, the branches form superior and inferior plexuses that innervate the orbicularis muscles (Knize, 2000, Ouattara et al., 2004).

Figure 1 Sagittal Section of the Upper Eyelid



a. Skin. b. Orbicularis oculi muscle. c. Levator palpebrae. d. Conjunctiva. e. Tarsus. f. Tarsal gland. g. Sebaceous gland. h. Eyelashes. i. Small hairs of skin. j. Sweat glands. k. Posterior tarsal glands.

Acknowledgement for Figure: Grays Anatomy (Gray, 1918)

Anterior Lamellar

The eyelid skin is the thinnest in the body, beneath the skin is the loose subcutaneous tissue of the eyelids with increased elastic fibers and minimal fat. The orbicularis oculi muscle is an elliptical muscle that surrounds the globe it is divided into two principal parts the innermost palpebral part that is present in the eyelids and an outer orbital part. The function of the orbicularis oculi is to close the eyelids like a purse string. The muscle is innervated by the facial nerve from temporal and zygomatic branches on the deep surface from the parotid area and is not injured by transcutaneous eyelid surgery. The orbicularis muscle is the antagonist to the levator aponeurosis (striated muscle) and Horner's muscle (smooth muscle) which opens the upper eyelids (Albert et al., 2008, Snell and Lemp, 1998, Bron et al., 1995, Wolff and Last, 1961).

Middle Lamellar

The orbital septum forms a fibrous divide between the skin and the orbital cavity, the layer is a continuation of the periosteum at the orbital rim. The septum lies posterior to the medial palpebral ligament and anterior to the lateral palpebral ligament, and blends with the levator aponeurosis above the superior tarsal border (Fuchs and Duane, 1924). The orbital septum provides an important functional barrier in the eyelid that protects the spread of infection from superficial skin tissues to the orbital cavity. Although preseptal cellulitis is a very common infection of the skin, direct spread through the septum to the orbital cavity is rare. In addition anatomical variation in the position of the septum changes the appearance of the periorbital soft tissues. A low riding orbital septum with the orbital fat advancing forward onto the eyelid results in a "full" appearance of the eyelid, conversely a high septum may result in a "hollow" appearance of the eyelid as the orbital fat is stopped from coming forwards (Bron et al., 1995).

Posterior Lamellar

The tarsal plates are a dense fibrous tissue that gives the eyelids a defined shape and structure. The tarsus in the upper lid measures approximately ten mm in height and twenty mm in length and is attached to the medially via the medial palpebral ligament to the lacrimal crest and laterally to Whitnall's ligament. Attached at the superior edge of the upper tarsus are the smooth muscle fibers of the levator superior tarsal muscle (Müller's muscle) and the aponeurosis of the levator palpebral superioris. Within the tarsus are a series of meibomian glands (tarsal glands) that are modified sebaceous glands, which consist of a long central canal surrounded by over ten acini. Their oily secretions reduce the evaporation of tears and their gland orifices exit the eyelid just posterior to the lashes. The non-keratinzed squamous epithelium of the tarsal conjunctiva is tightly adherent to the upper eyelid and the thin mucous membrane reflects upwards as the superior fornix.

Levator Complex

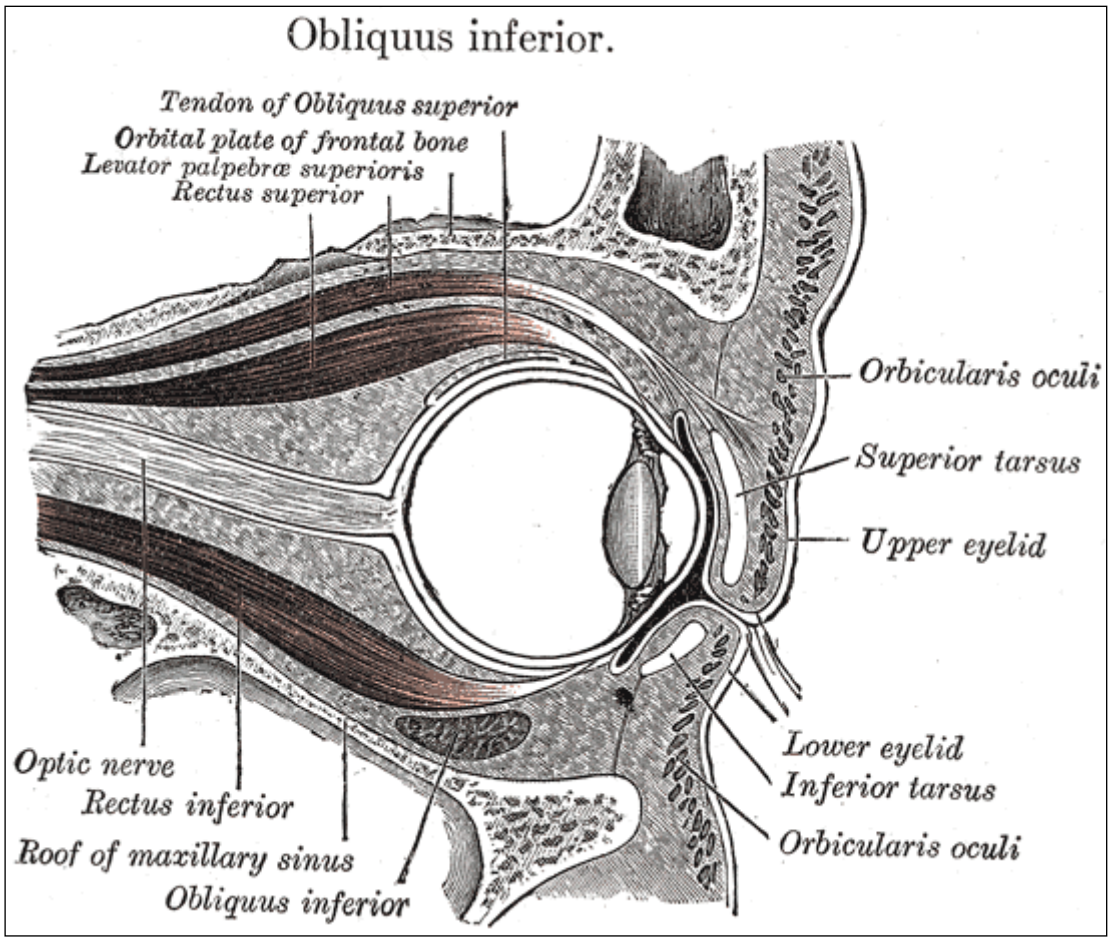
The upper eyelid is elevated by two muscles, the levator palpebral superioris (striated muscle) and the superior tarsal muscle (smooth muscle). The levator palpebral superioris originates from the lesser wing of the sphenoid bone, and just above the optic foramen it becomes the levator aponeurosis and is approximately fifty-five mm in length (Finsterer, 2003). The muscle transitions to an aponeurosis tendon approximately fifteen mm from the superior tarsus, attaching to the superior transverse ligament of Whitnall which acts as a check ligament of the levator (Anderson et al., 1990, Anderson, 1987, Anderson and Dixon, 1979c). Whitnall's ligament extends from the trochlea medially to the lacrimal gland capsule and frontal periosteum laterally, and the ligament changes the direction of Aponeurotic pull. The aponeurosis inserts into the anterior aspect of the superior tarsus and sends some fibers to the skin to form the upper eyelid crease. The aponeurosis extends in both medial and lateral expansions termed horns which may have a pathological role in upper eyelid retraction in conditions such as thyroid eye disease. The lateral horn indents the lacrimal gland partially dividing the gland into a smaller palpebral and thicker orbital portion. The lateral horn is attached to the marginal tubercle of the zygomatic bone and the medial horn fuses with the medial palpebral ligament. The levator palpebral superioris is innervated by the superior branch of the oculomotor nerve and elevates the eyelid by twelve to fifteen mm from pull closure to wide-eyed staring (Snell and Lemp, 1998, Carraway and Tran, 2009).

The superior tarsal muscle (Müller's muscle) is a vascularised smooth muscle that is innervated by the sympathetic nervous system. The muscle originates from the inferior surface of the levator aponeurosis and inserts into the superior tarsal plate. The muscle is approximately twenty by twenty mm with a one mm tendon, and elevates the upper eyelid by approximately two mm (Cohen, 1972, Finsterer, 2003). Müller's muscle is responsible for setting the upper lid level in conjunction with the levator palpebral superioris. Increased stimulation of the sympathetic nervous system such as stress or adrenaline elevates the eyelid, and corresponding damage to the sympathetic innervation results in one to two mm ptosis.

Eyelid Fat

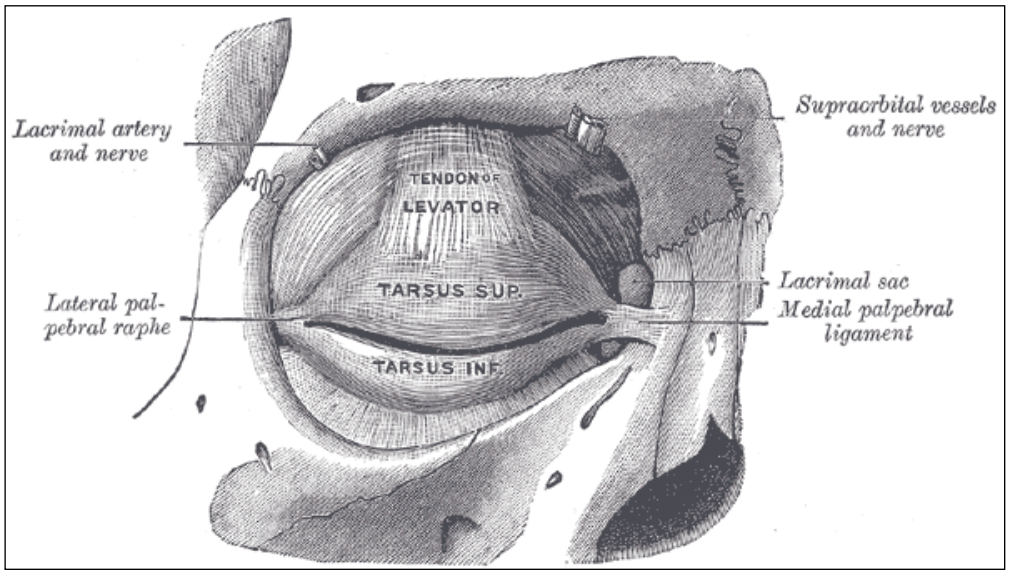
The upper eyelid has two pockets of orbital fat, the medial and central fat pads, laterally the pocket is filled by the lacrimal gland. The fat provides a lubricant and glide for the levator aponeurosis. Ageing of the tissues, results in atrophy of the fat pads that may result in a deep upper eyelid sulcus and sunken appearance.

Figure 2 Elevators of the Upper Eyelid: Sagittal Section



Acknowledgement for Figure: Grays Anatomy (Gray, 1918)

Figure 3 Elevators of the Upper Eyelid: Coronal Section

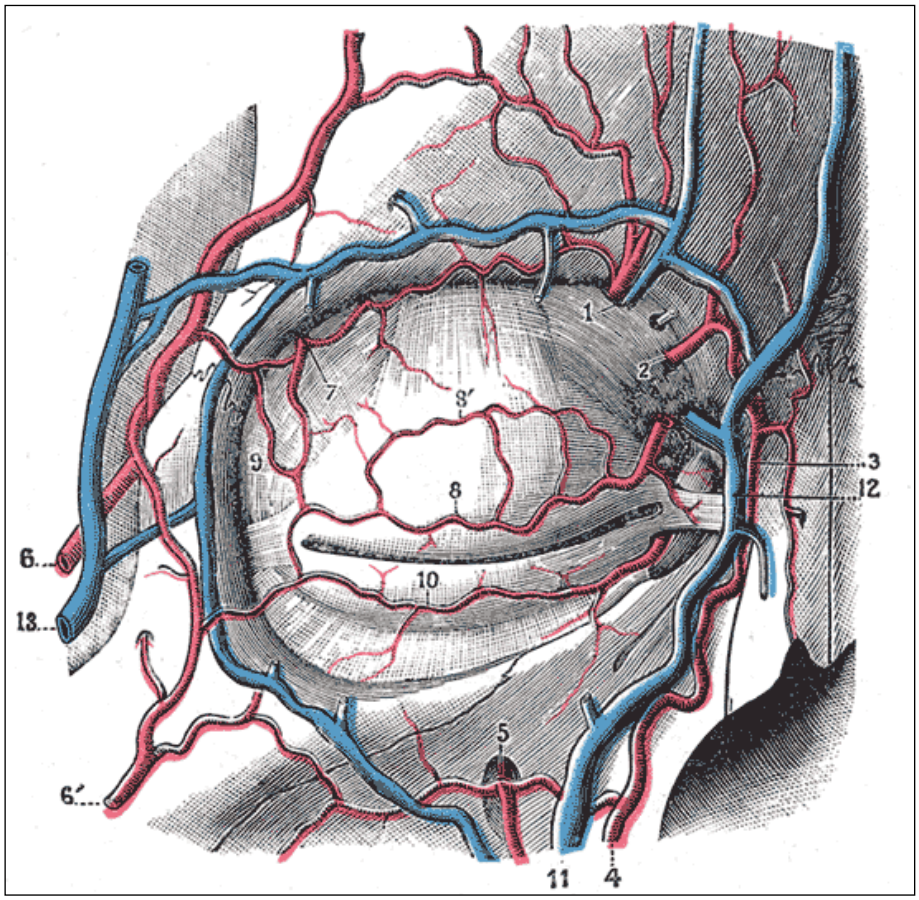


Acknowledgement for Figure: Grays Anatomy (Gray, 1918)

Blood Supply of the Upper Eyelids

The eyelids have a profuse blood supply from the lateral and medial palpebral arteries that form a marginal and peripheral arterial arch in the upper and lower eyelids. The lateral palpebral arteries are derived from the lacrimal artery and the medical palpebral arteries from the ophthalmic artery. The venous drainage of the upper medial one thirds of the eyelid is to the submandibular glands and from the lateral two thirds to the superficial parotid glands.

Figure 4 Blood Supply of the Upper Eyelids



1. supraorbital artery and vein. 2. nasal artery. 3. angular artery. 4. facial artery. 5. suborbital artery. 6. anterior branch of the superficial temporal artery. 6.' malar branch of the transverse artery of the face. 7. lacrimal artery. 8. superior palpebral artery. 8'. external arch. 9. anastomoses of the superior palpebral with the superficial temporal and lacrimal. 10. inferior palpebral artery. 11. facial vein. 12. angular vein. 13. branch of the superficial temporal vein.

Acknowledgement for Figure: Grays Anatomy (Gray, 1918)

1.3.2 Ptosis Definition

Ptosis has been defined as drooping of the upper eyelid and may be classified by several different means including; severity, aetiology, onset and levator function (Beard, 1989). The exact incidence of ptosis is not known, however the condition is common and has equal frequency among different races and between the sexes (Finsterer, 2003).

Elevation of the upper eyelid is the result of the levator palpebrae superioris which is a composite muscle made of a striated muscle, a long aponeurotic tendon and a non-striated sympathetically innervated (Muller's) muscle. The eyelid height is affected by local ocular and orbital tissues, as well as conditions effecting the cranial nerve and sympathetic nerve innervation and muscles(Jones et al., 1975). Ptosis may result from a condition affecting the eyelid elevator mechanism, in elderly patients there is attenuation of the insertion of the aponeurosis into the tarsal plate.

As the upper eyelid descends it covers the superior aspect of the cornea, restricting the superior visual field. With time the upper eyelid may eventually cover the visual axis resulting in a reduced visual acuity. Patients often describe some variability of the eyelid height, with worsening at latter parts of the day that may result from muscular fatigue, myasthenia gravis must be excluded.

1.3.3 Ptosis Causes

Ptosis may be caused by a large number of different aetiologies including age (involutional), birth defects (congenital), reduced innervation (neurogenic), eydlid lumps (mechanical) or other (e.g. following intraocular surgery), a comprehensive list is show in Table 1. The diagnosis of involutional ptosis (also called aponeurotic ptosis) is dependent on the exclusion of other causes of ptosis.

The upper eyelid may have a false appearance of ptosis which is termed pseudoptosis. This must be excluded for the condition to undergo the correct treatment. Causes of pseudoptosis include lid abnormalities, abnormal globe position and a small or sunken globe (Table 1).

Table 1 Ptosis- Classified by Aetiology

Aetiology of Ptosis	**Disorders**
Involutional	Age-related dehiscence of the levator aponeurosis from the superior tarsal plate
Congenital	Defined as the onset of ptosis within the first year of life. Idiopathic, localized myogenic dysgenesis. myogenic, neurogenic, mechanical and other causes
Myogenic	Aromatic L-amino acid decarboxylase deficiency, congenital myopathies (central core disease), congenital fibrosis of the extraocular muscles, facio-scapulo-humeral muscular dystrophy, glycogenosis, mitochondriopathy, myositis, myotonic dystrophy, myasthenia gravis, myaesthenic syndrome, oculo-pharyngeal muscular dystrophy, orbital rhabdomyosarcoma
Neurogenic	Apraxia of lid opening, blepharospasm (benign, essential), botulinism, botulinum toxin therapy, cerebellar vermis hypoplasia, cerebral tumour, cerebral, ocular, dental, auricular, skeletal anomalies (CODAS) syndrome, cerebral vasculitis and venovascular hypertension, chronic rhinocerebral mucormycosis, cluster headache, cortical dysplasia and maldevelopment of the basal ganglia, facial nerve palsy, hemifacial spasm, Horner's syndrome, Marcus Gunn jaw-winking syndrome, multiple sclerosis, mycotic meningitis, migraine ophthalmique, optic glioma, orbital dermoidal cyst, oxiliplatin neuropathy, paraneoplastic syndrome, Raeder Syndrome (acquired Horner's syndrome with ipsilateral headache), Recklinghausen's neurofibromatosis, rheumatoid pachymeningitis, Riley-Day syndrome, Schwartz-Jampel syndrome, sleep apnea syndrome, stroke (mesencephalic, hemispheric), SUNCT syndrome, syringomyelia, third-nerve palsy (carotid aneurysm, cavernous sinus thrombosis, congenital, degenerative CNS diseases, heavy metal intoxication, increased intracerebral pressure, trauma, superior orbital fissure syndrome, tumours (dermoidal cyst, fibrous tumour, neurinoma, non-Hodgkin's orbital lymphoma)), vascular lesions, Wernicke's encephalopathy
Mechanical	Scarring, excessive weight—dermatochalasis, eyelid mass (lid tumours: neurinoma, neurofibroma), orbital mass
Traumatic	Birth trauma, forceps delivery, corneal abrasion, corneal foreign body, eyelid laceration, hard contact lens embedding, orbital fracture (apex or floor), orbital haemorrhage, post-cataract ptosis, transorbital penetrating brain injury, trauma to the levator aponeurosis
Miscellaneous	Anophthalmos, atopic dermatitis, blepharochalasis, blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) due to FOXL2 gene mutations, capillary haemangioma, carotid aneurysm, carotid cavernous fistula, chalazion, chromosome 14q terminal deletion syndrome, combined valproate and hydantoin embryopathy, craniofacial syndromes, de-novo duplication dup (Xq22.1–q25), distichiasis with FOXC2 truncating mutations, double partial monosomy (10p13–10pter and Xp11.4–Xpter), Down syndrome, Duane syndrome, exophthalmos, eyelid oedema, foetal alcohol syndrome, fibrosis syndrome (CFEOM1 locus on chromosome 12), floppy eyelid syndrome, giant papillary conjunctivitis, glaucoma, iris coloboma, hypertelorism, mental retardation due to deletion on chromosome 2, Joubert's

	syndrome, King-Denborough syndrome, lacrimal gland hemangiopericytoma, mandibulofacial dysostosis, mucolipidosis type IV, mycotic aneurysm of the internal carotid artery, oculo-facio-cardiac-dental syndrome, orbital artery obstruction, orbital or preseptal cellulitis, orbital fat prolapse, orbital fibromatosis, orbital Langerhans cell granulomatosis, orbital osteoclastoma, orbital phlegmona, Parry-Romberg syndrome, partial trisomy 1q32–qter _pure,_ poorly fitting ocular prosthesis, Rubinstein-Taybi syndrome, Smith-Magenis syndrome, Smith-Lemli-Opitz syndrome, socket contraction, Sturge-Weber syndrome, supernumery chromosome
Iatrogenic	Intra-ocular surgery, contact lens wear, chronic inflammation of the conjunctiva
Pseudoptosis	Eyelid abnormalities (ipsilateral excess eyelid skin termed dermatochalasis, contralateral eyelid retraction), abnormal globe position (down-turning of the eye termed hypotropia) and a small or sunken globe (anophthalmos, enophthalmos, microphthalmos, phthisis bulbi, anisometropia)

Modified from: (Finsterer, 2003, Cetinkaya and Brannan, 2008)

1.3.4 Histopathology of ptosis

Intraoperative macroscopic evaluation of the levator aponeurosis in patients with involutional ptosis may identify a "normal" appearance of the levator with localized dehiscence or fatty degenerative change in the anterior part of the levator aponeurosis. These fatty changes may be associated with a relatively normal skin crease, more marked ptosis in the medial part of the lid (Collin, 1986). One study retrospectively evaluated the patient that required reoperation and found the rate double in the patients with fatty levator changes, the reoperation rate was 29% for the fatty-appearing levators and 14% of the normal-appearing levators (Tucker and Verhulst, 1999).

1.3.5 Assessment of Ptosis

The assessment of a patient with ptosis includes establishing the diagnosis, the aetiology and the corresponding development of a management plan. The evaluation is conducted in a systematic manner to ensure accuracy and consistency, including history taking, patient examination and where necessary further investigations.

History Taking

Patients with involutional ptosis often complain of a droopy upper eyelid and a sleepy appearance. With increasing severity the descent of the upper eyelid position occludes the superior visual field and eventually the pupillary axis. Patients may tilt their head backwards and adopt a chin-up position to improve their sight or use a finger to physically lift the eyelids. The restriction of superior visual field may interfere with the patient's lifestyle, as patients may have difficulty with driving, reading and going up stairs. Over time, patients may use their forehead muscles to elevate the eyelids this results in elevation of their eyebrow and may result in an unusual "surprised" appearance.

History taking must include family history, generalized systemic conditions (e.g. diabetes mellitus, cardiovascular disorders) and specific neurological disorders (including symptoms of fatigue, weakness, dysarthria and dysphasia). In addition should include the time of onset, associated symptoms (e.g. double vision, termed diplopia), trauma and previous contact lens wear.

Examination Findings

Patients with aponeurotic ptosis, aging of the eyelid tissues and long-term effects of gravity result in stretching of the levator aponeurosis and a loss of the muscle tone that can be seen macroscopically during surgery. In addition there maybe disinsertion of the aponeurosis from the superior tarsal plate, associated with a characteristic rising and eventual loss of the skin crease. Involutional ptosis is defined by a number of clinical characteristics that are summarized in the table 2. The classical signs of aponeurotic ptosis result from the detachment of the levator aponeurosis from the eyelid tarsus, resulting in a high or absent skin crease, increased lid show and deep upper eyelid sulcus.

Table 2 Examination Characteristics of Aponeurotic Ptosis

Assessment	**Characteristic**
Eyelid Measurements	Increased upper lid show
	High or absent skin crease
	Deep upper sulcus
	Thinning of the upper eyelid
	Bilateral although maybe asymmetrical
Exclusion on non-involutional ptosis	Normal levator function
	Normal ocular movements
	No fatigue
	Normal conjunctival tarsus
Others **(not commonly used in clinical assessment)**	Normal Muller function (cocaine test) Positive finger test (feel the edge of the ptosis with the tip of the finger on the upper eyelid during elevation) Iliff's Sign: (Positive, if when the eyelid is everted it does not flip back to the same position on upgaze)

(Anderson and Dixon, 1979a, Finsterer, 2003)

The diagnosis of involutional ptosis requires the exclusion of other causes through assessing levator function, ocular movements and slit lamp biomicroscopy. Ocular movement examination requires cover tests, pursuit, saccades, test for jaw-winking phenomena and fatigue on upgaze (Shields and Putterman, 2003). For example the presence of diplopia, fatigue on upgaze or slowed saccades is suggestive a myogenic cause for the ptosis and would require further evaluation of retina for pigmentary retinopathy and systemic assessment.

