"A ONE YEAR RANDOMIZED CLINICAL TRIAL TO EVALUATE THE EFFICACY OF CONJUNCTIVAL AUTOGRAFT WITH FIBRIN GLUE AND AUTOLOGOUS BLOOD IN PTERYGIUM SURGERY AT KLES DR.PRABHAKAR KORE HOSPITAL AND MRC, BELAGAVI."

BY

REG.NO.BK0117002

Dissertation

Submitted to the

KLE Academy of Higher Education and Research, Belagavi, Karnataka.

In partial fulfilment of the requirements for the degree of

MASTER OF SURGERY
IN
OPHTHALMOLOGY

DEPARTMENT OF OPHTHALMOLOGY,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
BELAGAVI, KARNATAKA.

APRIL 2020

KLE ACADEMY OF HIGHER EDUCATION AND RESEARCH, BELAGAVI,KARNATAKA.

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ABSTRACT

BACKGROUND:

Pterygium is a common ocular disorder.It is a degenerative condition ofthe conjunctiva in which the subconjunctival tissue proliferates as vascularized granulation tissue and invades the cornea mainly, superficial layers of stroma and Bowman's membrane.

Various methods of surgical excision have been described each having its own advantages and disadvantages. Currently, conjunctival autograft technique is the most widely practiced. Many modifications of the same have been introduced with advantages of lesser costs and lower rates of recurrence. Clinical trials have been done to compare the efficacy of graft with sutures or fibrin glue in comparison with that of autologous blood. If it can be proven that the outcomes with autologous blood is equivalent to that of fibrin glue or sutures then the advantages will include lower recurrence along with cost effectiveness.

AIMS AND OBJECTIVES: To compare the following parameters in pterygium excision surgery with conjunctival autograft with fibrin glue and autologous blood:

1. Graft stability

2. Postoperative outcomes like pain, foreign body sensation, lacrimation, discomfort during blinking, presence of subconjunctival hemorrhage, displacement of graft,overall appearance of the eye and complications like graft dehiscence ,graft retraction and graft site papilloma.

MATERIALS AND METHODS: It is a prospective,randomized clinical trial of patients with will pterygium in which 50% of the patients will undergo pterygium excision with conjunctivalautografting using fibrin glue and 50% patients will undergopterygium excision with conjunctivalautografting using autologous blood. The study population was selected from the

patients attending Ophthalmology OPD at KLES Dr.Prabhakar Kore Hospital and Medical Research Centre.The study periodwas from January 2018 to December 2018.

RESULTS: A total of 64 eyes were included in the study. Each group had 32 eyes. Cases with primary pterygium were included in the study. Mean age in Group I was 49.13 years and 47.22 years in Group II. In this study it was observed that 5.4% belonged to grade I, 63% to grade II and 2.3% to grade III. Maximum incidence of pterygium was seen in the age group of 41– 50 years. Majority of them were females (73.4%).At the first postoperative day, pain was seen in28% of patients in group I and 34% in group II which reduced to 0% in group I and 9% in group II at the end of first postoperative week.At the first postoperative day, foreign body sensation was seen in 44% of patients in group I and 69% in group II which reduced to 10% in group I and 28% in group II at the end of first postoperative week.Subconjunctival hemorrhage was present in one patient in group I and in three patients in group II. Displacement of graft was present in three patients in group I.

CONCLUSION: This study showed that the incidence of postoperative symptoms like pain, foreign body sensation and lacrimation were seen among fewer patients in the fibrin glue as compared to the autologous blood group.Though the displacement of graft was higher in fibrin glue.The main disadvantage of fibrin glue is its high cost. Autologous blood is a cost effective alternative and is the most commonly used method.

Key Words: Pterygium,conjunctival autograft, fibrin glue, autologous blood.

LIST OF ABREVIATIONS:

Ig G	**Immunoglobulin G**
Ig E	**Immunoglobulin E**
UV	**Ultraviolet**
LSCD	**Limbal Stem Cell Deficiency**
Ca Cl_2	**Calcium Chloride**
MMC	**Mitomycin C**
VEGF	**Vascular endothelial growth factor**

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INTRODUCTION

Pterygium is a degenerative condition ofthe conjunctiva in which the subconjunctival tissue proliferates as vascularized granulation tissue and invades the cornea mainly, superficial layers of stroma and Bowman's membrane.[1]

The term pterygium is derived from the ancient Greek word "pterygion" meaning wing.It is characterized by a triangular growth of the bulbar conjunctiva over the cornea located within the interpalpebral fissure and growing from the nasal side. This is a hyperplastic and elastotic degeneration proliferating as vascularized granulation tissue in the form of a wing shaped fold growing upon the cornea.More number of cases occurs in the "pterygium belt" located between 30 degrees north and 30 degrees south of the equator.[2]

The worldwide incidence ranges from 0.7% to 33%.[3]Pterygium is more common in tropical, dry, breezy, dusty and smoky conditions.[4,5]The UV type B light in solar radiation was implicated as the most significant environmental factor in the causation of pterygium[6,7]Koranyi et al proposed that pterygium occurs due to limbal stem cell deficiency. Damage or alteration of the deeper layers of the limbal epithelium results in an abnormal corneal surface. Conjunctival epithelial ingrowth, vascularization and inflammation are the diagnostic features.[8]Recent immunohistochemical studies have proved that p-53 mutation in limbal epithelial basal stem cells lead to the development of pterygium.[9]

Medical treatment may be tried initially which mainly provides symptomatic relief but does not alter the course of the disease process in the long run.

Surgical excision is the mainstay of available treatment. Several techniques have been developed with addition of adjunct therapies like betairradiation, thiotepa, 5-fluorouracil and mitomycin C. Amongst all methods, autologous conjunctival grafting appears to be the best with advantages of least recurrence rate and better safety profile.[10,11]

The technique of conjunctivalautografting was introduced by Kenyon et al in 1985 which showed a low recurrence rate of 5.3%.[12]In 2004, Koranyi et al used fibrin glue for the first time for conjunctival autografting.[8]

Fibrin glue is a tissue derived adhesive agent which has been used in various fields like Neurosurgery, Cardiovascular surgery, Otorhinolaryngology, Oral surgery, Gastroenterology and Plastic Surgery.[8]

It has been used in a variety of ophthalmic procedures like conjunctival transplant in refractory conjunctivochalasis, pterygium surgery, conjunctival wound closure in strabismus surgery, corneal surgery for perforated corneal ulcer, descemetocele,epikeratophakia, refractive surgery, glaucoma surgery and vitreoretinal surgery.[13]

Fibrin glue is an alternative to sutures for securing conjunctivalautografts in pterygium surgery and has the advantages of improved postoperative comfort, reduced surgical time, lesser postoperative complications like graft dehiscence, suture associated granuloma and abscess, lower recurrence rates and inflammation.[14]

The disadvantages of fibrin glue are its high cost and the risk of transmission of diseases like hepatitis B and human immunodeficiency virus infection when it is fractionated from pooled human plasma.[16]

Graft fixation with autologous blood is easily available, safe, economical, results in less patient discomfort and a shorter surgical duration.[15]

A study conducted byGayathri Nadarajah et al[16] it was shown that during the autologous blood method there was difficulty in controlling the amount of sub-graft blood. If more blood oozes, a larger clot forms beneath the graft and the contraction of this may cause dislodgement of the graft. Higher rates of recurrence and more complications as a result of exaggerated fibrovascular response were probably due to more growth factors in fresh blood.

This randomized control trial was conducted to study the efficacy of conjunctivalautograft in pterygium surgery with fibrin glue and autologous blood.

OBJECTIVE

To compare the following parameters in pterygium excision surgery with conjunctival autograft with fibrin glue and autologous blood:

1. Graft stability

2. Postoperative outcomes like pain, foreign body sensation, lacrimation, discomfort during blinking, presence of subconjunctival hemorrhage, displacement of graft, overall appearance of the eye and complications like graft dehiscence ,graft retraction and graft site papilloma.

REVIEW OF LITERATURE

HISTORY:

Sushruta, the world's first ophthalmologist in 1000 BC, described pterygium in detail and treated it by using powdered salt and charged with the branch of palm. In an inflamed and bulged pterygium, a toothed forceps was used to tear it followed by application of a flesh-stripping ointment to prevent any recurrences. [17]

In 469 BC, **Hippocrates** used eye drops composed of substances like lead, zinc, copper,iron, bile juices, urine and maternal milk.[17]

Bartisch in 1583 used a mixture of sugar, bloodstone (hematite powder), alum, white vitriol, camphor and wine tartar.[18]

Celsus(circa 25 BC-50 AD) described a procedure where he passed a thread behind the pterygium from the lower to upper edge. The pterygium was detached from the eye by moving it back and forth. Lastly, the thread was pulled forward and the pterygium mass was cut with a scalpel.[19]