Ophthalmic examination of patients with ptosis requires a thorough evaluation including generalized head position, eyelids and orbits assessment. Examination of the eyelids includes assessment of asymmetry, brow ptosis, dermatochalasis, orbital fat prolapse, eyelid contour and

position. Patients are often unaware of the additional factors affecting the position of their eyelid and need education as part of the management discussion. Evaluation of the conjunctiva, tarsal plates, superior and inferior fornices is routinely assessed. The visual acuity and visual fields should be recorded and may be necessary to justify surgical intervention.

Examination should include assessment for dry eye, exposure keratopathy and the ocular protective mechanism including orbicularis oculi strength and Bell's phenomenon, corneal sensation and tear film adequacy. Schirmer's test can be useful to make the diagnosis of dry eye and for evaluating the level of severity. Surgical management of ptosis results in increasing the patient's risk of postoperative dry eye.

The levator function is an important measure of the eyelid that aids both establishing the diagnosis and choosing the appropriate management plan. The levator function is defined as the distance measured from the upper eyelid margin looking in maximal downgaze, to the position of the upper eyelid margin looking in maximal upgaze without frontalis action. The levator function is graded as excellent (>10mm), good (8-10mm), fair (5-7mm) or poor (1-4mm) (Frueh, 1980, Fuchs and Duane, 1924). The diagnosis of involutional ptosis required an excellent levator function of greater than 10mm and any value less than ten mm would suggest the diagnosis of involutional ptosis is incorrect. Normal eyelid measurements are shown in Table 3. Although the average eyelid measurements are cited in textbooks, there is evidence that the values are affected by age, gender and race (Price et al., 2009).

Table 3 Eyelid measurements

Terminology	Measurement
Pupil reflex	Midpoint of pupil resulting from shining a torch in front of the eye
Primary gaze	Patient looking straight ahead at a torch at a distance of approximately 30cm
Mid-pupillary line	Vertical line drawn through the centre of the pupil
Marginal reflex distance	Distance from the upper eyelid to the pupil reflex in primary gaze (Normal >2.5mm)
Palpebral aperture	Distance from the upper eyelid to lower eyelid when looking in primary gaze
Levator function	Measurement of the upper eyelid from maximal looking down to looking up while preventing frontalis movement
Lid show	Distance from the skin crease above the eyelid margin to the upper eyelid margin
Skin crease	Measurement from the upper eyelid to the skin crease with the patient looking down (Normal 10-11mm in men, 8-9mm in women)
Interlid difference	The difference between the right and left upper eyelid heights when looking in primary gaze
Lagophthalmos	Measurement of the distance between the upper and lower eyelids with the patient closing their eyes (Normal: 0mm)
Bells phenomenon	Position of the cornea when the eyes are closed (Normal: eyeballs rotate superiorly)

Investigations

The diagnosis of involutional ptosis does not routinely require specific investigations and the diagnosis can frequently be made following clinical assessment. Uncommonly the assessment of ptosis patients may require blood tests, CT or MRI imaging, electromyography or muscle biopsy. In patients where a neurological cause is suspected, CT or MRI imaging may be used to exclude a space occupying lesion. In addition antibody assays, electromyography and muscle biopsies may be used to exclude myopathies.

1.3.6 Clinical diagnosis of ptosis

There have been several different definitions of ptosis described in the literature including; a measurement of the amount by which the upper eyelid covers the upper corneal limbus, the size of the vertical lid fissure (i.e. palpebral aperture) and the distance from the pupil/ light reflex to the upper eyelid (i.e. marginal reflex distance). One study that compared each of the three methods concluded that the most useful definition of ptosis is the marginal reflex distance (Small et al., 1989). Other definitions such as those that include the lower eyelid position are influenced by co-morbidity as they are affected by sagging or retraction of the lower eyelid which does not necessarily indicate a diagnosis of ptosis (Scoppettuolo et al., 2008, Small et al., 1989).

Table 4 Ptosis Measurements

Definition	**Marginal Reflex Distance/ mm**
Normal marginal reflex distance	2.5-5mm
Ptosis	≤2mm
Mild ptosis	>1mm, ≤2mm
Moderate ptosis	>0mm, ≤1mm
Severe ptosis	≤0mm

On evaluation of a patient with ptosis, assessment must be conducted to the fellow eye as involutional ptosis is frequently bilateral and asymmetrical. Hering's law of innervation states that equal and symmetrical innervation is sent to paired yoke muscles in the eyes, including the levator aponeurosis. When a patient attempts to elevate the upper eyelid of their more ptotic eye, this induces increased innervation to both levator complexes, the increased innervation to the contralateral eye that may

mask the mild ptosis. Following surgical correction of the more ptotic eyelid, innervation to the levator complex reduces which may unmask the ptosis in the fellow eye. Bodian reported a 1mm drop in the contralateral eyelid height following ptosis surgery in 10% of patients (Bodian, 1982). Preoperative assessment should include manual elevation of the ptotic eyelid, and assessment of the fellow eyelid for a drop in height (Erb et al., 2004, Parsa et al., 2001). Erb at al. evaluated contralateral lid height following unilateral ptosis correction and found that a negative Hering test could not exclude a contralateral postoperative drop in lid height and suggested that additional factors and variability of lid height may limit its usefulness (Erb et al., 2004).

One large study that looked at a large number of ptosis operations with mixed aetiology found the reoperative rate double in the bilateral group (13%) compared to the unilateral (5% group) (McCulley et al., 2003). Although this is suggestive of the importance of Hering Law (an exacerbation of contralateral ptosis with ipsilateral eyelid elevation) there is a selection bias that may influence results e.g. unilateral congenital cases may have more favourable results.

1.3.7 Factors affecting upper eyelid position

In addition to the upper eyelid complex (levator palpebral superioris and the superior tarsal muscle) that sets the height of the upper eyelid, the upper eyelid height may be influenced by the position of the brow, the muscle tone or neurological innovation. The upper eyelid height does vary during the day, with patients reporting increased ptosis when they are tired as a consequence of muscle fatigue, and with some medical conditions. In this study systemic conditions that are known to effect eyelid height and increase height variability were excluded e.g. myogenic causes of ptosis.

On measuring the eyelid position, there is a known variability that is dependent on the examiner described as inter-observer variability of up to 1mm. One study found that lid measurements are generally accurate to 1.5mm in 84% of patients (Small et al., 1989). In addition the same examiner may find different measurements on the same patient, termed intra-observer variability. Frueh and Small have described techniques to evaluate lid parameters in a relatively consistent manner to reduce inter-observer and intra-observer variability (Small et al., 1989, Frueh et al., 2004b).

Eyelid height is affected by ocular surface disease which may cause a secondary ptosis. For example chronic inflammation of the tarsal conjunctiva as a consequence of allergy or infection may result in ptosis. In this study to make the diagnosis of involutional ptosis all patients had their upper eyelids everted and the conjunctiva assessed.

1.3.8 Treatment of Ptosis

The treatment of involutional ptosis requires surgical intervention unless the patient is unfit for surgery. Involutional ptosis gradually worsens with time and conservative management with "ptosis props", spectacles with a crutch attachment to elevate the eyelid, are rarely used as they have limited benefit and fail to correct the underlying pathology of levator dehiscence from the tarsal plate. The surgical techniques that are used to treat ptosis are generally guided by the aetiology and severity of the ptosis, the levator function and the surgeon's personal preference. The surgery falls into three broad categories: external approach (transcutaneous), internal approach (transconjunctival) and frontalis suspension (brow suspension).

External Approach

The early surgery until the 1970s was based upon the preoperative measurements of the levator muscle function and the severity of the ptosis, however this technique had unpredictable results with a high incidence of overcorrection in up to 50% of cases of involutional ptosis (Berke, 1971, Berke, 1959). In 1975, Jones et al described repair of the aponeurosis by an anatomical technique, reviving a procedure first described by Eversbusch in 1883 (Jones et al., 1975, Eversbusch, 1883). Although the technique has undergone some modest modifications, the technique is the principal surgical technique used for the repair of involutional ptosis in the modern era (Anderson and Dixon, 1979a, Harris and Dortzbach, 1975, Older, 1978b). The advantage of this technique included that the surgery could be completed with local anaesthesia, the levator function action could be intraoperatively assessed and the lid height modified accordingly, resulting in vastly improved success rates (Older, 1978a, Anderson and Dixon, 1979a).

The transcutaneous approach involves an anterior skin crease incision, dissection through the orbicularis and orbital septum, and identification of the levator aponeurosis. The aponeurosis is sutured to the superior tarsus with mattress sutures, with the surgery under local anaesthesia the height of the eyelid can be adjusted intraoperatively resulting in a reduced risk of over or under correction. Levator advancement is the most common method of eyelid elevation, the technique allows the simultaneous removal of excess upper eyelid skin and skin crease reformation where indicated.

Levator resection is similar to levator advancement, the excessive tissue of the levator and Müller's muscle is resected from the tarsus and conjunctiva at the superior border of the tarsus (Lucarelli and Lemke, 1999, Frueh et al., 2004a). The effect of the resection is an increased elevation of the eyelid so is a more preferred surgical option in cases with reduced levator function. Increased

elevation results in increased risk of postoperative complications such as dryness, exposure keratopathy (corneal erosions secondary to dryness) and lagophthalmos (inability to close the eyelids; results in increased dryness) (Cetinkaya and Brannan, 2008). The current trend is towards minimally invasive surgery, and a smaller transcutaneous incision less than the standard 20 mm has been used. The results from 8-10mm incisions are comparable to conventional technique with advantages including a shorter operative time, lower risk of postoperative scarring, however the technique does not enable the treatment of dermatochalasis or fat prolapsed at the time of ptosis repair (Frueh et al., 2004a).

Internal Approach

The internal approach requires the surgeon to be more familiar with the anatomy of the upper eyelid, and is favoured for cases of mild ptosis with good levator function, notably for ptosis resulting from Horner's syndrome (denervation of the sympathetic innervations to the upper eyelid). Müller's muscle-conjunctival resection (MMCR) was first described by Putterman et al. for the management of mild ptosis (Putterman and Urist, 1975). The technique is relatively straightforward and following eversion of the eyelid, a predetermined amount of conjunctiva and Müller's muscle is excised (Putterman and Urist, 1975, Shields and Putterman, 2003). A further modification of the procedure has proposed additional excision of the tarsus for increased eyelid elevation (Perry et al., 2002). The technique is both effective and reproducible for mild ptosis, with a more predictable upper eyelid height that external approach levator aponeurosis surgery (Ben Simon et al., 2005, Dresner, 1991). The technique is limited by its use for cases with less than 3mm of ptosis, and complications include peaked upper eyelid and a small risk of eyelid instability. The technique is not commonly used for involutional ptosis as it fails to correct the pathophysiology and the ptosis is likely to reoccur with time.

Transconjunctival resection (known as Fasanella-Servat) had been reported effective for most types of ptosis with a levator function of greater than 8 mm (Fasanella and Servat, 1961). The technique has been described as the simplest procedure for the correction of ptosis and involves the excision of tarsoconjunctiva and Müller's muscle (Betharia et al., 1983). There is a risk of postoperative lid instability from excision of the tarsus, and the excision should be limited to 3mm from lid margin (Betharia et al., 1983).

Frontalis Suspension

Frontalis suspension is indicated in patients with poor levator function (<5mm) such as severe congenital ptosis and myogenic ptosis. The technique requires the use of sling material that suspends the upper eyelid to the frontalis muscle, with either autologous (e.g. fascia lata) or non-autologous (e.g. silicone tubing) material. The technique is not used for the correction of aponeurotic ptosis the levator complex of the eyelid is normal. Although effective in elevating the eyelid, the technique is not a preferred surgical technique as it is associated with specific complications including, prominence of the sling material, extrusion and poor eyelid contour (Ben Simon et al., 2005, Dresner, 1991, Park, 2007).

Skin Incision

Multiple modalities have been used for incising the skin including the traditional scalpel, electrosurgery, radiowave, and lasers (Niamtu, 2008). Radiowave (4.0 MHz system; Surgitron, Ellman International, Oceanside, NY) and CO_2 laser have the benefit of simultaneous incision and coagulation. Although alternatives to the scalpel incision have intraoperative advantages the surgical outcomes, including scar formation and healing are similar (Niamtu, 2008).

Contraindications to Surgery

Relative contraindications for surgery include patients with high risk of postoperative dry eye, including those with marked lagophthalmos, poor Bell's phenomenon, preoperative keratitis sicca, loss of corneal sensitivity (Finsterer, 2003). These are uncommon characteristics of involutional ptosis and may be suggestive of a different aetiology. There are few absolute contraindications as severe ptosis covering the visual axis has marked implications for patient's general health and risk of an adverse event resulting from reduced vision (Fuchs and Duane, 1924, Ritland et al., 2004).

Complications of Surgery

The complications of ptosis surgery and upper eyelid blepharoplasty are discussed in detail in 2.3.1 and summarized in table 13.

1.4 Upper Lid Blepharoplasty

The superior periorbital tissues have an important function in facial expression, protection of the eyeball and characteristic signs of aging. Ageing of the upper eyelid results from gravitational effects, loss of skin laxity and fat prolapse of the upper eyelid. The term dermatochalasis is used when there is an increased fold of upper eyelid skin that may impair the function of the eyelid reducing the superior visual field and visual acuity, for the condition to be considered debilitating the superior visual field will be restricted and may require assessment before surgery. The orbital fat pads of the upper eyelid may prolapse through the orbital septum causing focal or generalized bulging of the upper eyelids. Conversely atrophy of the orbital fat may result in increased hollowing and prominence of the upper lid sulcus (Morley et al., 2009).

Evaluation of the upper eyelid and dermatochalasis requires assessment of the eyebrow shape, position and symmetry. Ageing of the brow can result in brow droop, which may be disguised by frontalis contraction that elevates the eyebrow above the orbital rim. If the brow position is not corrected and the patient undergoes upper eyelid blepharoplasty it may not correct the underlying pathology, resulting in a postoperative brow ptosis as a consequence of loss of the stimulus for frontalis overaction to elevate the brow. Meticulous assessment is required preoperatively to identify brow droop and dual pathology (Gunter and Antrobus, 1997).

Traditionally upper eyelid blepharoplasty surgery involved the excision of lax skin and muscle of the upper eyelid including a crescent shape of skin and orbicularis muscle and if prominent, excision of orbital fat pads (Goldberg, 2000, Ciuci and Obagi, 2008, Seiff, 2002). There has been a change in the conceptual understanding of aging of the face, with greater emphasis placed on volume replacement and less excision of tissues (Rohrich et al., 2004). Modern technique preserves the orbital fat with repositioning to prevent hollowing of the upper eyelid sulcus and a “skeletal” appearance, and in some cases the volume of fat has been augmented with autologous fat transfer.

The complications of upper eyelid blepharoplasty are similar to those of ptosis surgery (Table 13). Vision threatening complications are rare following upper eyelid blepharoplasty however can result as a consequence of orbital haemorrhage or penetrating globe injury (DeMere et al., 1974, Schechter, 1985). The source of orbital haemorrhage following blepharoplasty or ptosis surgery is controversial. The haemorrhage may result from traumatic injury to the intraorbital fat without adequate attention to cauterization of vasculature. Blindness has not been reported to occur with an unopened orbital septum, hence without trauma to the intraorbital fat (Lowry and Bartley, 1994). Other theories including trauma to the orbital vasculature, postoperative vasospasm and rebound haemorrhage following local anaesthesia and adrenaline reabsorption (Lowry and Bartley, 1994).

1.5 Fibrin Tissue Adhesives

1.5.1 Overview of FTAs

There are two principal types of adhesives that are used in medical practice. The synthetic adhesives (e.g. cyanoacrylate derivatives) are compounds with very high tensile strength that rapidly polymerize on contact with substances such as water or blood. Synthetic adhesives are non-biodegradable and induce an inflammatory foreign body response that limits their clinical use. Fibrin-based adhesives are biological agents that have a lower tensile strength and slower polymerization. Their physiological properties make them biodegradable and their use induces only a mild inflammatory response, their favourable properties means have a much wider application in medicine (Chan and Boisjoly, 2004). The FTAs may provide a local environment that is more supportive of healing and scar remodelling such as cell migration and proliferation (Mogford et al., 2009).

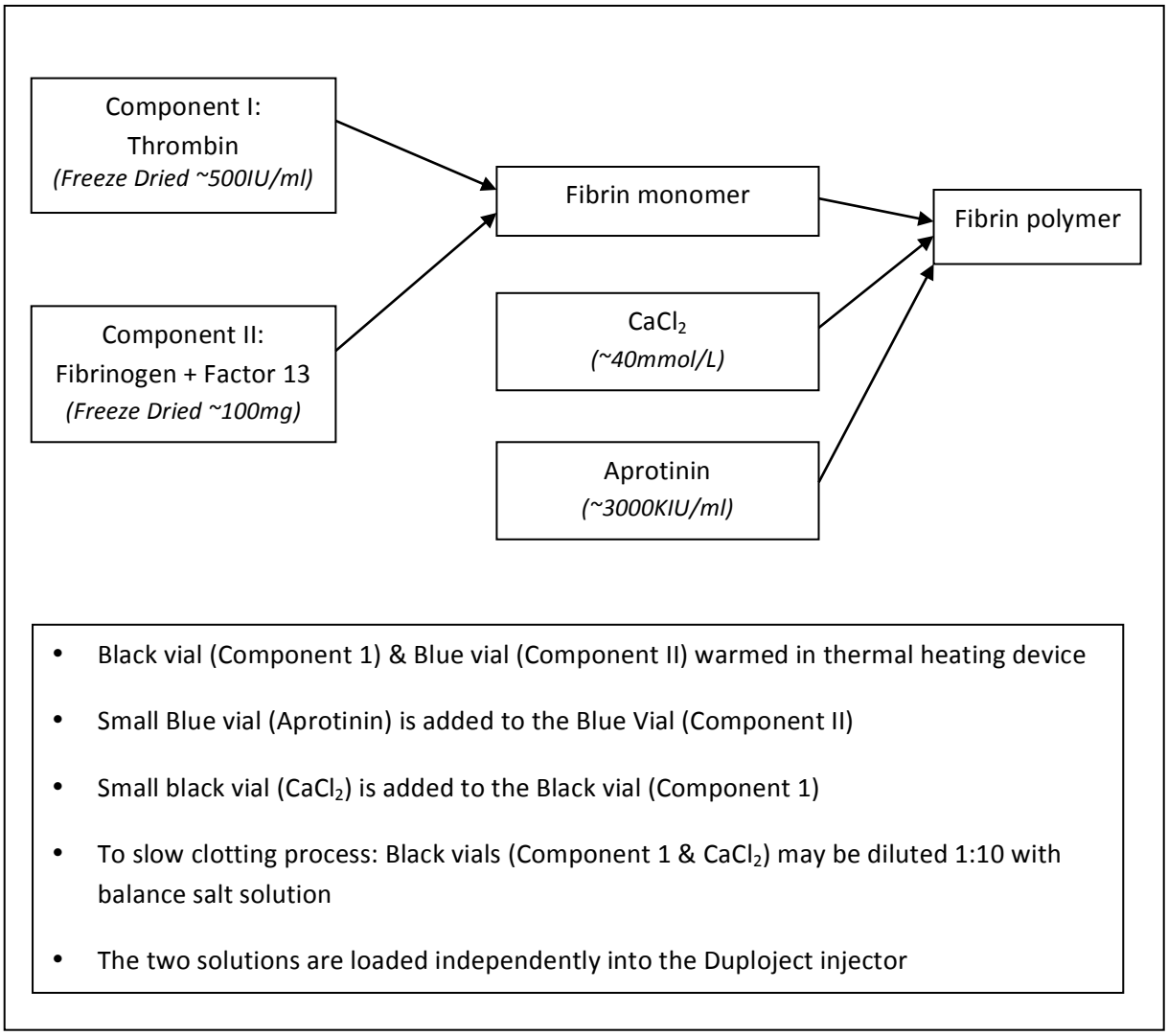
The first use of fibrin as an adhesive was in World War I to enhance the tissue adhesion of skin grafts in soldiers with severe burn injuries, however the low concentration of fibrinogen in plasma reduced its effectiveness and viability. In addition the screening of human plasma for infectious diseases was limited and many patients treated with early fibrin sealants became infected with viral hepatitis (Jackson, 2001b, Jackson, 2001a, Grey, 1915), Cronkite 1944). The fibrinogen concentration was increased and the FTA reformulated during the 1970s and Tisseel (Baxter AG Industries, Vienna, Austria) first became available in Europe in the 1970s. In the 1980s the Food and Drug Administration (FSA) did not approve the licensing of the FTA product because of the perceived high associated risk of hepatitis transmission from the pooled human plasma (Jackson, 2001b, Jackson, 2001a). In the 1990's substantial improvements to the formulation were made including the addition of aprotinin to slow fibrin clot lysis in addition to general improvements in the quality, consistency and cross-reactivity of the human clotting factors (Chan and Boisjoly, 2004, Radosevich et al., 1997) and in the US Food and Drug Administration approved it for clinical use in 2003 (Lee et al., 2009).

1.5.2 Mechanism of Adhesion

The FTAs mimic the physiological coagulation cascade as show in Figure 5. FTAs are composed of human plasma-derived mixture of thrombin and fibrinogen and result in fibrin clot formation. The coagulation cascade is triggered, factor X hydrolyses prothrombin to thrombin, and in the presence of thrombin, fibrinogen is converted to a lose fibrin polymer (Thompson et al., 1988). Thrombin activates factor XIII to trigger fibrin cross linking, replicating the common pathway of the

coagulation cascade resulting in stable clot formation. The normal degradation of the fibrin is blocked by the addition of aprotinin, a protease. The aprotinin was originally a bovine product that carried an increased risk of allergy, this has been subsequently replaced with synthetic aprotinin. The strength of the adhesion is proportional to concentration of fibrinogen (67-106 mg/ml) which in the commercially available products is approximately thirty times normal plasma (Mommaerts et al., 1996, Batman et al., 2009). In addition the FTA may promote the formation of a biomatrix scaffold that promotes cellular regeneration and wound healing through fibroblast proliferation and collagen deposition. The fibrin and fibronectin crosslinks with tissue collagen, and the fibrin forms covalent, hydrogen and electrostatic bonds to the local tissues (Radosevich et al., 1997). The fibrin sealant matrix enables the diffusion of nutrients, cytokines and other molecules required for subsequent healing and a scaffold for the in-growth of fibroblasts and capillary endothelial cells (Brown et al., 1992, Grabosch et al., 1994).

Figure 5 Fibrin Tissue Adhesives activate the Physiological Coagulation Cascade



1.5.3 Adhesive Properties & Use

The optimal adhesive for medical use should have characteristics including; good biodegradability, tissue compatibility, binding strength, safe and low cost (Mommaerts et al., 1996) (See Table 5). No known adhesive fulfils all of the characteristics, however FTAs have many favourable characteristics for medical use; non-toxic, physiological, quick drying, non-inflammatory, high tensile strength and straightforward to use. In addition some publications have proposed that it may reduce operational time compared to suture use. Uses have included the control of haemorrhage in surgical procedures involving cardiopulmonary bypass and traumatic splenic haemorrhage (Kram et al., 1991b). Documented advantages in facial surgery include reduced oedema and haemorrhage and a shorter down-time (Ellis and Pelausa, 1988, Kamer and Nguyen, 2007). There was no fundamental difference in wound healing from fibrinogen and suture fixed facial flaps after extensive skin undermining with total reabsorption of the adhesive in less than one week (Piechotta and Flemming, 1983). The natural degradation of the fibrin clot may be prolonged with the use of aprotinin and increased concentrations of fibrinogen over a period of weeks (Radosevich et al., 1997, Chan and Boisjoly, 2004). FTAs offer the advantage of continuous surface adhesion across the entire wound, compared to multiple point suture fixation, and in doing so may reduce the formation of both haematoma and seroma complications (Gibran et al., 2007).

In ophthalmic surgery, FTA has been used following intraocular vitreoretinal surgery. Suture closure of vitreoretinal ports can lead to suture irritation, discomfort, scleral necrosis, granuloma formation, wound leakage and postoperative astigmatism. FTA has been effectively used to close scleral and conjunctival wounds in patients, reducing suture related complications and hastening postoperative recovery (Batman et al., 2009). FTA have been used in the management of external eye diseases including the treatment of corneal thinning and perforations and ocular surface diseases (Lagoutte et al., 1989, Chan and Boisjoly, 2004, Sharma et al., 2003, Duchesne et al., 2001, Sumich et al., 2003, Watts and Collin, 1992, Grewing and Mester, 1997).

Table 5 Optimal Tissue Adhesive Properties

Adhesive Properties	**FTA**	**Sutures**	**Cyanoacrylate Adhesives**
Non-Toxic	Y	Y	N
Quick drying	Y	-	Y
Non-Inflammatory	Y	N	N
High Tensile Strength	Y	Y	Y
Straightforward to use	Y	Y	Y
Clear to permit vision	Y	Y	N
Permeable to permit fluids, prevent necrosis	N*	Y	N
Physiologically dissolve	Y	N	N
No risk of infection	Y**	N	N
Accessible	+/-	Y	+/-
Cost-Effective	-	Y	+/-

*Very rare reports of skin necrosis with use of FTA (Grossman et al., 2001) , **Small risk of systemic infection, screening of products to prevent transmission (Mommaerts et al., 1996), (Forseth et al., 1992, Panda et al., 2009)

Tissue injury initiates a cascade of local cytokine and growth factor production that leads to localized inflammation, granulation tissue formation, re-eptihelialisation and tissue remodelling (Eby et al., 2001). In animal models the use of FTA has shown accelerated healing with improved revascularization, reduced inflammation and fibrous formation in grafted tissues (Milanov et al., 2004). There is thought to be an optimal level of wound inflammation that results in an effective and uncomplicated healing of a wound. Some degree of inflammation provides a protective role, preventing infection and removing dead material and pathogens, which enabling restoration of normal tissue through collagen formation, angiogenesis and tissue remodelling (Chvapil and Koopmann, 1984, Clark, 1985, Hunt et al., 1984). Excessive inflammation is through to result in hypertrophic scar formation or continued inflammation or localized oedema (Chvapil and Koopmann, 1984,

Niessen et al., 1999). FTAs provide a protective barrier across the wound may function like a fibrin-rich haemostatic clot and some studies have identified an attenuation of the inflammatory response with the use of FTAs. However the evidence is controversial as other studies have identified a mild increase in inflammation (Days 5-30) in FTA wounds compared to controls (Eby et al., 2001, Scardino et al., 1999). Studies have identified an increase in the amount of granulation tissue and angiogenesis in FTA wounds, which hypothetically increase the oxygen and nutrient support to the healing tissue improving the wound-healing process (Dvorak et al., 1987).

There are several types of commercially available fibrin tissue adhesives. Tisseel (Baxter AG Industries, Austria) is a human plasma-derived mixture of thrombin and fibrinogen. The combination of these two products results in fibrin clot formation and effective adhesion between tissue surfaces. The Tisseel product does have a risk of hypersensitivity, allergic and anaphylactic reactions, although no adverse events of this type were reported during clinical trials. There have been reports of urticaria, pruritus and generalized flushing with skin and subcutaneous tissue use. Another FTA, Crosseal used tranxanemic acid rather than aprotinin, and has subsequently been discontinued and reformulated as Evicel (Johnson & Johnson-Wound Management, Somerville, New Jersey)(Lee et al., 2009).

Table 6 Available Commercial FTA products

FTA Commercial Products	Solution	Human fibrinogen (mg/mL)	Human factor XIII (U/mL)	Human thrombin (IU/mL)	Bovine aprotinin (KIU/mL)	Virus-inactivated fibrinogen	Virus-inactivated thrombin
Tisseel, Tissucol (Duo Baxter-Immuno AG, Austria)	Frozen solution	70–110	10–50	500	3,000	Two-step vapour heat at 60°C and 80°C	Two-step vapour heat at 60°C and 80°C
Tisseel, Tissucol (Duo Baxter-Immuno AG, Austria)	Lyophilizate	70–110	10–50	500	3,000	Two-step vapour heat at 60°C and 80°C	Two-step vapour heat at 60°C and 80°C
Tisseel (VH Kit Baxter-Immuno AG, USA)	Lyophilizate		75–115	500	3,000	Two-step vapour heat at 60°C and 80°C	Two-step vapour heat at 60°C and 80°C
Beriplast P (Aventis Behring, Germany)	Lyophilizate	90 (65–115)	60 (40–80)	500 (400–600)	1,000	Pasteurization (liquid solution, 10 h at 60°C)	Pasteurization (liquid solution, 10 h at 60°C)
Hemaseel (APR Haemacure, Canada) (As Tisseel VH Kit Baxter-Immuno)	Lyophilizate	75–115		500	3,000	Two-step vapour heat at 60°C and 80°C	Two-step vapour heat at 60°C and 80°C
Quixil (Omrix Biopharmaceuticals SA, Israel)	Frozen solution	60–100	None	1,000	None (tranexamic acid 92 mg/mL) treatment	Solvent–detergent, pasteurization	Solvent–detergent treatment, nanofiltration
Bolheal (Kaketsuken Pharmaceutical, Japan)	Lyophilizate	80	75	250	1,000	Dry heat (144 h at 65°C)	Dry heat (96 h at 65°C)
Biocol (LFB-Lille, France)	Lyophilizate	127	11	558	3,000	Solvent–detergent treatment	Solvent–detergent treatment
VIGuard F.S. (Vitex: VI Technologies, USA)	Lyophilizate	50–95	3–5	200	None	Solvent–detergent treatment, ultraviolet C light	Solvent–detergent treatment, ultraviolet C light

Modified from: (Jackson, 2001a)

1.5.4 FTA Risks & Complications

The potential disadvantage of FTA is that it is a human product that carries a small but inherent risk of disease transmission. The theoretical risk of infection includes blood-borne diseases such as hepatitis B and C, and immunodeficiency virus. Parvovirus B19 transmission has been attributed to the use of FTA, although generally a mild infection, it may be more serious in pregnancy and neonates (Hino et al., 2000). Since the publication of the report by Hino et al, manufacturers have eliminated this risk by polymerase chain testing for Parvovirus B19 (Jackson, 2001a). There was a theoretical risk of transmission of bovine spongiform encephalopathy from the use of bovine aprotinin, this has been reduced with the use of synthetic aprotinin. The human donors and plasmin product is rigorously screened for known diseases and the products undergo several stages of treatment which substantially reduces this risk of disease transmission (Lee et al., 2009, Pryor et al., 2008). The treatments include solvent-detergents, vapour heat or pasteurization, followed by additional treatments including dry heat, nanofiltration and other viral reduction treatments (e.g. chromatography) (Jackson, 2001b, Jackson, 2001a).

The Preparation of FTAs from plasma requires a series of stages of processing including the isolation of clotting constituents and treatment to eliminate risk of infection transmission (Hartman et al., 1992, Quick, 1967). In summary, the donor plasma is centrifuged to produce a precipitate of fibrinogen and supernatant of thrombin. The thrombin is further treated to convert residual fibrinogen to fibrin followed by filtered removal of the fibrin. The use of autologous platelet-rich plasma does eliminate the risk of infection transmission and potential allergic response. The strength of FTA is related to the fibrinogen concentration, and inter-patient variability of fibrinogen concentration is a source of increased unreliability, and the autologous adhesives have a lower tensile strength that limits their use (Mandel, 1992). The procedure does take longer to process and as a consequence increases both costs and time. Baxter is currently developing a recombinant fibrinogen for commercial use, and other proposed modifications include combination of the FTA with antibiotics and bioengineered stem cells (Yamada et al., 2003, Marone et al., 1999, Kram et al., 1991a).

Although the relative costs of FTA has come down over the past decade, the cost remains greater than conventional suture closure of the skin. The upfront cost of suture material does not take into account the resources required for a postoperative appointment to remove sutures. There are additional savings that have been proposed by FTAs including reduced complications and time of surgery for certain procedures.

1.5.5 Cyanoacrylates

Cyanoacrylates are another type of adhesives that are termed synthetic adhesives. These adhesives are non-physiological and potentially toxic to the human body. These adhesives have been effectively used to close skin following superficial injuries, however the cyanoacrylates are toxic to subcutaneous tissues inciting an acute inflammatory response, foreign body giant cell reaction, neovascularisation and tissue necrosis (Mommaerts et al., 1996). In ophthalmology the synthetic adhesives are most commonly used in the management of small corneal perforations without loss of tissue, however their use is not without potential toxicity (Tseng et al., 1990). Superficial use in the management of eye conditions may result in foreign body reactions such as giant papillary conjunctivitis, and corneal vascularisation and microbial keratitis (Carlson and Wilhelmus, 1987, Vrabec and Jordan, 1994).

1.5.6 Medical use of FTAs

The use of FTAs has had applications in other medical specialties including; general surgery, cardiovascular surgery, vascular surgery, neurosurgery, thoracic surgery, urologic surgery, otolaryngology and plastic and reconstructive surgery (Albala and Lawson, 2006, Lee and Jones, 2005).

The use of FTAs in ophthalmic surgery has become increasingly common over the past 5-years. Sealants have been used for closure of the conjunctiva (Erbagci and Bekir, 2007), corneal surgery (Patel et al., 1993), glaucoma surgery (Seligsohn et al., 2004), vitreoretinal surgery (Mentens and Stalmans, 2007), strabismus surgery(Mohan et al., 2003) and pterygium surgery (Koranyi et al., 2004). These studies have identified advantages over previous surgical techniques with less postoperative pain, reduced surgical time and an absence of complications relating to suture use such as infection, allergy, inflammation and delayed healing (Kavanagh et al., 2009). FTAs use in oculoplastics remains relatively uncommon although the technique has been proposed in eyelid surgery including reconstruction, fixation of free skin grafts and severe entropion (Steinkogler, 1986b).

Fibrin sealants have been found to offer advantages in facial reconstruction with the use of skin grafts, with increased 'take' of grafts at infected sites and reduced wound construction (Brown et al., 1992, Jabs et al., 1992). The use of FTAs in eyelid surgery has been evaluated in relatively few studies (Mommaerts et al., 1996). One study evaluated the used of FTA for skin closure following lower lid blepharoplasty found a reduction in operation time, postoperative ecchymosis and elimination of painful subciliary suture removal. These parameters were not objectively evaluated

and were reported as subjective comments (Mommaerts et al., 1996). Brown et al showed that FTA applied to sutured skin graft significantly reduced wound contraction (Brown et al., 1992). Other studies have shown that FTA assist topical haemostasis and reduce blood loss as a function of graft size (McGill et al., 1997). No study has investigated their effectiveness in a randomized control study.

Table 7 Surgical use of FTAs in Ophthalmology

Ophthalmology Sub-speciality	**Surgery**	**Reference**
External Eye Disease	Pterygium autografts Closure of Conjunctiva Corneal perforation & melt Limbal cell transplantation	(Kheirkhah et al., 2008, Bahar et al., 2007, Uy et al., 2005, Karalezli et al., 2008, Vrabec and Jordan, 1994)
Glaucoma	Management of postoperative bleb leaks	(Seligsohn et al., 2004, Asrani and Wilensky, 1996, Valimaki, 2006, Grewing and Mester, 1997, Freeman et al., Kahook and Noecker, 2006)
Strabismus/ Vitreoretinal surgery	Closure of conjunctiva	(Erbagci and Bekir, 2007, Mohan et al., 2003, Dadeya and Ms, 2001, Biedner and Rosenthal, 1996, Erbil et al., 1991, Batman et al., 2009, Batman et al., 2008)
Skin reconstruction Oculoplastic surgery	skin grafts, reconstruction	(Brown et al., 1992, Steinkogler, 1986a, Mandel, 1990, Mandel, 1992, Jabs et al., 1992, Steinkogler and Kuchar, 1994)

1.6 Surgical Outcomes

The outcomes of surgery have previously been traditionally evaluated by the recording of eyelid measurements and complications following surgery. Eyelid measurements that quantify ptosis would be expected to show improvements following successful surgery e.g. marginal reflex distance, inter-eyelid difference, and provide objective information that enables the comparison of surgical techniques. However these traditional methods of measuring outcome are with limitations, the number of patients willing to undergo further redo surgery is lower that the number of failed operations, as not all patients will be prepared to undergo a second operation when they are dissatisfied with the first operation. The Department of Health (DOH) report "High quality care for all" by Professor Darzi highlighted the importance of developing greater measures of quality and patient reported outcome measures (PROMS) (Darzi, 2007, Horton, 2008). Outcomes for clinical management should include aspects of patient experience, safety and greater transparency of information through publication. In this study three outcome measures were developed that are detailed in section 1.7.

1.7 Research Objectives

This study sets out to evaluate the quality and effectiveness of skin closure following eyelid surgery with conventional sutures compared FTA. In addition the study aimed to define a benchmark by which outcomes following eyelid surgery can be measured. Three patient outcome measures were developed from published studies, including patient satisfaction, surgical outcome and the standardized evaluation of photographs.

The null hypothesis for the research objectives was that there was no difference in outcome between the FTA and suture groups:

1.7.1 Objective I (Surgical outcomes and complications in the FTA and suture groups)

- Were the eyelid measurements following blepharoptosis and blepharoplasty surgery different between the two groups?
- Were the complication rates different between the two groups (e.g. amount of haemorrhage)?

1.7.2 Objective II (Patient satisfaction in the FTA and suture groups)

- Was patient satisfaction different between the two groups?
- Was patient satisfaction different to surgical outcomes?

1.7.3 Objective III (Photograph analysis in the FTA and suture groups)

- Was there a difference in photograph scoring between the two groups?
- Was there a difference of scoring between individual observers?

1.7.4 Objective IV (Comparison between three outcome measures)

- Were the outcome measures between surgical outcomes, patient satisfaction and photograph analysis different?
- Are all of the measures required to define surgical outcomes?

1.8 Project Challenges

High quality clinical research, including the use of randomized control studies that evaluate surgical techniques are rare in the field of oculoplastic surgery and a substantial number of challenges were encountered with the development of this project. Although ptosis is a common condition there are multiple causes and potential confounding variables. To reduce the number of confounding variables, inclusion and exclusion criteria were used to mitigate these variables. The implications for stringent trial criteria were to reduce patient numbers. As a consequence the trial was multi-centred, with recruitment over two hospital sites, and the patient entry ran over a 3-year period. FTAs are a relatively expensive technique at the time of conception of the study and Baxter (AG Industries, Austria) supplied the adhesives without any influence on study findings or conclusions. A further challenge was developing the outcome measures for the study, diagnosis of ptosis and successful outcomes have been relatively ill-defined in the literature. As part of the literature review the best evidence based medicine was used to further develop definitions and outcome measures. The trial took almost 5-years from design to final analysis of results and conclusions.

2.0 Materials & Methods

Randomized Control Study: A randomised control study was developed to evaluate surgical outcome following blepharoptosis correction or upper eyelid blepharoplasty, and skin closure with fibrin tissue adhesive compared to conventional sutures. The trial underwent complete ethical approval (Appendix 1) and complete pilot study before commencement. Patients were entered into the trial over a 3-year period according to the trial protocol (inclusion and exclusion criteria) and to multiple centres in London (Charing Cross Hospital and Western Eye Hospital) from 2003-2006.

Outcome measures: The literature was reviewed for methods of evaluation of skin closure and the grading of surgical outcome. The definition of patient outcome was derived with three specific elements listed below.

1. Surgical outcome defined by measurements of eyelid position and complications e.g. haematoma, infection, further surgery.

2. Pre and post-operative measurements and photographs were taken at each out-patient appointment. The aesthetic appearance was evaluated by independent evaluation of standardized photographs by three independent consultants. Published criteria were used for the grading of both facial appearance and quality of scar.

3. Patient satisfaction was evaluated by a published questionnaire of patient outcome.

2.1 Study Design

2.1.1 Ethical approval

Ethical approval by Local Research Ethics Committee (LREC) was completed before the study was commenced (Appendix 1).

2.1.2 Patient Selection

There may be unpredictability with the results of ptosis surgery, with approximately 10% of procedures being complicated with over or under correction. One of the limitations of previous studies has been the mixture diagnoses that have been evaluated in the same study (e.g. ptosis secondary to different aetiologies undergoing a range of a patient specific procedures including brow, upper and lower eyelid surgery). Ageing of the upper lid often co-exists with aging of the brow, mid-face and other facial changes. Additional procedures such as brow elevation, combinations of upper and eyelid procedures have been evaluated in previous studies with FTAs however does result in greater variability of the results. In this study there were defined inclusion and exclusion criteria to minimize the potential for confounding variables.

Inclusion Criteria

1. Patients requiring blepharoplasty procedure for involutional blepharoptosis or dermatochalasis
2. Informed consent obtainable
3. Patients available for follow-up 12 months after surgery

Exclusion Criteria

1. Previous eyelid surgery e.g. Tumour excision, ectropion, entropion, blepharoplasty
2. Non-involutional aetiology of ptosis or dermatochalasis
3. Complicated systemic conditions e.g. Thyroid eye disease
4. Patients with only one functional eye
5. Patients medically unfit for surgery or contraindications for FTA use e.g. pregnancy

2.1.3 Confounding factors

Eyelid height following ptosis surgery is unexpectedly high or low in approximately 10% of ptosis corrections. There a variety of potential confounding factors that influence the outcome following ptosis surgery and in this study steps were taken to mitigate these potential confounders.

Although the surgical procedure was standardized there remain sources of variability within the study. For example, the local anaesthesia contained a low concentration of adrenaline that was used to reduce intra-operative haemorrhage. Although the volume of anaesthetic and adrenaline were standardized between cases (1:200 000), its effects may vary on individual patients, tissue concentration and the direct effect of the adrenaline on the sympathetically innervated Müller's muscle that elevates the eyelid. Although the effect of the adrenaline is thought to be relatively small, they may cause postoperative variability in eyelid height.

Table 8 Confounding factors effecting postoperative eyelid height

Confounding Factor	**Mitigation**
Involutional ptosis	Exclusion of non-involutional ptosis Classification into mild, moderate and severe ptosis
Systemic conditions	Exclusion of systemic conditions known to effect eyelid height e.g. myaesthenia gravis
Pre-existing Ocular conditions	Exclusion of ocular conditions and factors known to effect eyelid height e.g. previous ocular surgery, history of contact lens wear
Intra-operative factors	Standardized operation, supervision by a single consultant surgeon (JMO)
Post-operative factors	Standardized post-operative procedures

Previous publications evaluating the use of FTAs on eyelid surgery have had considerable variability in diagnosis, surgical procedure and definition of surgical outcome. The variability in these studies makes comparisons between FTAs and non-FTA skin closure difficult to evaluate. There are very few RCTs that have evaluated the use of FTAs and no previous study has specifically evaluated skin closure following blepharoptosis or dermatochalasis.

Table 9 Published Studies on FTA use in Eyelid Procedures

Study	Patient Selection	Surgery	Surgical Outcome
(Mandel, 1990)	Upper and lower eyelid blepharoplasty, 16 patients	Mixture; facial and other procedures	Retrospective case series, recorded complications
(Mandel, 1992)	Upper and lower eyelid blepharoplasty, 32 patients	Mixture; facial and other procedures	Retrospective case series, recorded complications
(Mommaerts et al., 1996)	Heterogeneous mixture, mostly lower eyelid blepharoplasties, 18 eyelids	combined with brow and upper eyelid procedures	Non-randomized compared with suture closure, photograph analysis of scar
(Oliver et al., 2001)	Not discussed, aesthetic indications, 20 patients	Rhytidectomy	RCT, Haemorrhage from drains only
(Grossman et al., 2001)	Mixture of facial aesthetic procedures, 105 patients	Mixture; forehead, eyelid, midface & neck	Retrospective case series, recorded complications
(Foster et al., 2006)	No mention of diagnosis or aetiology of ptosis, 33 patients	Müller muscle-conjunctiva resection	Retrospective case series

2.1.4 Randomization

Patients that were diagnosed with involutional ptosis or dermatochalasis underwent preoperative assessment including evaluation against the checklist of inclusion and exclusion criteria. Randomization to the FTA or suture group was provided with sealed envelopes containing the treatment group, which were opened at the time of operative planning. Bilateral eyes were randomised as a singularity to as it was considered that a symmetrical procedure was ethical and the different surgical technique may result in an asymmetrical unsatisfactory outcome. Masking (blinding) with

respect to treatment was not possible following surgery because the distinctive attributes of treatment modalities.

2.1.5 Sample Size Justification

Sample size justification was completed using the most recently published FTA trial when the study was designed in 2002 (Table 9). No randomized control study has not been published that provided a measure of outcome in both FTA and no FTA groups. It was recognised that haemorrhage drained was not an ideal indicator of sample size as the level of haemorrhage in blepharoplasty surgery is generally very small, the measure provided the most objective measure available for the power calculation.

	FTA	**No FTA**
Total haemorrhage drained/ mls		
Mean	10	30
Standard deviation	21.16	37.74

OLIVER et al. 2001. A prospective, randomized, double-blind trial of the use of fibrin sealant for face lifts. *Plast Reconstr Surg,* 108**,** 2101-5, discussion 2106-7

Statistical calculation of patient numbers:

Haemorrhage drained mean (sd)

With use of FTA 10 (21.2)

No FTA 30 (37.7)

Using sample size formulae m= 2x[z(1-a/2)+ z(1-b)]2/ (delta)2

Calculating values for a significance level of 5% (z(1-a)2 = 1.96) and a power of 80%

m= 2x [1.96+1.2816]2/ (sd)2

m=24

2.2 Fibrin Tissue Adhesive Preparation

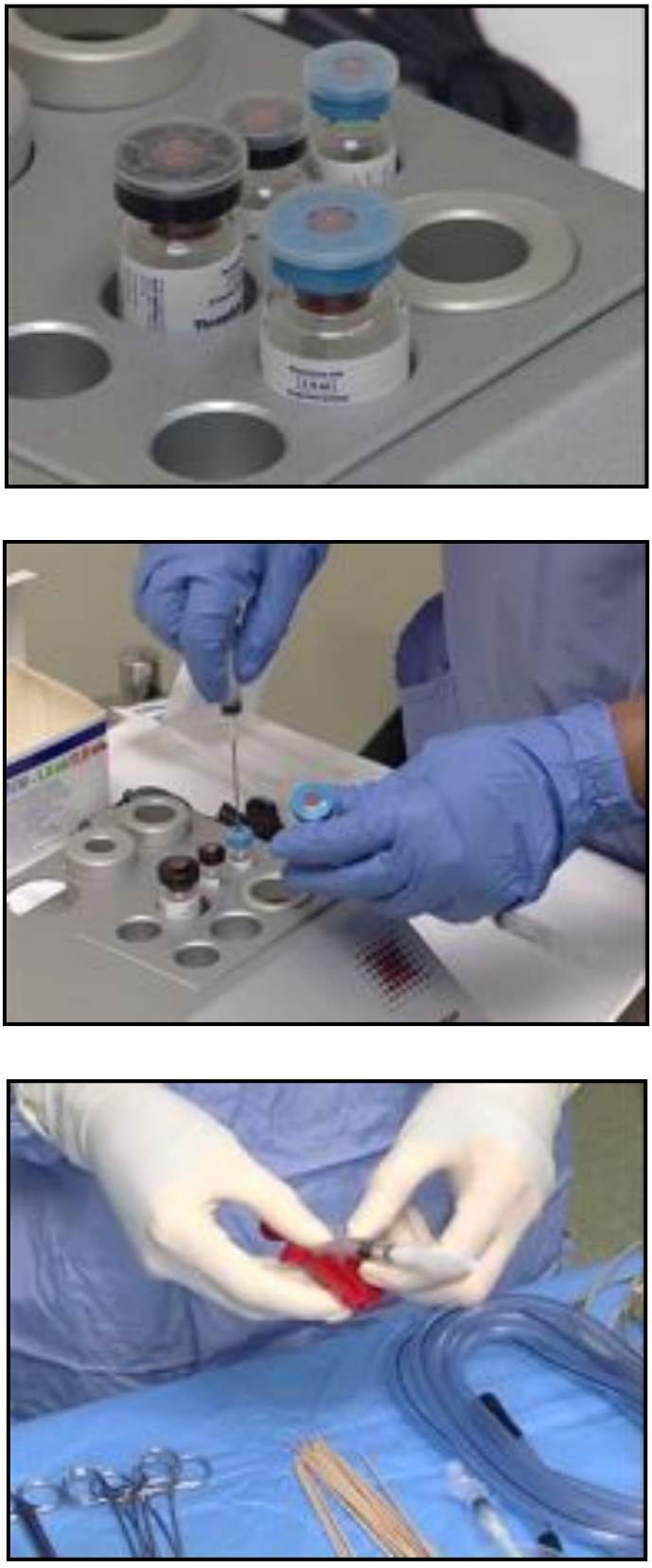
The Tisseel FTA was available as a commercial kit and was prepared in accordance with the manufacturer's instructions. The Tisseel kit was stored between 2 to 8°C before use. The product was prepared approximately 20minutes before use, with the components stored in four separate vials; 2 vials of solvents and 2 vials of powders. The Tisseel protein concentrate (containing human fibrinogen, plasminogen, plasma fibroectin, factor XIII) was reconstituted in the fibrinolysis inhibitor solution (bovine aprotinin). The dried human thrombin was reconstituted in the calcium chloride solution.