In 1000 AD, **Avicenna** proposed cutting of the pterygium with scissors.[20]

Scarpain 1802, described a procedure where he separated pterygium from the cornea by its head using forceps, dissected around four mm behind the limbus and this part was removed by an incision along the limbus.[21]

Arlt(1850) proposed a technique in which a rhomboid of tissue was excised and closure was done in a cruciate manner.[22, 23]

In 1855, **Desmarres** gave description of an operation in which pterygium was separated from the cornea by its head and incised along the superior and inferior

borders and extended inferiorly and temporally along the inferior incision. The pterygium was either buried downwards into the conjunctiva or sutured into the lower fornix. **Terrien's** modification incorporated the procedure of tucking and the flap was brought upward.[24]

Knapp (1868) removed the pterygium from the cornea, divided it into two vertically and incisions were made down the top as well as bottom margins. Divided parts were sutured as folds of conjunctiva. All the conjunctival flaps were sutured together at the limbus in the end.[22]

In the twentieth century:

McReynolds (1902) described a transplantation method where the pterygium was detached from base, a mattress suture was taken through the pterygium head and directed into the conjunctival pouch inferiorly and removed through the inferior fornix.[25]

Gifford (1909) proposed a method in which a small, very thin epithelial graft was taken from the flexor surface of the arm or forearm and placed over the bare sclera following excision of the pterygium.[26]

In 1911, grafts prepared from human corneas were used by Morax and Magitot.[22]

Terson in 1911 first used irradiation treatment in which he applied galvanocautery to the denuded area after covering it with a conjunctival flap.[20]

The use of keratoplasty was first recommended by **Magitot**in 1916 where the pterygium is excised and a flap is separated from the topmost part of the cornea and transplanted over the bare sclera. [22]

Elschnig (1926) described a technique where the pterygium was resected and a conjunctival flap taken from the other side of limbus was bridged across the defect.[27]

Amorin used diathermy coagulation for pterygium in 1936.[28]

In 1940, **Burnam and Neill**, the radon device was employed.[29]

Kamel described in 1946, a procedure in which pterygium excision was performed and cauterization of the bottom of the mass was done with carbolic acid.[30]

D'Ombrain(1948) performed excision of the subconjunctival tissue up to the caruncle and a bare strip of sclera about 4 mm. wide at the limbus is left.[31]

In 1957, **Haik** described a technique where total excision of the pterygium was done followed by immediate application to the limbus of a 900-rad dose with the strontium-90 applicator.[32]

In 1962, Triethylenethiophosphoramide(thiotepa) was used by **Meacham** to prevent recurrence following pterygium excision surgerybecause of its radiomimetic properties.[33]

In 1947, **Panzardi**was the first to use amniotic membrane transplantation after pterygium removal.[34]

Keratoepithelioplasty was proposed by **Thoft**(1977) in which lenticules of peripheral corneal epithelium with superficial stroma were removed and thereby, the ocular surface was repaired in cases of corneal stem cell deficiency.[35]

Kenyon et al introduced conjunctival autograft procedure in 1985 where the structure of the limbus is reformed which acts as the regenerative tissue for the limbal stem cells[12]

Maldonado MJ (1995) was the first to use intraoperative 5-fluorouracil as an adjuvant in pterygium management.[36]

PTERYGIUM [37,38,39,40,41]

ANATOMY

i) Gross:

The parts are head, a cap next to the head followed by the body.

Head:

This is the dynamic component which forms the cap anteriorly and the body behind it by activation of the subconjunctival connective tissue. It consists of admixture of fibrous and vascular tissue with vasculature contributed by the main mass. It can have varying appearances from stringy, plane and avascular to plump, ropy.

Body:

This gives the appearance of wing and covers the sclera. The head is pulled across the conjunctiva and is dragged resulting in folds superior and inferior to it.There is a classical orientation of the blood vessels towards the apex.

Cap:

This part is avascular and forms the apex, preceding the head. The cornea here is visible till the Descemet's membrane. The proliferation of fibroblasts causes biochemical changes leading to loss of transparency. A smooth or irregular line follows the anterior end and greyish white dots called the 'ilots de Fuchs may be seen extending beyond the margins.[41]

Pigment line:

It lies along the cap and around one millimeter in front of the cap. It is formed in a similar way to that of the Hudson Stahli line.