Table 10 FTA Constituents

	Vials	**Components**
Constituent 1	Protein concentrate	Fibrinogen, Plasminogen, fibronectin, Factor XIII
	Fibrinolysis inhibitor solution	Aprotinin
Constituent 2	Dried protein	Thrombin
	Solution	Calcium chloride

The Tisseel kit was prepared approximately twenty minutes before use. The two components were preheated (10 minutes) before being mixed in a magnetic spinner on a heating plate (15minutes) and then inserted into a specialized "Duploject" syringe (Hyland Division, Baxter Laboratories Corporation) (Figure 6). The syringe mixed the components at its tip for application to the two wound surfaces. Once mixed the sealant takes only one minute to activate and three minutes to solidify. The adhesive is only prepared immediately prior to use, and the skin tissues fully prepared before application of the FTA (Giampapa and Bitar, 2002). The thrombin comes in two concentrations (500IU and 41IU/ml) these result in a fast and slow setting solution respectively. The fast setting solution was used for skin closure and previous reports of the slow setting mixture have suggested it is unreliable for skin approximation (Mommaerts et al., 1996).

Figure 6 FTA Preparation



Upper: Preheating of constituents, Centre: Reconstitution of aprotinin, Lower: Insertion of syringe into Duploject

2.3 Surgical Procedure

2.3.1 Blepharoptosis surgery

The blepharoptosis was performed by a senior oculoplastic fellow under the supervision of a single consultant (JMO) by a previously reported technique (Anderson and Dixon, 1979b, Anderson and Dixon, 1979a, Mandel, 1990, Mandel, 1992, Linberg et al., 1988). All the procedures were performed under local anaesthesia with sedation as this enabled lid height, contour and symmetry to be adjusted using patient cooperation during the operation. The local anaesthesia use was combination of lidocaine 1% and bupivocaine 0.25% with 1:200 000 adrenaline. The bupivocaine has a longer half-life and provides postoperative analgesia. The low concentration adrenaline reduced local haemorrhage and aids in prolonging the effect of the local anaesthesia. A small volume of local anaesthesia (<1 ml) was injected subcutaneously, care was taken to ensure the anaesthesia was not injected deeply through the orbital septum as it may alter the levator superioris and Müller's muscle action. In the past, patients had surgery under general anaesthesia with a predefined "cookie-cutter" surgical technique that had limited results. To increase the postoperative predictability and consistency local anaesthesia was adopted as it enabled voluntary involvement of the patient to adjust lid height intraoperatively.

The surgical technique has been previous described by Anderson and Dixon (Anderson and Dixon, 1979b, Anderson and Dixon, 1979a), a summary is described below: Preoperative marking of the skin crease and excess skin was conducted with the patient in the supine position. A skin crease incision was made and the excess skin and underlying orbicularis muscle excised as a single crescent shaped flap (Figure 6). The orbicularis was then tented upwards and a full thickness incision made through the orbicularis to the anterior tarsal surface with the scissors perpendicular to the tissues. The orbicularis incision was then completed with a minimal number of cuts to reduce unnecessary haemorrhage from multiple incisions. Blunt dissection with a cotton bud was used to identify the orbital septum and levator aponeurosis. The orbital septum was opened and to aid identification of the levator aponeurosis the patient was asked to look up and down which corresponded to movement of the aponeurosis. If the fat pads were found to have prolapsed on preoperative examination they were identified, freed and excised with meticulous attention to haemostasis. The aponeurosis edge and posterior surface was released and the aponeurosis was reattached to the mid-tarsus with three 6/0 absorbable mattress sutures (Vicryl, polyglactin 910) (Figure 7). With each suture the eyelid was everted to ensure partial thickness tarsal bites to avoid secondary corneal erosions. The first central suture was placed just medial to the mid-pupillary line (highest point of eyelid) and two subsequent sutures medial and lateral to the first (Figure 8). The eyelid height and contour were checked with the patient looking in up and downgaze before the sutures were tied off, with the aim of 1mm overcorrection as there is usually a small drop of 1mm eyelid height in the postoperative period as a

consequence of the adrenaline and local anaesthetic effects having worn off. If the eyelid height was too high or too low, or the eyelid contour unsatisfactory, the suture positions on the levator or tarsus were adjusted accordingly. The skin crease was internally reformed using three 6/0 interrupted sutures (Vicryl) from the edge of the levator aponeurosis then through the lower orbicularis but not through the epidermis. The skin was then closed in accordance with its preoperative randomization to the FTA or suture groups.

Figure 7 Skin Crease Incision & Crescent Shaped Blepharoplasty

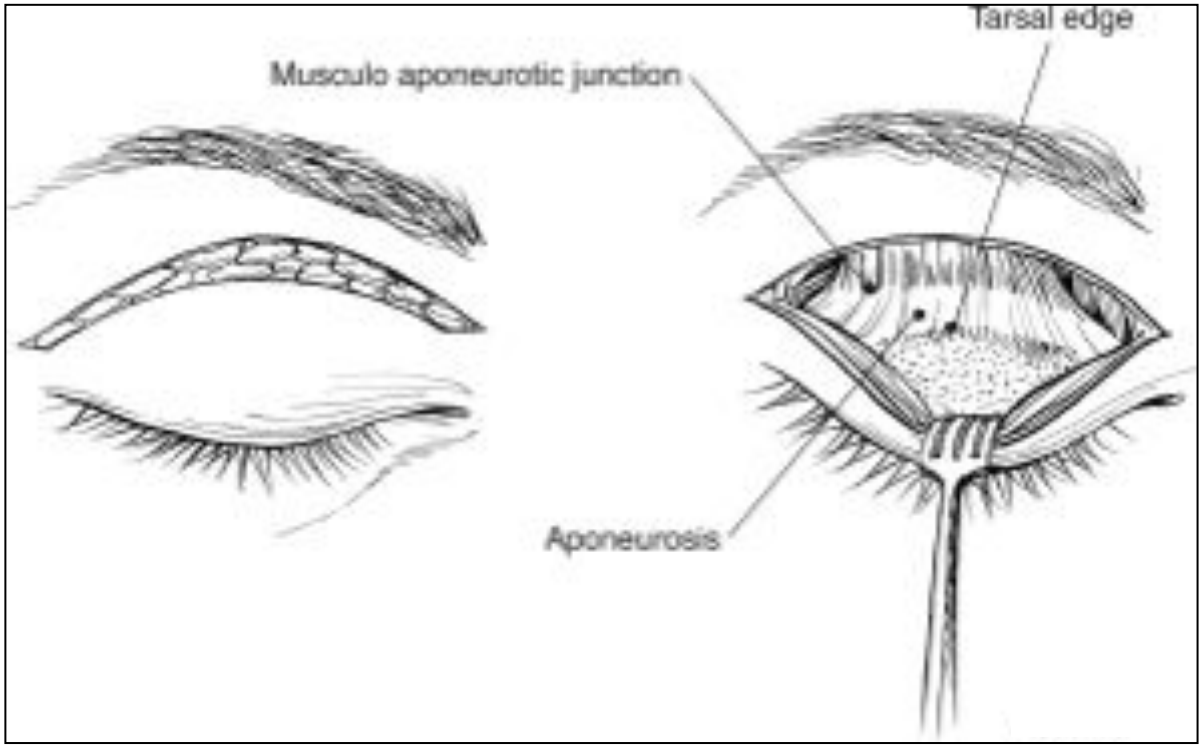


Figure 8 Aponeurosis Edge & Posterior Surface Release

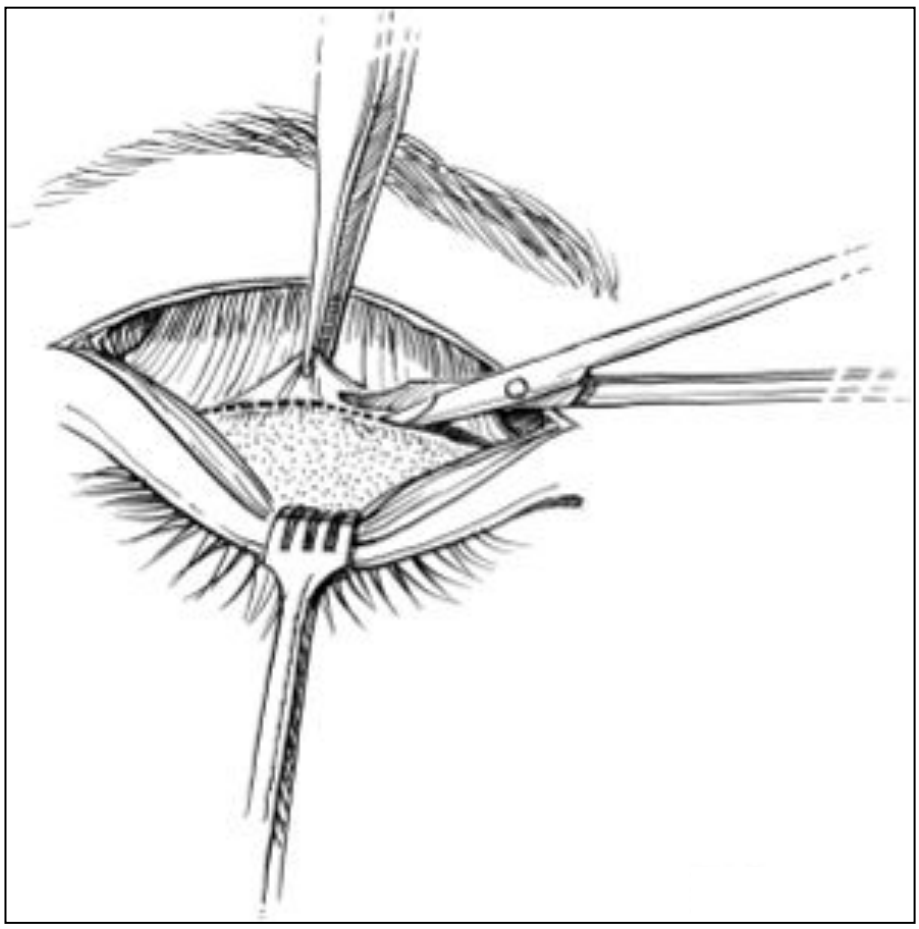
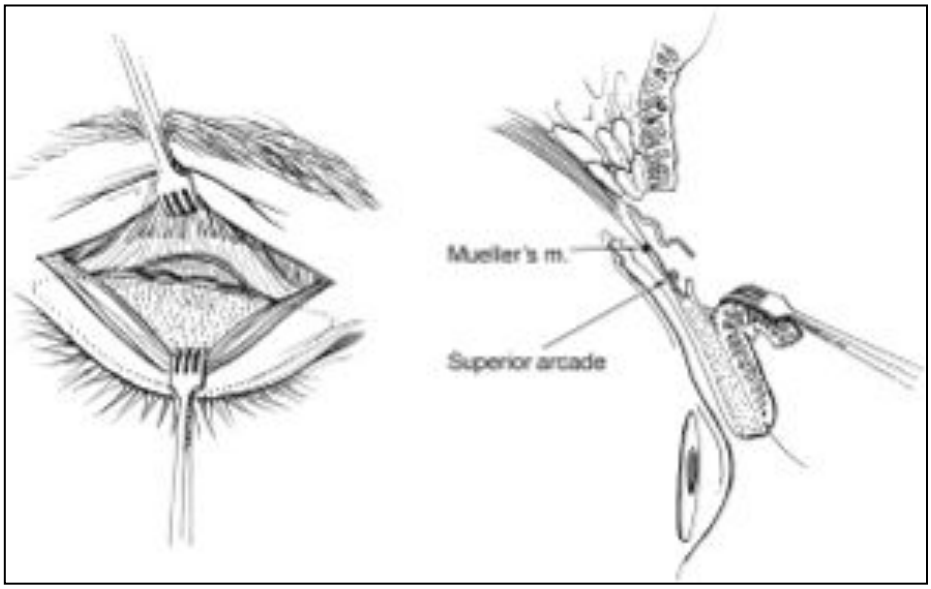
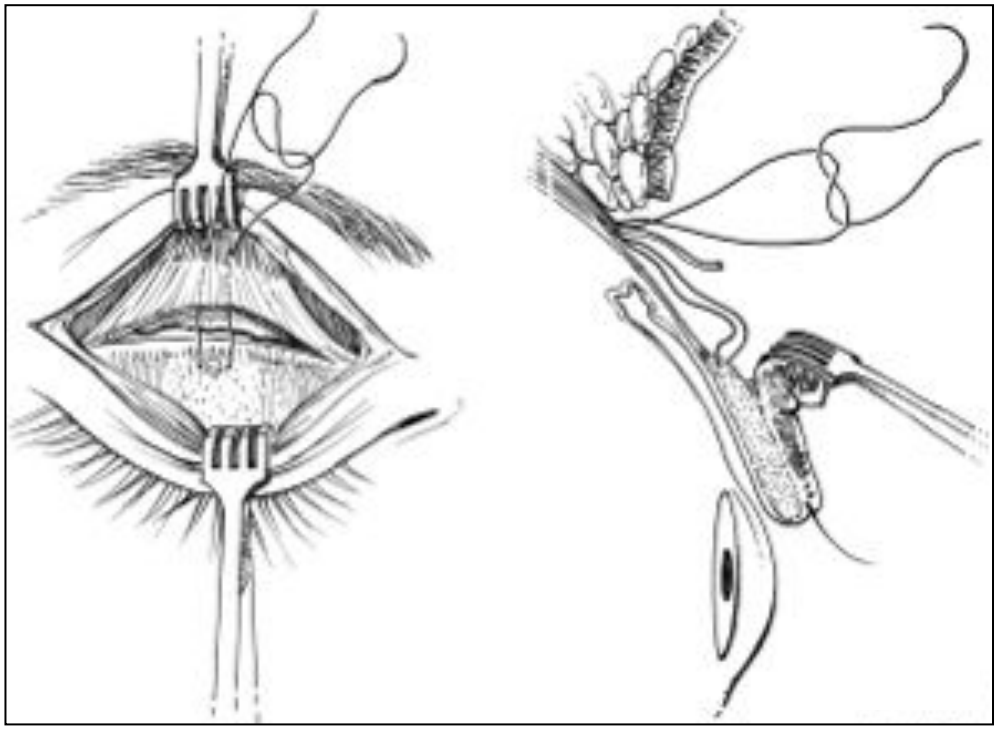


Figure 9 First Central Suture Just Medial to the Mid-Pupillary Line





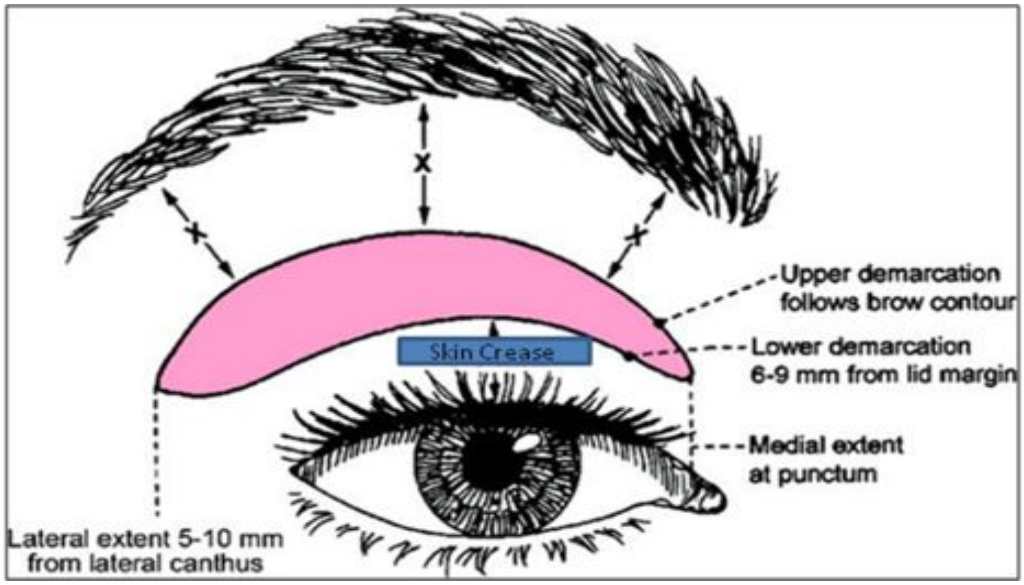
Acknowledgement for Figures 7-9 from McCord: (McCord et al., 2007)

2.3.2 Blepharoplasty surgery

The patients underwent preoperative marking of the excess upper eyelid skin and fat pad prolapse with the patient in the supine position, conservative excision was planned to ensure adequate closure of the eyelids post-operatively with a minimum residual measurement of 20mm from brow to upper lid margin. Local anaesthesia was applied subcutaneously under sedation in an identical manner to the blepharoptosis surgery. The surgical technique used was a relatively standard technique that has been summarized below (Fagien, 2002, Rohrich et al., 2004, Siegel, 1992). Skin excision was completed, followed by excision of a thin strip of orbicularis muscle. In patients where fat prolapse had been preoperatively identified and marked, the orbital septum was opened and fat excision completed with meticulous care to maintain haemostasis of the adipose tissue.

In the suture group, the skin was closed with 7/0 interrupted absorbable sutures (Vicryl) or continuous 6/0 non-absorbable suture (Ethilon) along the length of the incision. The wound was covered with a paraffin gauze dressing (Jelonet, Smith & Nephew) and bandaged for one hour.

Figure 10 Blepharoplasty Preoperative Marking



Acknowledgement for Figure, modified from (Rohrich et al., 2004)

2.3.3 FTA Application

In the FTA group, the adhesive (Tisseel: Baxter AG, Vienna, Austria) was reconstituted in accordance with the manufacturer's instructions approximately twenty minutes before use. The two constituents were inserted into a Y-shaped delivery system that ensured equal volume mixing of the two components immediately prior to application.

Meticulous attention was taken to ensure an absence of active haemorrhage and wound tension. The FTA was applied to the skin edges with apposition of the everted skin edges with two pairs of forceps for two minutes (Figure 10). The wound was checked for gapes and where necessary further FTA applied. The excess FTA was not wiped off and no dressing or antibiotic ointment was applied. A Cartella eye shield was used to protect the skin at night for the first week.

Figure 11 Intra-Operative FTA Application

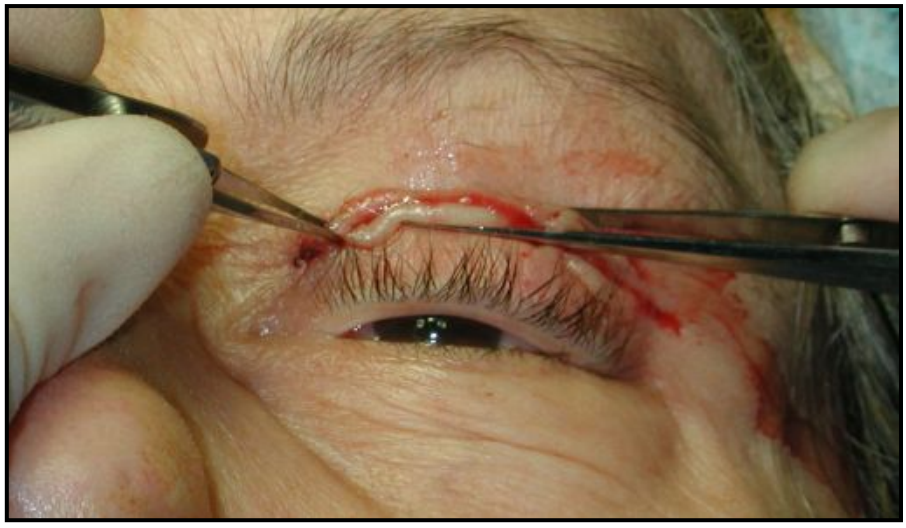
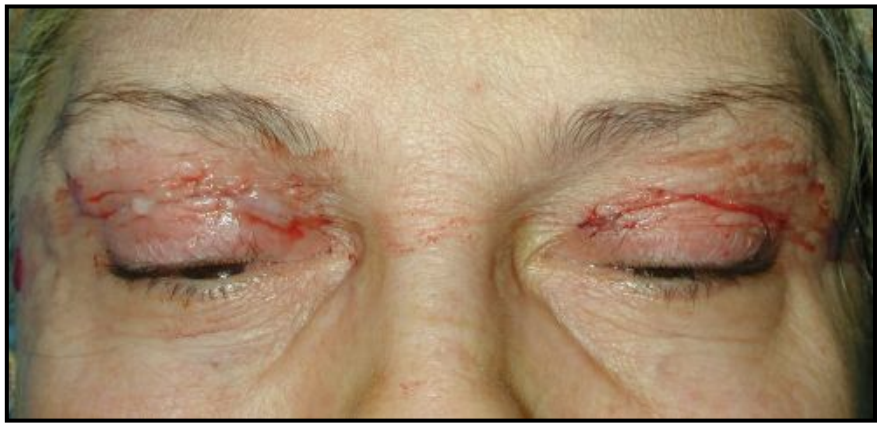


Figure 12 Post-FTA Application



2.3.4 Postoperative Management

Hypromellose (0.3%) and chloramphenicol (0.5%) drops were applied four times a day and chloramphenicol ointment (1%) once at night for a two-week period. Patients were advised to sleep with the head of the bed elevated with 2-3 pillows and to commence cold compresses 24 hours after surgery, applying the compress for 10-15 minutes, approximately 8x day for one week.

All patients attended postoperative outpatient appointments at 1 week, 3 weeks and 4 months. At each appointment assessment included visual acuity, intraocular pressure, lid measurements and standardized digital photographs.

2.4 Outcome Measures

2.4.1 Surgical Outcomes

The development of objective outcome measures for surgical procedures can be challenging to define. There are often multiple different parameters that can be measured some with greater objectivity (e.g. eyelid measurement) and some equally important yet less well defined criteria (e.g. asymmetry). The definitions can be controversial and developing outcomes that can be utilized in widespread clinical practise, such as PROMs, are not straightforward.

Surgical results from ptosis correction are commonly described in absolute proportions of success or failure. Closer evaluation of the definition of success however does identify different definitions of success, for example within 1mm of the desired height at 7-years is completely different to <0.5mm inter-lid difference at 3-months (Table 11). In addition there are multiple confounding factors that may influence outcomes, including the grouping of different aetiologies of ptosis and both surgical technique and experience. The large variations in success rates from 74% to 95% are a reflection of the considerable variability in study criteria.

Table 11 Publications of Involutional Ptosis Success Rates

Authors	Diagnosis, Surgery, Follow-Up period	No. of Eyelids	Definition of Success	Success
(Older, 1983)	Acquired ptosis, 6-months to 7-years	113	<1mm of desired height	95%
(Collin, 1986)	Involutional ptosis, anterior or posterior approach, up to 8-years	105	Absence of redo surgery	87%
(Berlin and Vestal, 1989)	Involutional ptosis, 6-weeks	174	Margin reflex distance 2-4mm	74%
(Shore et al., 1990)	Blepharoptosis, levator resection	157	Unsatisfactory results Absence of redo surgery	82% 88%
(Liu, 1993)	Levator function >8mm, single stitch, 1.5 to 8 years	169	Absence of redo surgery <1mm of desired height	93% 95%
(Tucker and Verhulst, 1999)	Involutional ptosis, anterior approach, 2 to 24-months	164	Absence of redo surgery <1mm of desired height	82% 95%
(Meltzer et al., 2001)	Single stitch, anterior approach, 3-months		<0.5mm inter-lid difference	90%
(McCulley et al., 2003)	Acquired ptosis, 6-weeks to 1-year	828	Absence of redo surgery Within desired range	91% 77%
(Frueh et al., 2004b)	Involutional ptosis, single stitch,	49	Absence of redo surgery, <0.5mm inter-lid difference, & 2-4 marginal reflex distance	98% 75% 67%
(Scoppettuolo et al., 2008)	Involutional ptosis, UK audit	223	1.Margin reflex distance 3-5mm 2.Interlid difference ≤1mm 3.Interlid crease ≤2mm 4.Symmetrical contour 5.Absence of redo surgery	74% 87% N/A N/A 97%

The outcomes used in this study were developed from the best evidence-based medicine (EBM) on surgical outcomes following blepharoptosis surgery. One of the landmark papers in the UK, was a national audit on ptosis surgery, that defined a number of surgical outcomes for ptosis surgery (Scoppettuolo et al., 2008). These outcome measures were developed by the British Oculoplastic Surgery Society (BOPSS) following consultant discussion (Scoppettuolo et al., 2008). These outcome measures developed by BOPSS focused on marginal reflex distance, this excluded errors induced by measurements of the lower eyelid position, which may itself be affected by confounding factors unrelated to the ptosis such as laxity or retraction. Ptosis was defined as drooping of the upper eyelid with a reduced marginal reflex distance of ≤2mm. Other measurements of the eyelid that have been used to describe successful outcome include interlid difference, lid show and skin crease and are shown in the table below.

Table 12 Definition of Successful Surgical Outcome

	Outcome Measure	**Definition of Success**
1	Margin reflex distance	3-5mm
2	Interlid marginal reflex difference	≤1mm
3	Interlid crease difference	≤2mm
4	Interlid show difference	≤2mm
5	Symmetrical lid contour	Yes
6	Redo surgery	No
	Complete success	All criteria met
	Partial success	One or more of the measurements was outside the defined range

Complications

The complications of ptosis can be classified anatomically into those affecting the skin relating to the skin, complications of the periocular tissues, generalized complications and very rare vision threatening complications.

Complications that are related to skin closure include the development of localized inflammation and granuloma formation, which may require conservative management with anti-inflammatory ointment or surgical intervention. Dehiscence of the wound may require surgical intervention and closure of the skin. Complications relating to the transcutaneous skin incision include scarring and absent crease, these maybe related to both the method of skin closure and the surgical technique. Seroma and necrosis are both very rare complications of eyelid surgery, however they have reported in patients who have undergone surgery with skin closure with the use of FTAs (Putterman and Urist, 1976, Smith and Nesi, 1979).

Complications relating to the eyelid height include overcorrection, undercorrection and unsatisfactory contour or asymmetry. Undercorrection, the most common complication relating to lid height may result from inadequate resection or elevation of the levator, failure to identify the anatomical structures, excessive scarring or misplaced sutures, and occurs in 10-15% of cases. Overcorrection results increased lagophthalmos, dry eye syndrome and keratopathy, preoperative assessment for dry eye and cautious patient selection are important to prevent this complication, lagophthalmos is common immediately after upper eyelid blepharoplasty and usually resolves (Lelli and Lisman). Hypertrophic scarring has been reported more in oriental and Afro-Caribbean patients, however no cases of keloid have been described following eyelid surgery (Lowry and Bartley, 1994).

Permanent visual loss is very rare after upper eyelid blepharoplasty, however may occur as a result of retrobulbar haemorrhage, globe perforation, ischaemic optic neuropathy and others (DeMere et al., 1974, Hass et al., 2004). Retrobulbar haemorrhage is the most common of the permanent visual loss with an approximate risk of one in 10, 000. Retrospectively there are often predisposing factors including hypertension, vascular disease and anticoagulation, however these factors are common in patients with involutional blepharoptosis (Lelli and Lisman, 2010).

Common generalized complications that occur in the majority of patients include some ecchymosis (bruising) of the tissues and swelling. The presence of severe swelling or bruising maybe pathological and indicate a more serious complication e.g. haematoma. Infections of the eyelids following surgery are uncommon complications, topical antibiotics are used routinely to reduce this risk. Elevation of the eyelid, often results in lagophthalmos and increased dry eye symptoms, these

usually settle over a period of weeks, however in some patients dry eye and exposure keratopathy may cause long-term symptoms.

Table 13 Complications of ptosis and blepharoplasty surgery

Classification	Complication	References
Low Morbidity		
Acute	Inflammation	(Grossman et al., 2001, Gausas, 1999, Lowry and Bartley, 1994, Morax and Touitou, 2006, Murakami and Plant, 1994) DeMere et al., 1974)
	Granuloma	
	Infection	
	Dehiscence	
	Haematoma	
	Inclusion cysts, milia	(Adams and Feurstein, 1986)
	Hypersensitivity, allergy, urticaria, pruritus*	(Lee et al., 2009)
Medium-Long Term	Undercorrection/ Overcorrection	(Collin and Tyers, 1985) (Collin, 1979, Beard, 1972, Rycroft, 1967, Tucker and Cabral, 2000)
	Asymmetry/ Absent skin crease/ Hypertrophic (prominent skin crease)	
	Dry Eye Syndrome & Lagophthalmos	
	Diplopia	(Syniuta et al., 2003)
	Lacrimal Gland Prolapse	(Smith and Lisman, 1983)
	Periocular pigmentation	(Adams and Feurstein, 1986, Putterman, 1983)
High Morbidity		
Localized	Necrosis	(Putterman and Urist, 1976, Smith and Nesi, 1979)
Generalized	Anaphylaxis	(Lee et al., 2009, Radosevich et al., 1997)
Permanent Visual Loss (0.0045% = 1 in 10 000)	Retrobulbar Haemorrhage	(DeMere et al., 1974, Hass et al., 2004)
	Globe perforation	(Darlington et al., 2006)
	Ischaemic optic neuropathy	(Kordic et al., 2005)
	Other: e.g. Angle closure glaucoma	(DeMere et al., 1974, Wride and Sanders, 2004, Moser et al., 1973)

* Hypersensitivity, allergic and anaphylactic reactions, although no adverse events of this type were reported during clinical trials

2.4.2 Photograph Analysis

Historically the evaluation of surgical results was focused on surgical outcomes that could be measured such as eyelid height or palpebral aperture, complications that could be identified by retrospective records or by straightforward observation of symmetry. The subjective evaluation of symmetry and aesthetic result is fraught with bias and provides poor quality of evidence based medicine (Parsa et al., 1998, Most et al., 2002). The use of standardized photographs that are evaluated by masked observers is a more objective evaluation of outcomes. The use of three observers and repetition on more than one occasion enables statistical analysis to evaluate the inter-test and intra-test reliability. This was the adopted methodology for this study to measure surgical outcome.

Photographs were taken of each patient at each post-operative appointment 1-week, 3-weeks and 4-months. All photographs were taken in standardized positions: primary gaze, upgaze, downgaze and high magnification of the surgical wound. The photographs were collated and randomly allocated to a PowerPoint slide (Microsoft Office, 2007). The masked photographs were then graded by three senior ophthalmic specialists who were not directly involved in the study other than to assess the outcomes. The reviewers were unaware of the treatments used in the study, assignment to suture or FTA group, time point of assessment or the identity of the patient or operating surgeon. The scoring was repeated one month later on a second occasion with the identical photographs presented in a different order.

The data obtained was analyzed using Spearman's rank correlation coefficient for intra- and inter-observer reliability (in addition to Bland Altman plot). To provide an overall assessment of the scar the two scores of each of the three examiners were averaged. The method of analysis was similar to that used by Mommaerts et al to compare the results of a heterogeneous group of patients that underwent photograph analysis of eyelid surgery (Mommaerts et al., 1996). A modified scoring system was developed based on the publications of both ptosis and scar evaluation. The scoring included the overall appearance and symmetry of the eyelids and a more detailed analysis of the scar shown in the table below.

Table 14 Photograph Evaluation of Outcome

Scoring		**Normal**	**Suboptimal**
Ptosis Evaluation (Frueh et al., 2004a, Carter et al., 2001, Feibel et al., 1993)	Superior lid crease	0	1
	Eyelid contour	0	1
	Superior sulcus	0	1
	Compared to pre-op	0	1
	Step-off border (borders not in same plane)	0	1
Scar Evaluation (1-4) (Hollander et al., 1995, Mommaerts et al., 1996, Toriumi et al., 1998, Greene et al., 1999)	Contour irregularity (wrinkled skin near wound)	0	1
	Margin separation (gap between sides)	0	1
	Edge inversion (wound not everted)	0	1
	Excessive inflammation (swelling, oedema)	0	1
	Overall cosmetic appearance	0	1

2.4.3 Patient Experience

The World Health Organization defines health as the state of "complete physical, mental and social well-being". Historically healthcare have been physician-centred and outcome measures focused around physical outcomes, surgical complications and procedure related measurements (Laine and Davidoff, 1996). There is an increased requirement to place patient's well-being at the centre of healthcare provision and ensure a patient-centred service. A combination of social changes with increased consumerism, media and access to information through the internet has fuelled increased levels of patient education and expectation (Neuberger, 2000). The measurement of patient experience and PROMs following facial surgery has importance for both functional and cosmetic procedures. Increasing importance has been placed on demonstrating the benefits of eyelid surgery to patients, to justify surgical intervention and demonstrate that surgery is both of low risk and high quality (Darzi, 2007).

There are few studies that have evaluated outcomes from facial surgery and none for eyelid procedures from the patient's perspectives. The patient's perspective is of critical importance in determining success and the primary determinant of patient satisfaction, yet measures of patient experience have been poorly developed (Ford et al., 1997, Linder-Pelz, 1982). There is evidence that greater patient satisfaction is associated with increased patient compliance with medical recommendations, reduced malpractice suits and increased profitability (Neuberger, 2000, Sherbourne et al., 1992, O'Brien et al., 1992, Hart et al., 1990, Hickson et al., 2002, Levinson et al., 1997). Although patient experience in its simplest form may involve straightforward questions, caution must be taken in interpreting simplistic measures as they are often inaccurate and subject to bias (Parsa et al., 1998). The medical literature is fraught with studies proposing a vague notion of patient experience (Alsarraf, 2002). For example, a surgeon verbally asking a patient in their clinic regarding the outcomes is likely to produce biased results as patients may not feel comfortable in answering such questions if they are negative and with implications to their future care, yet in the past this would have not been atypical. Therefore to measure patient experience requires adequate resources to support the development of validated questionnaires with a team of skilled researchers and surgeons. Effective and accurate questionnaires must be tested for validity, reliability and sensitivity to measure change.

The data collection may include a wide spectrum of assessment tools that collect information from either written or oral means, show in Table 16. The form of data collection includes three principal areas of measure. Firstly "*procedural satisfaction*" which is the most commonly measured outcome including satisfaction with the procedure itself, recovery period, side effects and complications. Without attention to methodology, bias that favours a more positive experience may

be introduced, for example a surgeon asking patient for satisfaction in the clinic. Secondly, "*functional and symptom improvement*" for example in blepharoptosis surgery symptoms measured prior to surgery could include reduced field of vision, reduced vision, difficulty with lifestyle measures such as driving. Post-surgery the same measures are reassessed. Thirdly "*psychological functions*" that includes self-perception, self-concept and psychological functions. Self-perception of facial appearance includes willingness of patient to change their appearance and to have additional procedures. Self-concept includes aspects of self-esteem, confidence, negative feelings on oneself and embarrassment of appearance. Psychological functions include anxiety, depression, avoidance of social situations and ability to enjoy life.

Despite a need for quantitative assessment of quality of life measures there is a relative paucity of research activity defining such outcome measures for facial procedures. Kosowski conducted a literature review to identify PROMs that has been developed to evaluate facial surgery outcomes (Kosowski et al., 2009). Only nine tools were identified that presented "*true*" PROMs and each had some limitations with respect to its data collection, data measures or validation. This review highlighted the challenges in developing accurate and effective PROMs and the need for specialized personnel and adequate resources for the development of useful outcome measures.

Table 15 Patient Reported Outcome Measures (PROMs)

Method	**Tools**
Data Collection	Written: Analogue scores
	Written: Validated questionnaire
	Oral: Structured interviews
	Oral: Patient groups
	Oral: Expert opinion
Data measures	Procedural satisfaction
	Functional/ symptoms
	Psychological functions (Psychological well-being, Self-perception, self-concept)
Test Validation	Reliability (inter-person, intra-person)
	Validity (compared to other measures)
	Responsiveness (sensitivity of measure)
	Acceptability
	Confounding factors/ Errors (e.g. missing data)

Modified from: (Kosowski et al., 2009)

The field of ophthalmology and the sub-specialty oculoplastics has limited research on patient expectations with the exception of outcomes following cataract surgery (Dawn and Lee, 2004, Tielsch et al., 1995). Although the subject of patient expectations has received increased attention and research in recent years the majority of research has been in the primary care setting and may have limited accuracy in the evaluation of surgical procedures.

A variety of measures of patient experience have been developed each with both advantages and limitations. The commonest limitations of patient experience tools were highlighted by Isenberg and Rosenfeld (Isenberg and Rosenfeld, 1997). The principal limitations included a lack of resources

for data collection, analysis and interpretations, inadequate communication between the tool researchers and the clinicians, and overly complex and long questionnaires that are limited in their practical application.

In this study we adopted a patient experience questionnaire that had previously been utilized, shown in Appendix 8 (Alsarraf, 2000, Alsarraf, 2002, Alsarraf et al., 2001). The questionnaire had previously been validated with excellent test-retest reliability and internal consistency (reliability coefficient $P<0.001$) (Alsarraf et al., 2001, Jaggi et al., 2009). In addition the test was straightforward to perform and took only a few minutes to complete. Each response was scored from 0 to 4, with the most negative response scoring a 0 and the most positive response scoring 4. The total of six questions resulted in a score between 0 to 24, the score was then converted to a percentage to give a scaled instrument score.

Table 16 Blepharoptosis Outcomes Evaluation and Data Measure

Data Measure	**Questions/ Each question scored from** **0 (Not at All) to 4 (Completely)**
Procedural satisfaction	How well do you like the appearance of your eyes?
	Would you like to surgically alter the appearance of your eyes?
Functional/ symptoms	Do you feel like the appearance of your eyes makes you look tired?
	How much do you feel your friends and loved ones like the appearance of your eyes?
Psychological functions (Psychological well-being, Self-perception, self-concept)	Do you feel the current appearance of your eyes limits your social and professional activities?
	How confident are you the appearance of your eyes is the best that it can be?

2.5 Data Collection & Analysis

2.5.1 Data Collection

Each patient was examined in the postoperative period at 1-week, 3-weeks and 6-months. At each appointment the patient underwent a comprehensive assessment based on a preoperative standardized form show in Appendix 6.

The assessment included closed questioning on symptoms, including irritation, watering and discomfort. Standardized measurements of the eyelids included marginal reflex distance, palpebral aperture, skin crease, lagophthalmos and slit-lamp biomicroscopy with examination of the cornea.

2.5.2 Statistical Analysis

The data from the two groups were compared with t-testing and Chi-square testing. Photograph analysis scores were evaluated with Mann-Whitney test, an α-risk of 0.05 was accepted as clinically significant and the analysis completed using Microsoft Office Excel® 2007.

The photograph scores were evaluated for test reliability and internal consistency. Pearson's correlation coefficients were used to evaluate the test reliability and consistency.

In this study both unilateral and bilateral eyelids were treated as a singularity for the purpose of the study. This represented a compromise as measurements such as the marginal reflex distance were considered independent variables that would not be the case in bilateral eyelids. For measurements dependent on a comparison with the second eyelid such as the interlid difference, these measurements were excluded for bilateral cases.

3.0 Blepharoptosis Results

Fifty-one patients were entered into the blepharoptosis trial between 2003 and 2006. Three patients declined entry into the trial and seven patients were excluded for associated co-morbidity. Of the 51 patients (27 men; 45%), the average age was 67 years (median 70 years; range 41-88 years), Twenty-three (45%) of the patients were male and thirty-six cases (71%) were unilateral. Of the 51 patients 38 (75%) were Caucasian, 10 (20%) were Afro-Caribbean and 3 (5%) were Asian.

3.1 Patient Demographics

Following diagnosis of involutional blepharoptosis patients were randomized to the FTA and suture group for skin closure. A summary of the demographic information for the two groups is show in the table below. The ages (t=0.27; p=0.79), proportions of unilateral cases, race and follow-up period were similar in the two groups (p>0.05).

Table 17 Demographic Information for Blepharoptosis Patients

	FTA group	**Suture group**
Number of Patients	27/51 (53%)	24/51 (47%)
Age		
Mean	67	66
Median	72	69
Range	41-88	48-86
Proportion of Males	12/27 (44%)	15/24 (46%)
Proportion of Unilaterals	19/27 (70%)	17/24 (71%)
Race		
Caucasian	19/27 (70%)	19/27 (79%)
Afro-Caribbean	6/27 (22%)	4/27 (17%)
Asian	2/27 (7%)	1/27 (4%)
Follow-up Period (months)		
Mean	11	13
Median	11	15
Range	10-17	11-19
Blepharoptosis surgery included blepharoplasty	12/27 (44%)	12/24 (50%)

3.2 Surgical Outcomes

The surgical outcome measures are summarized in Table 18 and 19 below. The FTA group had a mean preoperative MRD of 0.9 mm (range -3.0 to 3.0 mm, SD 1.0), difference to contralateral eyelid of 2.7 mm (range 1.0 to 8.0 mm, SD 1.5) and levator function of 13 mm (range 10-18 mm, SD 2.7). There was no statistical difference with the suture group, MRD ($t=0.34$, $p=0.73$) (Table 2).

In the suture group the outcomes were statistically better in the FTA group for the inter-MRD ≤1mm (suture group 0.4 ±0.6mm, FTA group 0.8 ±0.7mm, t-test = 2.2126, p= 0.043). The MRD distance (Success: 3-5mm) was higher in the FTA group (3.3 ±1.4mm) compared to the suture group (suture group 3.0 ±1.3mm), however not of statistical significance.

Table 18 Surgical Pre-Operative and Post-Operative (6-months) Measurements for Blepharoptosis Patients

		FTA Group	Suture Group	Statistic Test (t-test)
Pre-operative	Margin Reflex Distance (mm)	0.9 (1.0)	1.0 (1.2)	t = -0.34, p=0.732
	Mild (≥1.5mm) Moderate (0.5-1.0mm) Severe (≤0mm)	7 (20%) 18 (51%) 10 (29%)	9 (29%) 12 (39%) 10 (32%)	
	Difference to contralateral eyelid (mm)	2.7 (1.5)	2.7 (2.4)	t = -0.032, p=0.975
	Levator function (mm)	13.3 (2.7)	13.5 (1.8)	t = -0.33, p=0.744
Post-operative (6-months)	Margin Reflex Distance (mm)	3.3 (1.4)	3.0 (1.3)	t = 0.943, p=0.349
	Difference to contralateral eyelid (mm) *	0.8 (0.7)	0.4 (0.6)	t = -2.126, p=0.043**

*excluding bilateral cases, **p < 0.05, ( ) = Standard deviation

The measurements were evaluated by the UK National audit definition of complete and successful outcome of ptosis surgery (Scoppettuolo et al., 2008). Although not statistically significant, the proportion of successful and partially successful operations were higher in the suture closure group. The outcome measure results are show in the table 19 below.

Table 19 Successful Outcomes for Blepharoptosis surgery

	Successful Outcome Measure	**FTA Group**	**Suture Group**	**Statistic Test** (Chi-Squared)
1	Margin reflex distance (3-5mm)	69% (24/35)	81% (25/31)	$\chi = 0.263$, P>0.05
2	Interlid marginal reflex difference (≤1mm)*	82% (22/27)	96% (23/24)	$\chi = 0.112$, P>0.05
3	Redo surgery (No)	94% (33/35)	97% (30/31)	-
	Complete success (All criteria met)	63% (22/35)	77% (24/31)	$\chi = 0.199$, P>0.05
	Partial success (One or more of the measurements was outside the defined range)	91% (32/35)	97% (30/31)	$\chi = 0.234$, P>0.05

* Bilateral cases counted only once, Postoperative outcomes in FTA and suture closure groups from UK national ptosis audit (Scoppettuolo et al., 2008)).

Overall there were similar proportions of short-term complications between the two groups. Although the levels of post-operative (Weeks 1-3) irritation were double in the suture closure group (FTA group n=3, Suture group n=6), the numbers were not of statistical significance. One patient in the suture group had a post-operative suture granuloma that was managed conservatively.

There were no intra-operative complications that occurred as a consequence of the FTA or sutures, and no cases required a change in management as a result of FTA randomization. The surgical outcome measures are summarized in the table below.

Table 20 Symptoms following Blepharoptosis Surgery: 1-3 Weeks

	Symptoms	**FTA Group**	**Suture Group**
	Discomfort/ Pain	1	1
	Pruritus/ Irritation	3	6
	Other (Watering, Discharge)	3	3
Total		20% (7/35)	32% (10/31)

Table 21 Complications following Blepharoptosis Surgery: 1-3 Weeks

	Complication	FTA Group	Suture Group
Low Morbidity	Inflammation/ Swelling	2	2
	Granuloma	0	1
	Infection	0	0
	Dehiscence	0	0
	Ecchymosis/ Haematoma	2	2
	Absent skin crease	0	0
	Prominent skin crease/ Asymmetry	1	0
	Exposure keratopathy	3	3
High Morbidity	Necrosis	0	0
	Anaphylaxis	0	0
	Retrobulbar haemorrhage	0	0
	Globe perforation	0	0
	Ischaemic optic neuropathy	0	0
Total	Complications	23% (8/35)*	26% (8/31)*

* $\chi = 0.218$, $P>0.05$

Four months post-surgery there was mild asymmetry in one eyelid in the suture group and four eyelids in the FTA group. Three patients were subsequently excluded from the study with inadequate follow-up. In both groups there was no evidence of wound dehiscence, allergic reaction or infection. In addition to the three cases of redo ptosis surgery, one patient in the suture group required subsequent upper lid blepharoplasty. There was one case of dry eye syndrome in both groups that was managed conservatively with long-term tear lubricant drops and ointment.