The tear accumulation at the head of pterygium and the lacus lacrimalis are considered as causative. An iron trapping protein named as lactoferrin is present in tears and is said to prevent deposition of free radicals. This leads to iron deposition at the anterior end of the pterygium, the Stocker's line.[17,39,40]

ii) Microscopic[41,42] :

Histopathological examination of the advancing end of pterygia by Cameron revealed the respective features:

1. The basal epithelial cells of the cornea are demarcated from the Bowman's membrane by fibrous tissue.
2. There is elevation of lowest layer of epithelial cells and their axes altered to oblique from vertical.
3. Erosion of the Bowman's and superficial stroma by the fibrous tissue.
4. Uninvolved corneal tissue ahead of the apex of the pterygium.

Ocular pterygia and pinguecula have characteristic histologic features:

1. Substantiapropria contains subepithelial connective tissue which becomes hyalinized and eosinophilic granular material is deposited in a diffuse or localized manner with proliferation of fibroblasts.

2. Excessive thickened and tortuous fibres that show strong positive staining with elastin specific stains, next to and below the hyalinized region.
3. Concretions are seen among hyalinized and granular areas exhibit either excess of eosinophils or basophils.[37]

Pseudoelastic nature of Pterygium:

The hallmark of elastotic degeneration seen in pterygium and pinguecula, is the appearance of worm-like, tangled and knotted fibres which mimic the staining taken up by true elastic tissue. They are partially or not acted upon by pancreatic elastase.

The characteristic alterations occurring in the conjunctivalstroma are collagen hyperplasia, subconjunctival congestion and new vessel formation. In the predegenerative stage, the collagen fibres are fragmented and show least twisting. This is present in pterygium in the initial stages which distinguishes it from pinguecula.

Elastic tissue stain is taken up when the collagen ages, or degenerates in pathologic conditions because it loses its natural staining character. Since surface chemicals take up stain mainly, a degenerative substance resembling a normal component of elastic tissue may be found in the degenerated area and hence, takes up the stain.[43]

DEFINITIONS AND SYSTEMS OF CLASSIFICATION:

Pterygium has been defined in different ways by different writers.

Sir Stewart Duke Elder: True pterygium is a processin which the conjunctiva shows degenerative and hyperplastic changes with invasion of the cornea. The cornea is covered by a triangular growth of the bulbar conjunctiva.[17]

William M. Townsend: Pterygium is condition in which the epibulbar conjunctiva is covered with a triangular mass of a mixture of fibrous and vascular tissue.[23]

Pseudo pterygium: A condition in which a corneal ulcer or its margin gets attached by the conjunctiva due to an inflammatory process.

True Pterygium [37,38,39,40]**:** It forms in the inter-palpebral area of the eye growing from the bulbar conjunctiva. Itgradually grows in the shape of a wedge or triangle towards the limbus. It originates from the caruncle in nasal pterygium and from lateral canthus in temporal pterygium.[39,40]

It is restricted to conjunctiva without corneal involvement when the growth is hampered. Appearance is that of a tense, wing shaped and triangular mass running towards the sclera from the cornea.

Shift of the plicasemilunaris and the straight path of the vessels are evidence of an ample amount of tension induced by the pterygium. At few instances, the upper end of the plica is pulled out so that it lies at a more horizontal level.

Due to the inflammation produced in pterygium, horizontal bands of fibrous tissue are formed in the involved bulbar conjunctiva. These bands either pull the cornea towards the conjunctiva or the conjunctiva is dragged towards the cornea in a triangular pattern.

CLASSIFICATION BY DIFFERENT AUTHORS:

1. "William M. Townsend[23]:

A. Advancing pterygium.

B. Malignant or fleshy pterygium.

C. Slowly growing pterygium.

D. Stationary pterygium.

E. Atrophic pterygium."

2. "Doherty Classified[17]pterygia as:

A. Progressive type.

B. Regressive type."

3. Fuch's[41] classification on the basis of vascularity, color, thickness and clinical aggressiveness:

A. Pterygium Crassum.

B. Pterygium Vasculosum.

C. Pterygium Camosum.

D. Pterygium Sarcomatosum.

E. Pterygium Membranosum.

4. Winther[17] (1856) Classified as:

"A. True pterygium. "

"B. Pseudopterygium."

Pseudopterygium: If the conjunctiva gets fixed to a corneal ulceration, it leads to the formation of pseudopterygium.

Mechanism of formation of pseudopterygium: A pseudopterygium forms when an inflamed portion of conjunctiva gets attached to a corneal ulcer margin as in marginal corneal ulcer, membrane forming conjunctivitis, growth excision and post iris prolapse.[37,38,39]

Pterygium Staging[44]:

Stage 0: Pinguecula, posterior to the limbus

Stage I: Tissue involvement up to the limbus

Stage II: Tissue just on to the limbus

Stage III: Tissue between the limbus and pupillary margin

Stage IV: Tissue central to the pupillary zone.

Clinical Classification of Pterygium by LucioBurrato: [22]

Based on the clinical characteristics of pterygium and corneal invasion, three main clinical types of pterygia are:

Type I: Small Primary Pterygium:

a. Classical.

b. Fibrous.

c. Pinguecular.

Type II: Advanced primary or recurrent pterygium without involvement of optical zone.

Type III: Advanced primary or recurrent pterygium with involvement of optical zone.

Grading on the basis of degree of corneal involvement:[44]

Grade I - crossing limbus

Grade II - halfway between limbus and pupil,

Grade III - reaching up to pupillary margin,

Grade IV - crossing pupillary margin.

c) Prevalence:

The worldwide prevalence rates have been estimated to range from 0.3% to 37.46% on the basis of multiple studies[45]. Most cases occur in the tropical and dry areas of the world extending from 37^{o} above and below the Equator known as the 'pterygium belt'. In India, the prevalence of pterygium is higher in Maharashtra, Andhra Pradesh, Gujarat and Assam.

Risk factors for pterygium site [17]:

The explanations for nasal pterygium being more common than temporal pterygium is as follows:

1. Light falling on the bridge of the nose reflected onto the nasal limbus.
2. Limbal stem cells in the nasal limbus may be more exposed to increased amounts of UV radiation due to focusing of light and leading to molecular genetic mutations of these cells resulting in pterygium development.
3. Longer upper eyelashes on the temporal side and the increased inferior bending of the lateral part of the upper eyelid and greater amount of sunlight exposure on the lateral part of conjunctiva and cornea.
4. Normally, tears drain from lateral to medial side into the punctum and contains

with it any dust granules entering the forniceal conjunctiva and collects in lacus lacrimalis.

5. Medial fibres of orbicularis oculi are more curved and hence, the nasal subconjunctival tissue is more squeezed.
6. Two anterior ciliary arteries are present on the medial part and the lateral part has only one. Due to this, any irritant will cause more congestion on nasal side and contributes to the formation of nasal pterygia more commonly.

ETIOLOGY AND PATHOGENESIS OF PTERYGIUM:

1. THE DEGENERATIVE THEORY:[30]

Parsons, Schoninger, Duke-Elder, Fuchs proved that pterygium grows from pinguecula and suggested that the pterygium as a further step in this pathologic outgrowth.

Proposed on the basis of following findings:

1. Signs of elastic and hyaline tissue degeneration occurring in the interior portions of the tissues earlier in the course of disease.

2. Occur more commonly following pingueculae.

This degeneration seen in the inner parts of the pterygium tissue are mostly following inflammation for the following explanations:

1. Infiltration of round cells in the outer layers of the cornea in pterygia which are progressive is considered as a marker of chronic inflammations.

2. The steep amplification of conjunctival goblet cells in pterygium cases which is indicative of chronic inflammation.

3. Accumulation of abundant fibrous and connective tissue in the conjunctivalsubmucosa and between Bowman's membrane and corneal epithelium which can only be due to chronic inflammation.

4. No other degenerative process starts in a vascularised and well-nourished region, like the limbus, advances towards the nonvascular cornea and is self-limiting.

5. The increased number of blood vessels of the pterygium, the recurrent episodes of acute inflammatory congestion, age distribution of the patients, pterygium in a fixed location in the uncovered portion of the bulbar conjunctiva— point to an inflammatory origin.

Khalil et al.[46] (1982) concluded from his study that degenerative as well as inflammatory changes occurred in cases of pterygium but it could not be confirmed which process started first or may be both changes started at the same time.

Karai and Hariguchi[47] (1984) claimed that a pinguecula is not always a precursor for a pterygium.

2. The inflammatory Theory:

Gerundo[48](1951) isolated Axenfeld-Moraxella bacillus in 3 among 25 pterygium cases.

Saifet al.[49] (1967) mentioned that exposure to various extrinsic irritants causes a triple response (congestion secondary to dilated capillaries and exudation of fluid from the dilated capillaries and arterioles leading to edema) occurring multiple times leading to an inflammatory reaction.