Table 22 Symptoms following Blepharoptosis Surgery: 4 months

	Symptoms	**FTA Group**	**Suture Group**
	Discomfort/ Pain	0	0
	Pruritus/ Irritation	1	1
	Other (Watering, Discharge)	1	1
Total		6% (2/35)	6% (2/31)

Table 23 Complications following Blepharoptosis Surgery: 4 months

	Complication	FTA Group	Suture Group
Low Morbidity	Inflammation	0	0
	Granuloma	0	0
	Infection	0	0
	Dehiscence	0	0
	Absent skin crease	0	0
	Scarring (including prominent skin crease)	0	0
	Exposure Keratopathy	1	1
High Morbidity	Necrosis/ severe scarring	0	0
	Reduced visual acuity	0	0
	Systemic infection	0	0
Total	Complications	3% (1/35)	3% (1/31)

3.3 Photographic Outcomes

An example of the pre and postoperative photographs are show in the subsequent figures.

Figures 13 and 14 shows a right side blepharoptosis in primary gaze and down gaze.

Figures 15 and 16 shows the same patient in the 3rd postoperative week following FTA skin closure, the right eyelid has been corrected and the patient has a good symmetrical appearance.

Outcomes for the photography analysis were significantly worse for ptosis evaluation in the FTA group (Score=2.7) compared to the suture group (Score 0.6, Mann-Whitney test P= 0.0029). The outcomes for the scar evaluation were similar in the FTA group (Score=1.8) and FTA group (Score=1.4) (P>0.05). The surgical outcome measures are summarized in the table 22 below.

Figure 13 Ptosis Pre-Operative Photograph in Primary Gaze

Figure 14 Ptosis Pre-Operative Photograph in Down Gaze

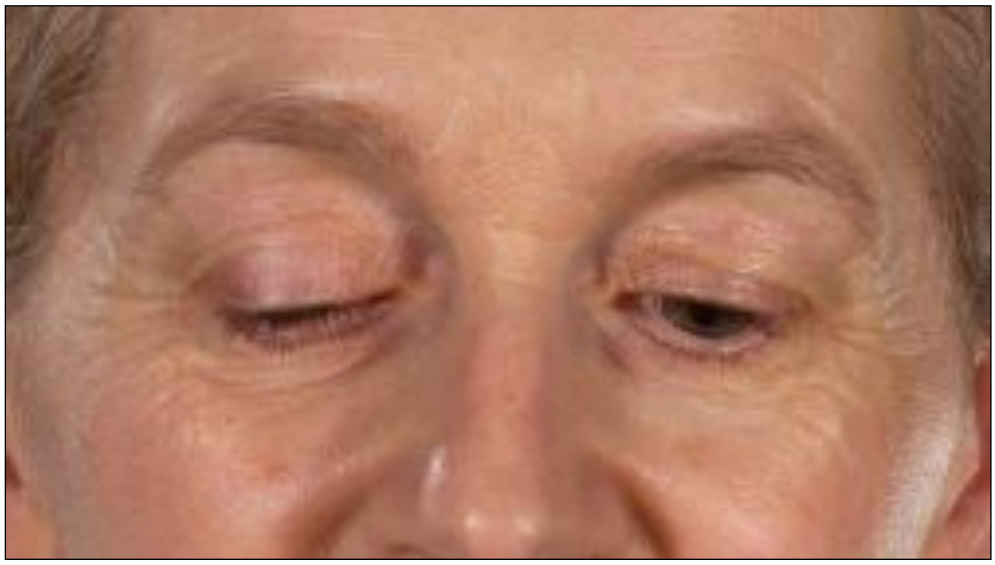


Figure 15 Ptosis Post-Operative Photograph Week 3 in Primary Gaze

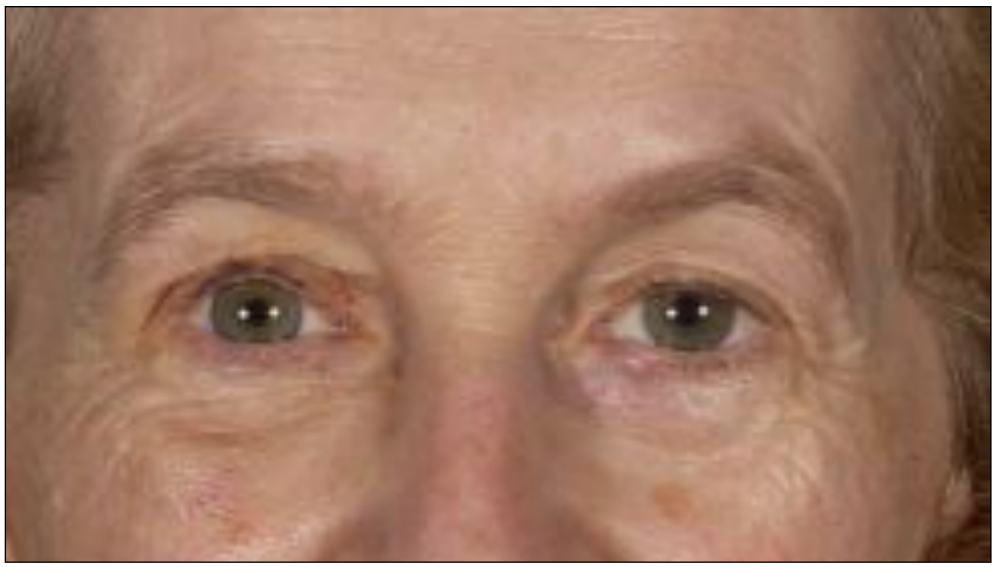


Figure 16 Ptosis Post-Operative Photograph Week 3 in Down Gaze

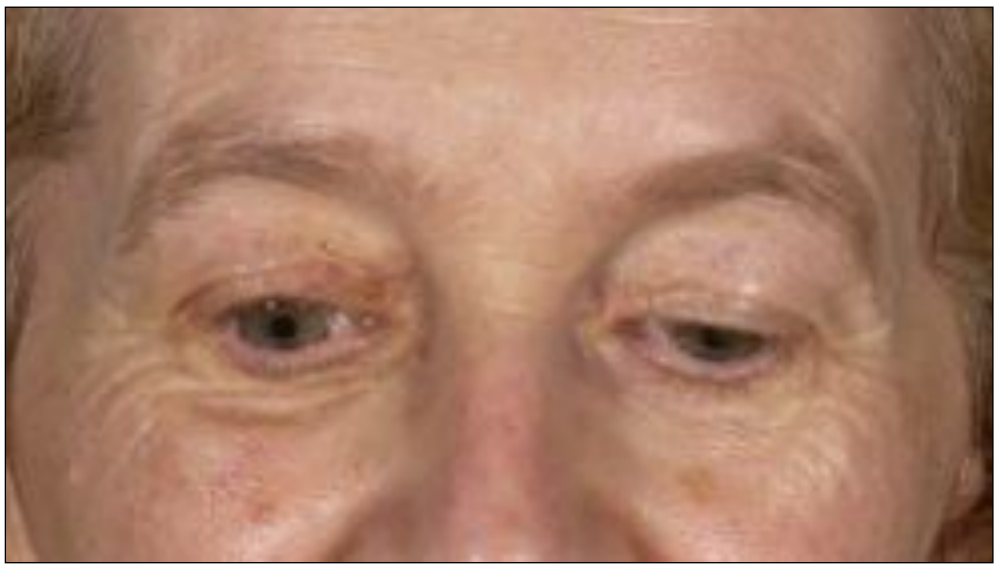


Table 24 Photographic Outcomes for Blepharoptosis at 6-months Post-Surgery

		FTA Group Score	**Suture Group Score**	**Statistic Test** (Mann-Whitney)
Ptosis Evaluation	Superior lid crease Eyelid contour Superior sulcus Compared to pre-op Step-off border (borders not in same plane)	2.7 (2.2)	0.6 (0.8)	MW = 42.5 P = 0.0029*
Scar Evaluation	Contour irregularity (wrinkled skin near wound) Margin separation (gap between sides) Edge inversion (wound not everted) Excessive inflammation (swelling, oedema) Overall cosmetic appearance	1.8 (1.3)	1.4 (1.1)	MW = 90.0 P = 0.3397
Total Score		4.4 (3.1)	2.1 (1.8)	MW = 75.5 P = 0.0471*

* = $p < 0.05$, Score 0 (Normal) -> 10 (Maximal suboptimal), ( ) = Standard deviation

The three observers evaluated the standard photographs on two separate occasions and the results were evaluated using Spearman's rank correlation coefficient for intra- and inter-examiner reliability. The results are summarized in the table below, the intra-examiner scores ranged from 0.47 to 0.61 with a probability of <0.05.

Table 25 Intra-Examiner Correlations between the Photograph Scores

	Observer	**Correlation**	**Probability**
Total Score	Observer 1	0.47	0.0081
	Observer 2	0.61	0.0003
	Observer 3	0.51	0.0041

3.4 Patient Satisfaction Outcomes

Patient satisfaction as evaluated by the validated questionnaire was similar in the two groups (FTA group score=18.6 and suture group score=17.4). The majority of patients were satisfied in both treatment groups, although it was noted that individuals who had lower level of satisfaction were not necessarily the patient who had a poorer outcome on objective assessment of eyelid measurements or photograph scores.

Table 26 Patient Satisfaction Outcomes for Blepharoptosis Surgery

Questions / Each question scored from: **0 (Not at All) to 4 (Completely)**	**FTA Group**	**Suture Group**
Q1) How well do you like the appearance of your eyes? *0 (Not at All) to 4 (Completely)*	2.6 (1.2)	2.7 (1.6)
Q2) Would you like to surgically alter the appearance of your eyes? *0 (Completely) to 4 (Not at all)*	3.4 (0.8)	3.0 (1.7)
Q3) Do you feel like the appearance of your eyes makes you look tired? *0 (Not at All) to 4 (Completely)*	3.3 (0.8)	3.1 (1.3)
Q4) How much do you feel your friends and loved ones like the appearance of your eyes? *0 (Always) to 4 (Never)*	2.9 (0.9)	2.8 (1.6)
Q5) Do you feel the current appearance of your eyes limits your social and professional activities? *0 (Not at All) to 4 (Completely)*	3.5 (0.7)	3.3 (0.9)
Q6) How confident are you the appearance of your eyes is the best that it can be? *0 (Definitely) to 4 (Not al all)*	2.9 (0.9)	2.6 (1.5)
Mean Score (Maximum score = 24)	18.6 (4.0)	17.4 (8.3)
Total Score (Percentage of maximum)	76.8%	74.4%

( ) = Standard deviation

3.5 Summary

In summary the blepharoptosis surgery identified a lower proportion of success in the FTA group as defined by eyelid measurements and the photographic analysis. Patient satisfaction was similar in the two groups and was not related to failed objective measurements. A summary of the results is shown in the table 27 below.

Table 27 Summary of Trial Results for Blepharoptosis Surgery

	Outcome Measure	**FTA Vs Suture Group** **Statistical Test & Significance**
Surgical Outcomes	Eyelid Measurements: MRD, Severity, Difference, Levator function Difference to contralateral eyelid	t-test, chi-squared test No difference **Worse in FTA group** (p=0.043)
	Successful Outcome Measures: MRD, Interlid MRD, Redo, Complete & Partial Success	t-test No difference
	Complications: Symptoms, skin closure, generalized	chi-squared test No difference
Photographic Outcomes	Photograph analysis: ptosis, scar and overall score	Mann-Whitney test **Worse in FTA group for ptosis and overall score** (P=0.0471)
Patient Satisfaction Outcomes	Patient Satisfaction Outcomes	chi-squared test No difference

4.0 Blepharoplasty Results

The patients diagnosed with dermatochalasis without ptosis underwent upper eyelid blepharoplasty with randomization for skin closure to the FTA and suture groups. The defined outcomes were similarly to those of the blepharoptosis surgery with assessment of surgical outcomes, photographic scores and patient satisfaction.

4.1 Patient Demographics

A summary of the demographic information for the two groups is show in the table 28 below. The ages of the patients, gender, proportions of unilateral cases, race and follow-up period were similar in the two groups ($p>0.05$).

Table 28 Demographic Information for Blepharoplasty patients

	FTA Group	**Suture Group**
Number of Patients	15/32 (47%)	17/32 (53%)
Age		
Mean	58	55
Median	58	68
Range	50-67	45-86
Proportion of Males	9/15 (60%)	6/17 (70%)
Proportion of Bilaterals	15/15 (100%)	13/17 (76%)
Race		
Caucasian	12/15 (70%)	12/17 (71%)
Afro-Caribbean	0/15 (0%)	1/17 (5%)
Asian	3/15 (30%)	4/17 (24%)
Follow-up Period (months)		
Mean	13	8
Median	11	8
Range	8-19	6-18

4.2 Surgical Outcomes

Following blepharoplasty surgery there was a small and non-significant increase in the marginal reflex distance, which is consistent with the upper eyelid blepharoplasty surgery. In addition the difference in eyelid height compared to the contralateral side was similar in both groups.

Table 29 Surgical Pre-Operative and Post-Operative (6-months) Measurements for Blepharoplasty Patients

		FTA Group	Suture Group	Statistic Test (t-test)
Pre-operative	Margin Reflex Distance (mm)	2.9 (0.8)	2.3 (1.2)	t = 1.558, p=0.067
Post-operative (6-months)	Margin Reflex Distance (mm)	3.5 (1.1)	3.1 (1.2)	t = 0.894, p=0.194
	Difference to contralateral eyelid (mm)	0.7 (0.5)	0.4 (0.5)	t = 0.660, p=0.278

( ) = Standard deviation

The blepharoptosis defined criteria for success were also use for the blepharoplasty patients. Although the success rates were around 90% following upper eyelid blepharoplasty, as the surgery did not involve the upper eyelid levator complex a higher success rate may have been anticipated. On evaluation of the individual patients, all three eyelids the FTA group that had a marginal reflex distance of less than 3mm in the post-operative period, had borderline blepharoptosis preoperatively. Only one of the patient in each group went onto have redo surgery.

Table 30 Successful Outcomes for Blepharoplasty surgery

		FTA Group	**Suture Group**	**Statistic Test** (Chi-Squared)
1	Margin reflex distance (3-5mm)	90% (27/30)	83% (25/30)	$\chi = 0.7448$, $P>0.05$
2	Interlid marginal reflex difference (≤1mm)	93% (14/15)	94% (15/16)	-
3	Redo surgery (No)	97% (29/30)	97% (29/30)	-
	Complete success (All criteria met)	83% (25/30)	80% (24/30)	$\chi = 0.739$, $P>0.05$
	Partial success (One or more of the measurements was outside the defined range)	100% (30/30)	100% (30/30)	-

The complication rates from the upper eyelid blepharoplasty were similar in the two groups in the postoperative period. There was a higher level of irritation in the suture group (n=4) although the difference was statistically non-significant compared to the FTA group (n=1). In the FTA group one patient had early dehiscence of the wound in the early post-operative period, this was managed with the insertion of sutures under local anaesthesia. The dehiscence was attributed to the early learning curve, a more cautious approach to confirmation of wound adhesion at the end of surgery was adopted and no further cases of dehiscence occurred.

Table 31 Symptoms following Blepharoplasty Surgery

		FTA Group	Suture Group
Symptoms	Discomfort/ Pain	0	0
	Pruritus/ Irritation	1	4
	Other (Watering, Discharge)	0	0
Total		3% (1/30)	13% (4/30)

Table 32 Complications from Blepharoplasty Surgery

	Complication	**FTA Group**	**Suture Group**
Low Morbidity	Inflammation/ Swelling	0	1
	Granuloma	0	0
	Infection	0	0
	Dehiscence	1	0
	Ecchymosis/ Haematoma	0	2
	Absent skin crease	2	0
	Scarring (Prominent skin crease)	0	0
	Exposure Keratopathy	0	0
	Other*	3	0
High Morbidity	Necrosis	0	0
	Anaphylaxis	0	0
	Reduced visual acuity	0	0
	Systemic infection	0	0
Total	Complications	20% (6/30)	10% (3/30)

* Excess FTA removed 1-week post-operatively

4.3 Photographic Outcomes

An example of the pre and postoperative photographs are show in the subsequent figures.

Figures 17 and 18 shows an early postoperative photograph of the patient in primary gaze and down gaze, one week after skin closure with FTA.

Figures 19 and 20 shows the same patient in the 3rd postoperative week and the patient has a good symmetrical appearance.

Figure 21 shows a high magnification of the skin crease 1-week after skin closure with FTA. The skin crease is difficult to see without magnification there are no marks, minimal inflammation or ecchymosis.

Figure 17 Blepharoplasty Post-Operative Photograph Week 1 in Primary Gaze

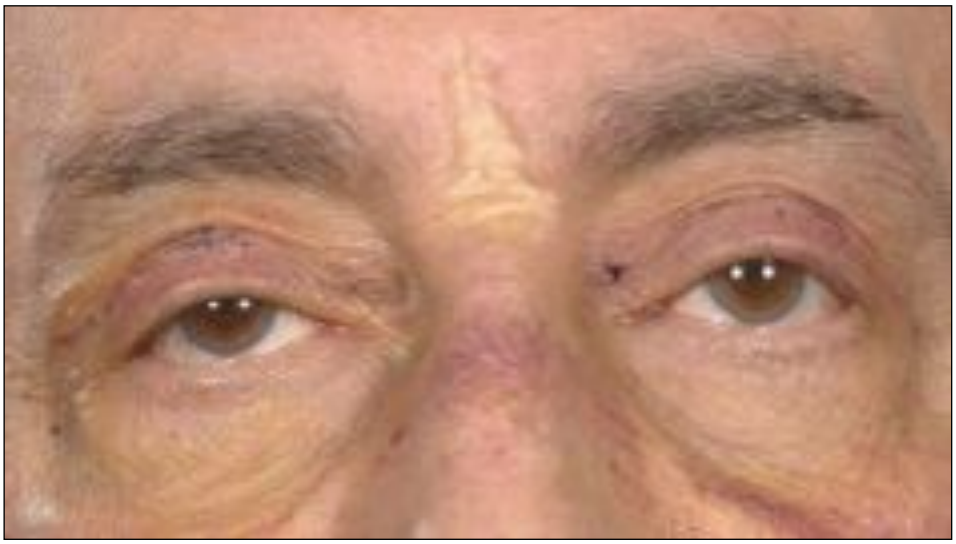


Figure 18 Blepharoplasty Post-Operative Photograph Week 1 in Down Gaze

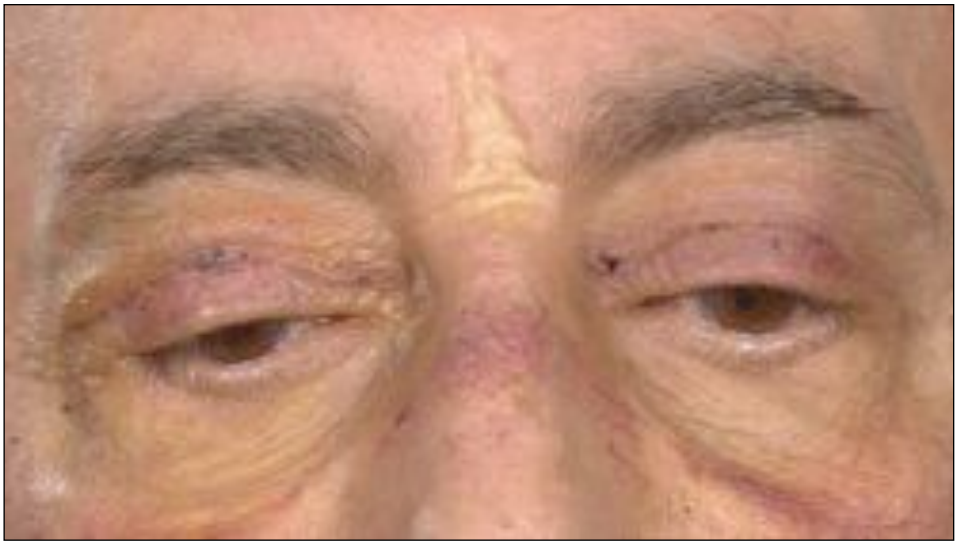


Figure 19 Blepharoplasty Pre-Operative Photograph Week 3 in Primary Gaze

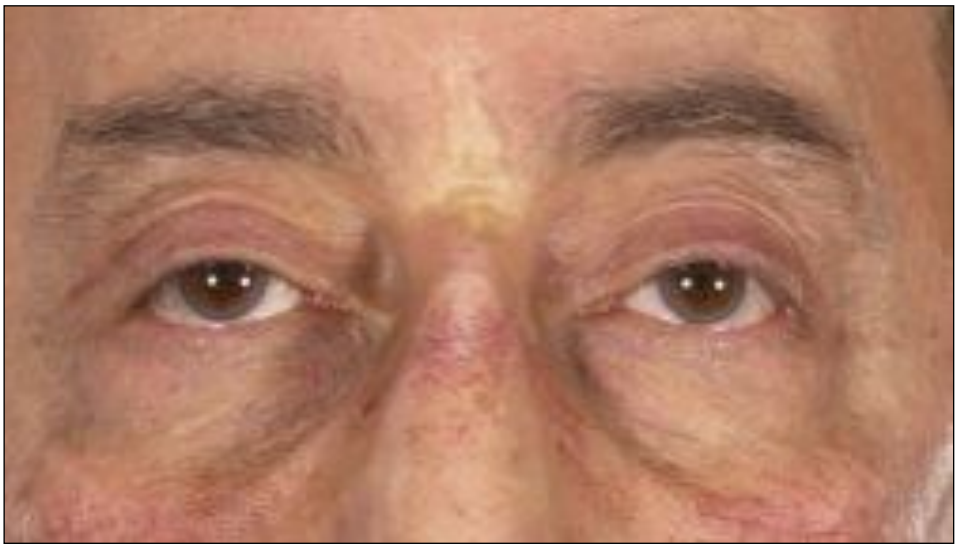


Figure 20 Blepharoplasty Pre-Operative Photograph Week 3 in Down Gaze

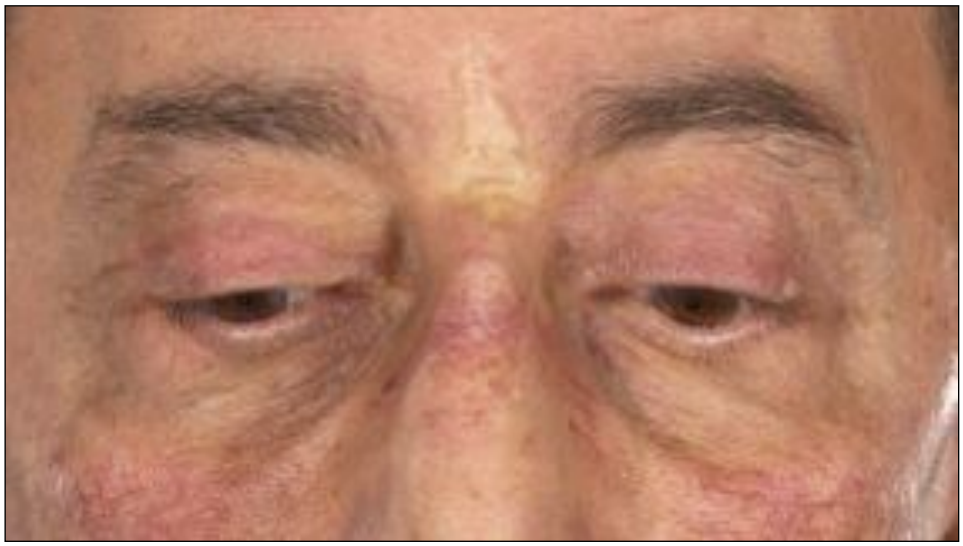
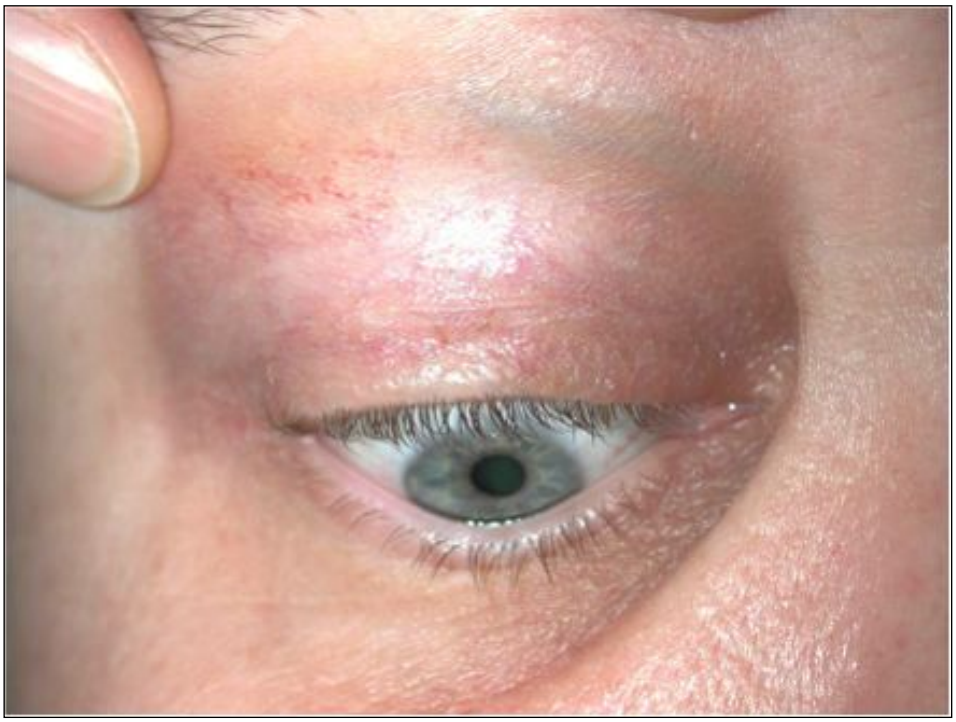


Figure 21 Blepharoplasty High Magnification Photograph Week 1



Outcomes for the photography analysis were similar in the FTA group (Total Score=2.4 ±2.4) compared to the suture group (Score 3.5 ±2.1). The surgical outcome measures are summarized in the Table 33 below.

Table 33 Photographic Outcomes for Blepharoplasty

		FTA Group Score	**Suture Group score**	**Statistic Test** (Mann-Whitney)
Eyelid Evaluation	Superior lid crease Eyelid contour Superior sulcus Compared to pre-op Step-off border (borders not in same plane)	1.3 (1.3)	2.3 (2.1)	MW = 63.0 P = 0.1658
Scar Evaluation	Contour irregularity (wrinkled skin near wound) Margin separation (gap between sides) Edge inversion (wound not everted) Excessive inflammation (swelling, oedema) Overall cosmetic appearance	1.2 (1.1)	1.3 (0.5)	MW = 58.5 P = 0.2932
Total Score		2.5 (2.4)	3.5 (2.1)	MW = 46.5 P = 0.3598

Score 0 = Normal, Score 1 = Abnormal, ( ) = Standard deviation

4.4 Patient Satisfaction Outcomes

Patient satisfaction as evaluated by the validated questionnaire was similar in the two groups (FTA group score=21.9 and suture group score=20.1) and the majority of patients were satisfied in both treatment groups.

Table 34 Patient Satisfaction Outcomes for Blepharoplasty Surgery

Questions/ Each question scored from	**FTA Group**	**Suture Group**
Q1) How well do you like the appearance of your eyes? *0 (Not at All) to 4 (Completely)*	3.7 (0.8)	3.1 (0.7)
Q2) Would you like to surgically alter the appearance of your eyes? *0 (Completely) to 4 (Not at all)*	3.4 (1.5)	3.6 (0.8)
Q3) Do you feel like the appearance of your eyes makes you look tired? *0 (Not at All) to 4 (Completely)*	4.0 (0.8)	3.7 (0.5)
Q4) How much do you feel your friends and loved ones like the appearance of your eyes? *0 (Always) to 4 (Never)*	3.0 (0.8)	3.1 (0.7)
Q5) Do you feel the current appearance of your eyes limits your social and professional activities? *0 (Not at All) to 4 (Completely)*	4.0 (0.7)	3.7 (0.9)
Q6) How confident are you the appearance of your eyes is the best that it can be? *0 (Definitely) to 4 (Not al all)*	3.7 (0.9)	3.0 (1.5)
Mean Score (Maximum score = 24)	21.9 (3.0)	20.1 (2.7)
Total Score (Percentage of maximum)	91.1%	83.9%

( ) = Standard deviation

4.5 Summary

In summary the outcomes of the upper eyelid blepharoplasty surgery were similar in the FTA and suture groups as defined by the surgical outcomes, photographic outcomes and patient satisfaction outcomes. A summary of the results is shown in the Table 35 below.

Table 35 Summary of Trial Results for Upper Eyelid Blepharoplasty Surgery

	Outcome Measure	**FTA vs Suture Group** **Statistical Test & Significance**
Surgical Outcomes	**Eyelid Measurements**: MRD, Severity, Difference, Levator function	t-test, chi-squared test No difference
	Successful Outcome Measures: MRD, Interlid MRD, Redo, Complete & Partial Success	t-test No difference
	Complications: Symptoms, skin closure, generalized	chi-squared test No difference
Photographic Outcomes	**Photograph analysis**: ptosis, scar and overall score	Mann-Whitney test No difference
Patient Satisfaction Outcomes	**Patient Satisfaction Outcomes**	chi-squared test No difference

5.0 Discussion & Conclusion

5.1 Discussion

Few high quality studies have evaluated the use of FTAs for skin closure and this randomized control study compared the use of FTAs compared to conventional suture closure of skin for blepharoptosis and upper eyelid blepharoplasty. Previous studies have shown limited effective evaluation of surgical outcome following eyelid surgery and this research project utilized three independent evidence-based measures for the evaluation of eyelid surgery outcomes.

Blepharoptosis Surgery

The blepharoptosis patients in the study had a significantly lower rate of success in the FTA group with respect to the contralateral eyelid measurements and the photographic outcome scores. Although the procedure to elevate the eyelid was identical in the two groups, the results suggest the FTA may have affected the eyelid height leading to a lower outcome. The FTA was placed at the dermal edges anterior to the eyelid levator complex, and some FTA may have made direct or indirect contact with the levator mechanism resulting in a change in the eyelid height. Although not of statistical significance, the skin crease was on average 1.2mm higher in the FTA group.

The overall complication rates were similar in the Tisseel FTA group and the suture group. One patient in the suture group was complicated with a suture related granuloma. The granuloma was managed conservatively with removal of residual suture and topical antibiotic and anti-inflammatory ointment, the patient went on to have a satisfactory result with good surgical outcome. Twice as many of the patients in the suture group reported postoperative irritation compared to the FTA group. The irritation from the skin sutures did resolve on their removal. The literature had reported reduced haemorrhage following the use of FTAs in facial surgery. In this study there was no difference in the recorded ecchymosis between FTA (n=2) and suture (n=2) groups and no cases of haematoma formation in either group.

Transcutaneous levator repair is one of the commonest treatments for involutional ptosis. Although the technique is relatively standardized there is recognized unpredictability of postoperative eyelid height. This study identified a complete success rate of 63% in the FTA group and 77% in the suture group, which is comparable with published results, the BOPSS national ptosis audit had a 57% success rate (Scoppettuolo et al., 2008). The proportion of success rates based on MRD was 69% in

the FTA group and 81% in the suture group, again comparable with the 71-74% reported in the literature (Berlin and Vestal, 1989, Meltzer et al., 2001).

Previous publications evaluating the use of FTAs on eyelid surgery have had considerable variability in patient selection, surgical technique and surgical outcome (Table 9). The variability in these studies makes comparisons between FTA and non-FTA skin closure difficult and compromised with confounding factors. This study reduced the potential for confounding factors with defined inclusion and exclusion criteria. Randomization of the patients to the FTA and suture groups for skin closure reduced the potential for selection bias, which is a common weakness of the majority of FTA publications. The downside of strict criteria for entry into the study was the reduced numbers of patients in the study. The complications of eyelid surgery such as granuloma formation and infection were relatively uncommon and the impact of reduced patient numbers is relatively few complications in each group and limitation in the statistical findings.

On evaluation of the photographic outcomes for blepharoptosis surgery, the outcomes were statistically worse for the blepharoptosis scores in the FTA group. This is consistent with the eyelid measurements, and finding that the FTA group had more measurements outside the defined success for MRD (3-5mm) and interlid measurements (≤1mm) that corresponds to increased eyelid asymmetry on photograph analysis. The photographic evaluation of the scars in the two groups was similar. Although some studies had identified increased wound healing and the potential for increased scarring in the suture closure group as a result of point fixation this was not reflected in the results of this study.

On comparison of the three different outcome measures there was consistency between the objective eyelid measurements and the standardized evaluation of postoperative photographs. With both outcome measures the suture group outcomes were statistically better than the FTA group. The third outcome measure that evaluated patient satisfaction from a validated questionnaire was similar in the two groups. On evaluation of the individual patient satisfaction scores there was no pattern between success rates of surgery as defined by eyelid measurements and patient satisfaction. This finding is consistent with studies that highlight the importance of patient expectation in the preoperative assessment of patients and highlights that surgical success by eyelid position and appearance may not necessarily result in favourable patient satisfaction.

Blepharoplasty

In the blepharoplasty groups of patients there was no statistical difference in the outcomes between the FTA and suture groups. Blepharoplasty is a common surgical procedure and post-operative symmetry, wound healing and aesthetic appearance are all important for a successful result. Skin closure following upper eyelid blepharoplasty may be challenging as the upper eyelids are mobile and skin closure is under tension compared to lower eyelid blepharoplasty and these perpendicular forces impact post-operative healing (Greene et al., 1999, Mommaerts et al., 1996). The majority of studies that have evaluated tissue adhesive skin closure have been retrospective and highlighted advantages of the FTA technique (Mandel, 1992) with proposed improvements including wound healing and reduced suture related complications including cysts, granulomas and scars. However our study found complications in both groups to be rare and transient. There were 4 eyelids with irritation in the suture group compared to only one in the FTA group and these symptoms resolved on removal of the sutures. There was one case of dehiscence of the wound in the FTA group, this was early in the study and attributed to the learning curve of the technique and the patient went on to have a satisfactory result with good surgical outcome. Overall the complications were similar between the FTA and suture groups.

The photographic analysis showed good outcomes that were similar in both groups. The overall scar formation was similar in both groups including inflammation, irregularity and cosmetic appearance. Anecdotally the wound healing in the FTA group was fast and resulted in minimal recovery time, as illustrated in Figure 19, in some patients there was minimal evidence of surgery at 1-week post surgery.

The patient satisfaction outcomes were similar in both the FTA and suture groups with both groups having high levels of patient satisfaction, 91% in the FTA group and 84% in the suture group. The results are consistent with those published for blepharoplasty surgery with the same patient satisfaction questionnaire (Mean satisfaction = 90%; (Alsarraf et al., 2001). The proportion of satisfaction was higher in the blepharoplasty patients than in the blepharoptosis patients which is consistent with the literature, and may be a result of the increased unpredictability of postoperative lid height in the blepharoptosis patients.

FTA

There are theoretical advantages of the use of FTA in patients with increased risk of haemorrhage including those with drug induced clotting abnormality (e.g. aspirin, NSAIDs) as FTAs are independent of platelet factors, haemorrhage can be controlled with FTA use (Mandel, 1992). In this study there were relatively few complications relating to haemorrhage following blepharoptosis or blepharoplasty surgery, and the FTAs did not offer an advantage with respect to haemorrhagic complications in this study.

The FTA is relatively straightforward to use, including the preparation of the FTA and its application. The adhesive sets quickly once applied and had good tensile strength at the end of the procedure. As with most surgical techniques there is a learning curve towards using the FTA effectively. In this study one patient had wound dehiscence and presented within a week of surgery, this was thought to be a result of inadequate FTA application during the procedure and confirmation of effective wound adhesion at the end of surgery. This case was early in the study and believed to be a consequence of the learning curve of FTA application. Other authors have similarly expressed a learning curve associated with the technique, Grossman et al had five cases (4.7%) localized ischaemic necrosis following rhytidectomy that was explained by overzealous undermining, flap tension and cautery for haemostasis in early cases (Grossman et al., 2001). Thick areas of sealant may cause ischaemia that act as a barrier limiting normal capillary growth and oxygenation of tissues. There were no cases of necrosis in our study. FTA has advantages in triggering the clotting cascade thereby reducing haemorrhage and the likelihood of haematoma formation, is not however a replacement for meticulous surgical technique as the adhesive is ineffective if the skin surfaces were not dry.

There are two important complications that have been associated with the use of FTAs; the transmission of infection and allergic reaction (Kawamura et al., 2002, Oswald et al., 2003). Although there were no serious adverse reactions associated with the use of FTAs in this study, these complications are very rare yet with important implications. In over a decade of use of FTA in a range of clinical specialties, the only report of transmission of infection is of parvovirus B19 (Kawamura et al., 2002). Although extensive screening and processing is conducted to prevent the risk of infection, the risk cannot be completely eliminated. A recombinant FTA is in development and long-term the use of recombinant formulations of FTAs would eliminate this infection risk. Allergic or anaphylactic reactions to FTAs are very rare, and are thought to have resulted from the use of bovine products such as bovine derived aprotinin in the early manufacture of the FTAs. The modern day manufacture has eliminated this product with the use of synthetic aprotinin. In addition the cases of anaphylaxis have occurred with sensitization to the sealant after repeated use, the use of FTA to

close central spinal fluid leaks in association with intracranial hypertension (Schievink et al., 2008, Shirai et al., 2005). The cases of anaphylaxis were thought to have resulted from inadvertent intravascular injection of the FTA during percutaneous injection into the epidural space (Schievink et al., 2008). There are no reported cases of anaphylaxis following relative superficial use of FTAs for soft tissue or skin closure.

Cost-effectiveness is an important aspect in the delivery of healthcare and one potential disadvantage of the use of FTAs for skin closure is the additional cost of FTA purchase relative to sutures. In this study the FTA group were assessed at 1-week post surgery, to enable comparison with suture group. The additional out-patient appointment for suture removal could be avoided in the FTA group which would make the use of FTAs more cost-effective. A number of studies that have looked at skin closure with tissue adhesives have identified a shorter operating time compared to suture skin closure (Mommaerts et al., 1996). This study did not evaluate surgical time, it was noted that the preparation of the FTA including warming, mixing and loading of the FTA takes both resources and expertise. Since this study was completed, Baxter had developed a frozen ready-to-use product that required no preparation time.

Summary

- Avoid the use of FTAs in blepharoptosis cases: FTAs effects eyelid height and outcomes were not as successful compared to suture closure of skin
- The use of FTAs for skin closure following upper eyelid blepharoptosis surgery is comparable in effectiveness with suture closure
- FTAs promote rapid healing of the wound, often barely visible at 1-week post surgery
- Minimal complications occur with the use of FTAs or sutures for upper eyelid blepharoplasty
- Increased cost of FTA purchase, counterbalanced by savings on suture-removal appointment
- Theoretical risk of infection and allergy remain with the use of both human and bovine components of FTAs

5.2 Recommendations

The conventional closure of skin with sutures for blepharoptosis surgery is recommended as the outcomes from this study suggest that the use of FTA skin closure has a less favourable outcome. The use of FTAs or suture have good outcomes following upper eyelid blepharoplasty, and there may be an increased rate of healing in the FTA group (Figure 17).

The use of several eyelid measurements to determine operation success (as devised by the BOPSS ptosis audit) is comparable with "blinded" observer evaluation of standardized photographs following eyelid surgery. The results of the patient satisfaction questionnaire were independent with the eyelid measurements and photographic outcome measures. Patient satisfaction is an essential aspect of eyelid surgery and the findings in this study suggest further evaluation of individual patient's expectation would be useful to determine their influence on postoperative satisfaction.

5.3 Limitations of Study

The eyelid height following blepharoptosis surgery may be inconsistent, with an unpredictable postoperative upper eyelid height, and a relatively high reoperation rate. Variability can result from a variety of factors including patients' demographics and gender, surgical methodology and surgeon. Despite identical surgical technique, surgery and perioperative management, outcomes are not predictable. This study aimed to minimize the variability with inclusion and exclusion criteria. A larger number of cases would have added further validity to the statistical power. The clinical part of this study took over 2-years to complete, and a drawback of the inclusion and exclusion criteria that reduced the confounding bias was reduced patient entry to the trial. With the potential for variability of surgical technique with different oculoplastic consultants, this trial was limited to the patients seen under the care of an individual consultant, where the surgical technique was consistent and less subject to the variability that would result from a multi-surgeon trial.

In this study, histological analysis through biopsies of the two groups at different postoperative stages wound have added further information on wound healing. However there are ethical considerations as tissue biopsies in these patients would be an additional and avoidable procedure that may have led to complications e.g. scarring, delayed healing.

This study may be limited owing to the learning curve associated with the use of the FTAs, however unsatisfactory surgical outcomes were not seen in larger quantity in the early period of the trial. An optimal comparison of post-operative lid surgery would involve randomization of one site to

suture and the other to FTA skin closure, however this was considered to be unethical as it may introduce asymmetry.

5.4 Future Research

The use of FTAs in clinical practice has continued to increase, and with this there have been improvements in the reported effectiveness, reduction in costs and complications in surgical practice. The combination of FTAs with the use of stem cells and antibiotics offers long-term physiological advantages in reconstruction and eyelid procedures (Marone et al., 1999, Kram et al., 1991a). One of the principal limitations of the current FTA products is their use of human donor tissue and risk for infection, the development of recombinant non-donor FTA offers elimination of the potential risk and is currently under development. In addition the use of a laser activated adhesive has been trialled, the laser causes cross-linking of a hyaluronic acid compound, with the potential use for closing corneal incisions or injuries (Kalayci et al., 2003).

The need for standardized and validated tools for measuring PROMs in oculoplastic surgery has been highlighted by the recent Department of Health. Following on from this research project, we plan to develop further measures for the evaluation of oculoplastic procedures by further research and clinical networks.

Tisseel FTA components are made from human plasma and blood collected from screened transfusion centres across the USA and some European countries. Plasma donors undergo screening for the presence of known viruses and viral markers and components are subjected to virus inactivation process. Although no cases of the transmission of infectious diseases has been reported in the literature the transmission of infective agents cannot be totally excluded (Saltz, 1992). The development of recombinant fibrinogen may lead to eventual elimination of infection risk (Chan and Boisjoly, 2004, Mandel, 1990) .

Since the completion of this study, the applications of FTAs have continued to grow in clinical practice. Baxter have developed further FTA related products including a pre-prepared frozen FTA product that required no preparation or mixing process, this may become the product of choice in surgical practice in the future. Although in some countries Baxter has chosen to replace the bovine aprotinin with a recombinant protein, the company has no plans to change the bovine aprotinin in the UK manufacturing process in the short-term future.

5.5 Conclusions

The eyelids have an important functional role in maintaining good visual acuity, involutional changes with increasing age may result in compromised function. Eyelid surgery may be essential to restore normal anatomy and function to the eyelids. There are numerous complications that may result from eyelid surgery and techniques that propose improved patient morbidity require systematic evaluation for both effectiveness and safety.

Few high quality studies have evaluated the use of FTAs for skin closure and this research project evaluated the use of FTAs in two randomized control studies of blepharoptosis and upper eyelid blepharoplasty. The study suggests that sutures should be used for skin closure following blepharoptosis repair, as FTAs may detrimentally impact surgical outcome. This study supported the use of specific eyelid measurements and the evaluation of standardized photographs as outcome measures for eyelid surgery. Further evaluation of patient satisfaction in surgical assessment is required as this was found to be independent of both eyelid measurements and photographic analysis.

6.0 Appendices

6.1 Appendix 1- Local Research Ethics Committee Form

ST MARYS LOCAL RESEARCH ETHICS COMMITTEE

Mailbox 121, St Marys Hospital, Praed Street, London W2 1NY

Tel: 020 7886 6514 Fax.1529 Email: Ros.Cooke@st-marys.nhs.uk

DATE SUBMISSION is sent to LREC office……

1. FULL TITLE OF PROJECT:
A randomised prospective study to evaluate blepharoplasty skin closure by tissue adhesive in comparison with conventional suturing techniques.

What do you regard as the most important ethical issue that necessitates review of your project by the LREC?
Approval of tissue adhesive use for skin closure in blepharoplasty.

Is the research being done at other centres?	NO

If YES, where else is it being done?

Is St Marys the Lead Centre?	YES

If NO, who is the lead centre?

Main research question:
Identify the advantages of blepharoplasty skin closure using tissue adhesive over conventional suturing techniques.

Brief methodology:
1. Pilot Study of 10 patients to identify number of patients required for the prospective

randomised control study.

2. Entry to trial. Patients will be assessed according to a clearly defined protocol incooperating both inclusion criteria, exclusion criteria, patient information leaflet and written consent.
3. Randomization of patients to tissue adhesive and suturing skin closure groups.
4. Post operative assessment of both all patients at 1 week, 3 weeks and 2 months.
5. Post operative assessment of by standardized photographs and patient satisfaction.

Proposed start date: 2/2003

End date: 10/ 2003

Number of participants/subjects in research:

Pilot study of 10 patients.

Prospective randomized control study, patient no. determined by pilot study.

Brief outcome measure description:

1. Standardized photographs.

2. Patient satisfaction.

Name/address/tel no. of Drug Company sponsor (if applicable):

Baxter Healthcare Ltd,

Bioscience, Wallingford Road, Compton, Newbury, Berks, RG20 7W

Tel. No. 01635 206 140

Amount be granted by drug company:

2. INVESTIGATORS

Principal Investigator(s): Miss Jane Olver and Sheng Lim

Name Signature Designation

All other Investigator(s): D Julian De Silva and Doris Zuercher

Name Signature Designation

Head of Dept/consultant/GP/Community Physician, etc, in overall charge if different from above: Miss Jane Olver

Name Signature Designation

Name, address, tel. No, fax No & Email of investigator to whom all correspondence will be sent:

Miss Jane Olver, Consultant Oculoplastic Surgeon

Western Eye Hospital, London, NW1 5YE

Tel. No. 0207 886 3265

3. AIMS OF PROJECT:

This study aims to compare the success rates of skin closure following blepharoplasty surgery, by tissue adhesive versus conventional suturing techniques.

4. BACKGROUND OF PROPOSED STUDY:

Blepharoplasty is one of the most commonly performed functional as well as cosmetic ophthalmic plastic surgical procedures. The operation may be used to remove skin and lid obstruction of the visual field and to remove involutional change in the eyelids secondary to ageing.

The procedure is most commonly performed under local anaesthesia as a day case procedure. The excess skin and skin crease are first marked. An incision is made through the marked skin and the skin and underlying orbicularis muscle excised as a single crescentic flap. The orbital septum is identified and opened. The fat pads visualized and excised with caution to maintain haemostasis. Sutures are then placed in skin, muscle and levator aponeurosis to form the eyelid skin crease. The skin is conventionally closed by suturing technique. Sutures are place along the length of the blepharoplasty wound. Sutures cause an individual tissue healing response and variable scar formation. Patients attend outpatients at 1 week for suture removal, which is an uncomfortable procedure. Patients are then seen for further follow up at 3 weeks and 2 months. The patients are assessed by lid measurements and photography.

We propose the use of a tissue adhesive to close the skin following blepharoplasty. The adhesive will be applied as in conjunction with the manufacturing guidelines to both surfaces of the wound, which are then gently opposed to allow sealing. The adhesive has been used in a number of other oculoplastic procedures such as; entropion skin closure, skin transplants, fixation of orbital implants following enucleation and reconstruction of lacerated lacrimal canaliculi. The use of tissue adhesive will reduce the need for 1 week postoperative suture removal, decrease the length of blepharoplasty operating time and indirectly may reduce waiting list time. Tissue adhesive is likely to generate less inflammatory healing response and may improve the aesthetic appearance. In addition, tissue adhesive may improve patient satisfaction as a combination of these factors.

To date, there have been no randomised prospective comparative studies comparing the use of tissue adhesive and conventional suturing in blepharoplasty skin closure. We have chosen to compare these two techniques and determine whether there is a significant difference between these two treatments using a carefully designed study. A multicenter prospective randomised comparative study design appears to be the best way to answer this question.

References.

Fibrin sealant in Ophthalmic plastic and Reconstructive surgery. FJ Steinkogler, A Kuchar; Fibrin sealing in surgical and nonsurgical fields. Springer-Verlag, Berlin-Heideelberg 1994.

5. DESIGN OF STUDY:

Give a brief description of what will be done and how it differs from normal practice.

1. Entry to trial, according to inclusion criteria.

2. Randomization to suturing and tissue adhesive groups.

3. Surgery; the patients will undergo the same blepharoplasty procedure. Only the skin closure will differ. The patients will either undergo suture skin closure or tissue adhesive closure.

4. All patients will be followed up at 1 week, 3 weeks and 2 months. The sutured skin closure groups will have skin sutures removed at 1 week.

5. All patients will be assessed in outpatients according to a standardized protocol and patient satisfaction.

6. POTENTIAL BENEFITS AND HAZARDS: If the patient is to be given a placebo or to be deprived of active treatment, or if the patient's regular treatment of known efficacy is to be changed for the purpose of the study, describe the justification for these intentions.

For questionnaire studies, state what steps are to be taken to ensure reliability and to minimise anxiety or embarrassment.

No patients will be deprived of treatment or given a placebo in this study.

7. **LOCATION OF STUDY:**

a. **Laboratory/Hospital/other:**

Western Eye Hospital, London, NW1 5YE

Charring Cross Hospital, Fulham Palace Road, London, W6 8RF

b. Name & address of responsible organisation if not St Mary's NHS Trust, or ICSM (Remember you need the approval of the establishment before starting the research)

8. RECRUITMENT OF SUBJECTS:

Patients presenting to the participating hospitals requiring blepharoplasty and fulfilling the inclusion criteria will be invited to take part in the study.

a. Will they be patients, staff, students or other volunteers?

Patients.

Record inclusion and exclusion criteria.

Inclusion Criteria

1. Patients requiring blepharoplasty procedure.

2. Informed consent obtainable.

3. Patient clinical follow up 12 months after surgery.

Exclusion Criteria

1. Previous blepharoplasty surgery that has failed requiring redo surgery.

2. History of previous lid surgery. E.g. Tumour excision, ectropion, entropion.

3. Complicated blepharoplasty requiring multiple operations or other procedures. E.g. Reconstruction.

4. Patients with only one functional eye.

5. Patients medically unfit for surgery.

Record any ethnic or social class implications. Nil

How many will be recruited? To be calculated following pilot study.

How is recruitment to be achieved?

Patients requiring blepharoplasty procedure from the oculoplastic clinics at the participating hospitals who meet the entry criteria will be invited to take part in this study. If they agree, they will be entered into the study and randomised. A standardised pre-operative assessment form will be completed, written informed consent obtained and a patient information sheet given to the patient.

Will medical/nursing staff or students be involved as volunteers?

No

b. If recruiting patients who are not your direct clinical responsibility, has the permission of the consultant in charge or the co-ordinator of research in your patient group been obtained?

Not Applicable

Name Signature

c. Is the patient's GP to be consulted over an individual's recruitment?

YES

At what stage will the GP be informed?

Entry to trial.

Do you intend to send the GP a copy of the patient information sheet?

YES

If you don't intend to inform the GP, state why not:

d. **Will recruits be paid an honorarium?** NO

If YES: how much?

e. Will travelling expenses be reimbursed: NO

If NO please give reasons

Travelling to and from hospital for both surgery and follow up appointments remains unchanged from conventional surgical management of blepharoplasty. No funding available for patient travelling expense.

9. ADMINISTRATION OF STUDY

a. Insurance / Indemnity cover

What arrangements will be in place to cover subjects/patients

(If you are unsure about this please contact Donna Twyman, Research & Contract Office, Medical School, W2 Ext 020 7594 3664)

b. If this is a drug study, at what stage is this in its evaluation?

c. Is this drug being supplied by a company with a clinical trial certificate in response to an investigator with a clinical trial exemption.

NO

d. If the drug is licensed but being used in a non-licensed context which is not being sponsored by the pharmaceutical company concerned, investigators must obtain a DDX from the Medicine Control Agency (020 7273 0327/8). Clinical Research must not be undertaken in patients unless a CTX or DDX is in operation.

NO

Give the Clinical Trial Certificate (CTC) or Clinical Trials Exemption (CTX) numbers if relevant.

e. If this is a company sponsored trial, are the investigators free to publish their results (subject to a reasonable period of consultation with the company)?

NO

g. If any form of radiation is to be used (eg. X rays, radioactive isotopes, heat, UV, laser, etc) this form must be signed by the Radiation Protection Advisor, or a separate letter attached.

Not applicable.

Name: Signature:

10. SUBSTANCES TO BE ADMINISTERED. *The Committee must be informed immediately of any severe or unexpected adverse side effects.*

a. Please give details of substance to be administered, route, amount, frequency, risks to subject and others, and side effects.

Tisseel adhesive.

A thin layer of Tisseel adhesive is applied proportional to the wound area.

The wound is help clamped for 3-5 minutes to allow adequate time for setting.

Side effects include thromboemoblic complications and allergic reactions. The Tisseel adhesive contains extracts of human plasma and although extensively screened , the transmission of infective agents cannot be totally excluded. No cases of such transmission have been reported.

11. WHAT WILL BE DONE TO SUBJECTS BECAUSE THEY ARE TAKING PART IN THE STUDY?

Describe *briefly* under headings below, what will be required of subjects; indicate if anything is additional to normal clinical management; indicate discomfort and risk to subject & others.

a. Are any treatments or procedures being withheld, which would otherwise be given?

NO

b. Samples to be taken: NIL

c. Tests to be undertaken: (Please circle appropriate test and give details)

Photographs- Standardized to enable a comparison of adhesive and sutures outcomes.

Biopsies: NIL

Anaesthesia: Local

Other invasions: NIL

Non-invasive tests: NIL

Physical Stress Tests: NIL

Psychological Tests: NIL

Psychiatric evaluations: NIL

Questionnaires: Patient satisfaction questionnaire

Hospital admissions for purposes of project: Day case surgery

Outpatient visits: 1 weeks, 3 weeks and 2 months.

Describe what results you expect and how they will be analysed.

The results of blepharoplasty skin closure will be compared between the tissue adhesive and the suturing closure techniques. We hypothesize:

1. Tissue adhesive to reduce operating time for blepharoplasty procedure.

2. Tissue adhesive to reduce the number of follow up appointments.

3. Tissue adhesive to improve aesthetic appearance of blepharoplasty result.

4. Tissue adhesive to improve patient satisfaction.

List discomfort, inconvenience, possible side effects and dangers, untoward signs or symptoms.

We expect discomfort and inconvenience to be unchanged from conventional blepharoplasty surgery, and adhesive may reduce discomfort compared to conventional suturing.

Specific side effects of Tisseel adhesive include thromboemoblic complications and allergic reactions. The Tisseel adhesive contains extracts of human plasma and although extensively screened , the transmission of infective agents cannot be totally excluded.

List precautions which are to be taken with regard to above, and what arrangements will be in place for medical cover. If relevant indicate whether patient information sheet will include name(s) and phone nos. of investigator(s) to be contacted in the event of unexpected reactions of incidents.

Patients will be monitored during and after surgery for both allergic reactions and thromboemobolic complications. Patients will be given specific advice regarding complications and indications to obtain medical help. Contact numbers will be provided.

12. OTHER RESOURCES (Contact your Directorate General Manager to discuss)

a. Will this project make use of hospital resources? (eg,. beds, X rays, NMRI, ECGs, operating time, blood tests, etc?)

NO

b. List departments / Outpatients / Inpatient involvement

Outpatient department – 3 Visits

Photography – 3 Visits

c. How much will they cost?

d.	**Is the cost being met by a research grant?**
NO	

e.	**Obtain signatures of approval from head of each department involved**

Name Signature

f.	**If a compound/drug/device is to be used/tested as part of the study, state the source of funding for its provision.**
Tisseel adhesive, provided by Baxter Healthcare Ltd.	

g.	**Will a questionnaire be used?**
YES	
If YES, and less than 4 A4 sheets, attach a copy with each form copy. If questionnaire is standard, validated, and / or longer than 4 sheets send 2 copies only.	

f.	**Will a semi-structured interview be used?**
NO	

13. HAVE YOU HAD STATISTICAL ADVICE?

YES

a. From whom did you get it?

b. …in preparing the protocol? NO

c. …in designing the analysis? NO

d. …in deciding the power of the study and number of subjects needed?

YES

14. SENIOR NURSE OUTPATIENT / WARD

The senior nurse should be supplied with a copy of patient information sheet relating to studies on patients under her supervision.

a. Do you plan to ensure this is achieved? YES

15. CONFIDENTIALITY

a. What steps will be taken to safeguard the confidentiality of patients' records?

Patient records for the trial will be stored separate to conventional hospital notes in a secure location in the Western Eye and Charring Cross Hospitals. Access to the records will be limited to staff associated to the study.

b. Is data to be recorded automatically?

Data is to be recorded according to standardized protocols. These will include both outpatient assessments and photographic records.

If non coded information is being collected, provide copy of your data registration form. It is necessary to comply with the requirements of the data if in doubt contact District Data Protection Officer (020 7594 5535)

c. If the study is a company sponsored trial, will the company require access to the patients' notes? YES

If YES provide documentation to the effect that confidentiality will be respected.

16. CONSENT AND PARTICIPANT INFORMATION SHEET

Inadequate or incomprehensible information is the most common reason for delay in projects being approved by the LREC. Information for participants must be fully comprehensible by lay individuals. Read the Guidelines carefully and make sure your sheet addresses appropriate headings, eg opt out clause, researcher's name/tel no., invite to do research, risks and benefits, etc.

a. IS CONSENT REQUIRED? YES

If YES, will consent be: WRITTEN – Customised form.

If WRITTEN is the LREC Consent form to be used? If you are customising this form please send a copy with each application form copy.

If NO, explain why consent is not required, or explain any difficulty that might arise in obtaining consent.

c. IS A PATIENT INFORMATION SHEET TO BE MADE AVAILABLE?

YES / NO If YES please enclose a copy with each application form copy.

Consult the guidelines carefully for necessary headings.

* *Ensure this includes statements to the effect:*

* *Entry to the study is entirely voluntary*

* *Failure to enter, and subsequent decision to withdraw from the study will not effect the patient's medical care.*

* *Paragraph about indemnity cover is included: (eg. ABPI Guidelines for drug sponsored studies)*

* *Risks and benefits*

c. What arrangements will be made for subjects for whom English is not a first language?

Patients who are unable to comprehend a basic understanding of the English language are not appropriate for local anaesthesia technique under conventional suturing or tissue adhesive technique.

d. Who will obtain consent?

Doctors directly involved in the project, who have received detailed training in the protocol.

e. Will participants be informed of the nature and risks of their participation?

Patients will be informed of the principles of the trial in a patient information sheet.

f. I / we confirm that the following will be placed in the patient's records and in the case of research volunteers these will be held by the named investigator for the study:

* the signed consent form: * patient information sheet:

Name(s) of those who will be obtaining consent Signature:

17. PAYMENTS / SPONSORSHIP

a. Are any / all of the investigators in receipt of any payments / sponsorship?

NO

b. Who is funding the investigation?

Baxter Healthcare Ltd.

c. How much money may be provided for this project alone? Give details, specifying whether this funding is part of a larger sum granted for a number of projects.

18. WILL THE INVESTIGATOR(S) / DEPARTMENT RECEIVE GRANTS/PAYMENTS/SPONSORSHIP FOR THE WORK UNDERTAKEN?

YES

a. How is the money to be spent? (List major items of equipment, staff, etc) Tisseel tissue adhesive kits + Surgical equipment Digital Camera + Photography Medical Records + Data Storage Stationary + Secretarial Time

b. Please give details of any other related payments

19. WHAT PROBLEMS MAY HINDER A SUCCESSFUL COMPLETION OF THIS STUDY? (This may include ethical problems that may arise during the course of the project). NIL

20. OTHER FACTORS Please indicate any other factors relevant to approval from LREC.

---

*Please send **11 photocopies** of this application form + additional information as specified, to:*

Rosalind Cooke, Mailbox 121, R&D St Marys Hospital, Praed Street, London W2 1NY

Tel: 020 7886 6514 fax: 1529

6.2 Appendix 2- Patient consent form

Clinical study comparing two types of skin closure following blepharoplasty. (COREC number)

1. This study compares 2 different skin closure techniques; Conventional suture closure of skin and tissue adhesive closure.

2. I confirm that I have read and understood the information sheet for patients relating to the above study and have had the opportunity to ask questions.

3. I understand that my participation is voluntary and I am free to withdraw at any time, without giving reasons, without my medical care or legal rights being affected.

4. I understand that sections of my medical notes may be looked at by responsible individuals from within this hospital or from regulatory authorities where it is relevant to my participation in research. I give permission to these individuals to have access to my records.

5. I give permission for information which is collected in the above study to be stored both as paper and electronic records. I also give permission for this information to be analysed as part of this research.

6. I agree to participate in the above study.

_____ Signature of doctor obtaining consent

_____ Name of doctor

_____ Date

_____ Signature of patient

_____ Name of patient / guardian

_____ Date

6.3 Appendix 3- Patient Information Sheet

Patient information sheet : Blepharoplasty study

Thank you for considering participation in the blepharoplasty study.

Purpose of study

This study compares two surgical techniques in closure of the wound following blepharoplasty.

Why have I been selected ?

You have an eyelid/ s which requires surgery. Surgery is the only method by which the shape of your eyelid may be changed. The surgical method to do this is well established. We would like to compare the results of closure of the wound following blepharoplasty.

1. Traditionally the wound is closed using sutures. These sutures are then removed one week after the operation.

2. A tissue adhesive is available that can seal the wound in a few minutes avoiding the need for sutures and one week suture removal. Tissue adhesive has been used by plastic surgeons for a number of years to close skin with good cosmetic results.

The blepharoplasty surgery technique would be unchanged except for wound closure at the end of the operation. We would like to find out if there is a difference between the two methods that would justify using only one method in the future. There have not been any studies done before comparing these methods and the answer would help us determine the best way to close skin following blepharoplasty.

Do I have to take part?

You are not obliged to take part. If you decide to take part, you will be given this information sheet and be asked to sign a consent form. The operation is similar to what you would be offered if you

were not part of the study. You are free to withdraw at anytime and without giving a reason. If you decide not to take part, the quality of your care will not be affected in any way.

What is involved if I decide to take part?

Half of the patients taking part in this study will be randomised to have one type of surgery and the other half to the other. The surgery is normally done under local anaesthetic. Whatever surgery you have been allocated to, we will check you eyelid in the clinic at 1 weeks, 3 weeks, and 2 months after the operation. If you notice any problems with your eyelid before or between these scheduled visits then, you should contact one of your treating doctors.

Are there risks in this operation?

The risks of the blepharoplasty operation are recurrence, over or under correction, infection and inflammatory reaction. This operation is not a new procedure and is very safe, however very rarely blepharoplasty may be complicated with blindness. Tissue adhesive has been used for a range of plastic surgery techniques and rarely has been complicated by allergy or an increased risk of blood clots. The tissue adhesive is made from human blood products and is extensively screened for infectious material. No reports of infection spread by tissue adhesive have been reported.

What happens if something goes wrong?

If you wish to complain about the way you have been treated during the course of the study, the normal NHS complaints mechanisms will be available to you. If you are harmed due to someone else's negligence, then you may have grounds for legal action but you may have to pay for it. There are no special compensation arrangements attached to this study.

Will information on me taking part in this study be kept confidential?

All information collected about you during the course of the study will be kept strictly confidential.

What will happen to the results of the study?

The results of the study will be published after 2 years of you completing your treatment. You will not be identified in any report or publication.

Who has reviewed the study?

The research ethics committee of the NHS Trust of your local hospital has reviewed and approved this study.

For further information, please contact your own Consultant Ophthalmologist or The Project Co-ordinator :

Miss Jane Olver, Consultant Ophthalmologist,

The Western Eye Hospital

Marylebone Road,

London NW1 5YE

Telephone : 020 7886 3264

Fax : 020 7886 3259

6.4 Appendix 4- Information sheet for the patient's general practitioner

Blepharoplasty surgery : A comparison of skin closure techniques following blepharoplasty, using conventional suturing techniques compared to tissue adhesive. (COREC number)

Name :
Date of birth :
Hospital Number :
Male / Female

Dear Doctor,

Your patient has agreed to participate in the above study. It is a multicentre prospective randomised study aimed at comparing the results of suturing and tissue adhesive surgical skin closure.

All patients will undergo blepharoplasty in the same manner. Skin closure will be randomized to conventional suturing and tissue adhesive. Suture closure requires additional operating time, suture removal at 1 week post-operation and may give a variable tissue healing response and resulting scar. Tissue adhesive has been utilized for a number of plastic and oculoplastic procedures with favourable aesthetic results. However, there have been no randomised controlled prospective studies comparing these two procedures.

Our study aims to determine whether there is any significant difference in the success rates of these two operations.

If you have any enquiries about this study, please contact the local Consultant Ophthalmologist in charge of your patient or the Project Co-ordinator :

Miss Jane Olver,

Consultant Ophthalmologist,

The Western Eye Hospital,

Marylebone Road,

London NW1 5YE

Telephone : 020 7886 3264

Fax : 020 7886 3259

6.5 Appendix 5- Operative Record

Operative record

Name : Date of birth : Hospital Number : Male / Female	Hospital : (Please circle) Western Eye Hospital, London Charing Cross Hospital, London

1. Date:

2. Type of surgery(please circle): Suture Vs Adhesive

3. Surgeon (Name and grade) :

4. Study eye (please circle) : Right / Left/ Both

5. Anaesthetic : Local

6. Operative complications (if any):

7. Comments (eg. if procedure or materials different from protocol)

6.6 Appendix 6- Postoperative record

Name : Date of birth : Hospital Number : Male / Female	Hospital : (Please circle) Western Eye Hospital, London Charing Cross Hospital, London

1. Date:

2. Type of surgery(please circle): Suture / Adhesive

3. Time after surgery (Please circle) : 1 Week/ 3 Weeks/ 2 Months

4. Study eye (Please circle): Right / Left/ Both

5. Form completed by (Name and grade) :

6. Symptoms (please circle):

Irritation	Discharge	Pain	Other:
Stickiness	Foreign body sensation	Epiphora	

7. Signs:

	Right eye	**Left eye**
Visual Acuity		
Visual Field Testing		
Brow Height		
Margin reflex distance, (upper and lower, mm)		
Position of eyelid crease		
Lagophthalmos		
Cornea (SPK / erosion / ulceration / other)		
Tear Film/ BUT		

8. Postoperative complications (please circle) :

Ptosis/ Infection / Stitch granuloma / Wound dehiscence / Other (please state):

9. Photographs requested Yes/ No

10. Result (please circle) : Success / Failure(please state reason for failure):

11. Any other comments (eg. further surgery needed)

6.7 Appendix 7- Photographic record

Name : Date of birth : Hospital Number : Male / Female	Hospital : (Please circle) Western Eye Hospital, London Charing Cross Hospital, London

1. Date:

2. Type of surgery(please circle): Suture / Adhesive

3. Time after surgery (Please circle) : Pre Op/ 1 Week/ 3 Weeks/ 2 Months

4. Study eye (Please circle): Right / Left/ Both

5. Photographs taken by:

6. Photograph standardization:

	YES / NO
Both eyes- primary position	
Both eyes-looking up	
Both eyes-looking down	
Close up-incision site	
Close up-opposite side	

7. Any other comments

6.8 Appendix 8- Patient Satisfaction Questionnaire

We would appreciate you completing this form so we can assess your treatment completely and aim to improve the oculoplastic service further. Your comments are confidential

Please **circle** your choice:

Were you happy with your blepharoplasty surgery? Yes/ No

Is there any part of the surgery you were not happy with?

Prior to operation Yes/ No

Operation Yes/ No

After operation Yes/ No

1. How well do you like the appearance of your eyes and eyelids?

Not at all	Somewhat	Moderately	Very much	Completely
0	1	2	3	4

2. Do you feel like the appearance of your eyes makes you look tired?

Completely	Very much	Moderately	Somewhat	Not at all
0	1	2	3	4

3. How much do you feel your friends and loved ones like the appearance of your eyes?

Not at all	Somewhat	Moderately	Very much	Completely
0	1	2	3	4

4. Do you feel the current appearance of your eyes limits your social or professional activities?

Always	Usually	Sometimes	Rarely	Never
0	1	2	3	4

5. How confident are you that the appearance of your eyes is the best that it can be?

Not at all	Somewhat	Moderately	Very much	Completely
0	1	2	3	4

6. Would you like to surgically alter the appearance of your eyes?

Definitely	Most likely	Possibly	Probably not	No
0	1	2	3	4

Other Comments regarding your surgery:

Are there any other ways we could continue to improve the oculoplastic service?

6.9 Appendix 9- Ethics Approval Letter

EC No: 02.222
R&D No:
Registered Date: 25.2.03

St Mary's NHS
NHS Trust

Local Research Ethics Committee, R&D Office
Mailbox 121, St Mary's Hospital, Praed Street, London, W2 1NY
Tel No: 020 7886 6514: Fax No: 020 7886 1529
Email: Ros.Cooke@st-marys.nhs.uk

22 May 2003.

copy to Doriz
Sheng at Moorfields
Jules at CoW
me here
me at home

Mr Sheng Lim
Specialist Registrar
Western Eye Hospital
Marylebone Road
London NW1 5YE

Dear Mr Lim

A randomised prospective study to evaluate blepharoplasty skin closure by Tissseel glue in comparison with conventional suturing technique.
Miss Oliver, Bunce, Zuercher Mr Lim, Dr De Silva, WEH
EC no: 02.222 R&D no:

On behalf of the members I am pleased to say that St Mary's Local Research Ethics Committee (LREC) discussed the above project at their meeting on 1 May 2003. The following grid shows the documents reviewed.

Research documents approved	Original date	Decision date
LREC application form	undated	22.5.03
Study Protocol	31.1.03	22.5.03
Information sheet and consent	31.1.03	22.5.03

The members of the Committee present agreed there is no objection on ethical grounds to the proposed study, I am therefore happy to give you the favourable opinion of the committee in accordance with the ICH Good Clinical Practice Guidelines.

This decision is given on the understanding that the research team will observe strict confidentiality over the medical and personal records of the participants. It is suggested that this be achieved by avoidance of the subject's name or initials in the communication data. In the case of hospital patients, using the hospital record number can do this; in general practice, the National Insurance number or a code agreed with the relevant GP.

Vice Chairman's initials

EC No: 02.222
R&D No:
Registered Date: 25.2.03

A randomised prospective study to evaluate blepharoplasty skin closure by Tisseel glue in comparison with conventional suturing technique
Miss Oliver, Bunce, Zuercher Mr Lim, Dr De Silva, WEH
EC no: 02.222 R&D no:

It should be noted:

The Committee's decision does not cover any resource implications, which may be involved in your project. **Approval by the REC does not automatically mean that the study may proceed.** It is the responsibility of the NHS body under whose auspices the research is to take place to decide whether or not a study should go ahead, taking account of the ethical advice of the REC. Therefore, investigators should seek Trust approval before proceeding with the study.

Although the Committee's decision is for the life of the project, the LREC must be sent an Annual Progress Report. We also need to be informed of any adverse events, amendments or changes to the study that may occur during the course of your investigations, quoting the Ethics Number in any correspondence. Where research involves computer data, this may be subject to the Data Protection Act. The GPs of any volunteers taking part in research projects should be aware of their patients' participation. Every care should be taken to obtain the volunteers' informed consent to participate in the research project with the necessary help being provided for volunteers with language difficulties.

Yours sincerely

Barrie Newton

Barrie Newton
Vice Chairman
21 May, 2003

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