Mortada et al.[50] (1968) proved that a true pterygium is due to chronic, non-specific inflammation resulting in fibrosis of the sub-epithelial connective tissue of the nasal limbus mainly secondary to the influence of the environmental factors like dust or ultra violet rays.

3. The neoplastic theory:

Redslob[51] (1933) stated that pterygium is a neoplastic polypoid growth of conjunctiva concluded from the high rate of recurrence.

Kamel[30] (1953) mentioned that the neoplastic theory does not hold true as nothing in the pathology of pterygia is suggestive of a neoplastic origin.

Khalil et al.[46] (1982) supported the non-neoplastic nature of pterygium as the changes in the epithelium were mainly in the form of alternating regions of thinning and hyperplasia and the layers of the epithelium were always orderly arranged and the basement membrane of the epithelium was always normal with no signs of breach or downward invasion of the epithelium.

4. The tear film abnormality (dry eye) theory:

Elliot[52] (1966) and Goldberg and David (1976) claimed that abnormalities of tear film leads to localized corneal and conjunctival drying predisposing to pterygium formation.

Paton[47] (1975) postulated that exposure to dryness, heat, ultra-violet rays, glare and reflections of strong light cause formation of a mass at the limbus causing elevation of limbus, ultimately leading to exposure of the cornea due to poor lid apposition on it.

Taylor [7](1980) stated that dryness of the cornea and conjunctiva occurring due to disruption of the tear film, as a result of either evaporation or micro-trauma from micro-patches of dust, seems to be the primary factor in pterygium development. Drying of the inter-palpebral tear film occurs most easily in the medial third of the inter-palpebral fissure as it is farthest from the lacrimal gland and nearest to puncta.

Caldwell[53] (1985) stated that drying and exposure may produce an anoxic condition of the cornea. This anoxia probably produces an angiogenic factor which in turn leads to neovascularization of the dellen area causing fibrovascular ingrowths onto the cornea.

Coroneo[54] (1999) reported that evaporation of the tear film by wind destroys tissues of the inner third of the palpebral aperture and damage occurs to the conjunctival and corneal epithelium and Bowman's membrane by solar radiation.

5. The immunological theory:

Pinkerton et al [55] (1984) mentioned that the presence of lymphocytes and plasma cells in the stroma of the pterygium tissue indicates that an immunological process may be involved in the pathogenesis of pterygium. He also added that the localization of Ig G and Ig E indicates an immunological mechanism and the presence of Ig E suggests a possible involvement of type I hypersensitivity.

Ibrahim et al [56] (1991) mentioned four points in support of the immunological theory:

1) The demonstration of immunoglobulins and complements in pterygium tissue are suggestive of an immune complex mediated type III hypersensitivity reaction.
2) The presence of immunoglobulins along the walls of the epithelium may be indicative of a type II hypersensitivity reaction.
3) Deposition of fibrinogen attributed to vascular injury mediated by immune complexes.
4) The fibrinogen in inflammatory cells may represent phagocytosedfibrinoid material due to necrosis resulting from local antigen antibody interaction.

6. The ultra-violet rays theory:

Blum [17](1959) concluded that UV rays are the most important nuclear damaging agent based on the observation in his experimental study of epithelial hyperplasia, degeneration of the Bowman's membrane and vascularization of the corneal stroma induced in mice by large doses of UV rays.

The ultra-violet theory of pterygium causation proposed by Moran and Hollow [6] (1984)was based on studies conducted on rural Australian and Japanese welders. A causative relation was established between environmental ultra-violet radiation and pterygium on the basis of an Australian study. Non-aboriginal women in rural Australia generally stay indoor most of the time compared to men and thereby, protected from solar radiation, both direct and scattered.

Taylor et al.[4] (1989 & 1992) divided ultra-violet radiation into three bands based on its biologic activity: UV-A(400-320nm), UV-B(320-290nm) and UV-C(290-100nm). The ultraviolet C does not naturally reach the earth's surface as the cornea absorbs almost all the radiation below 290nm.

Coroneo[57] (1993) proposed that the outermost part of the eye behaves like a lens, light is focused from the side of the cornea and light is transmitted by transcorneal pathways to the opposite side. Using computer assisted optical ray tracing techniques, predisposing individuals can be identified. He also stated that the peak intensity of light at the nasal limbus is approximately 20 times greater than that of intensity of incident light. The corneal epithelial stem cells are struck from behind and are not protected by the more superficial layers of the epithelium in this area.

7. The limbal stem cell dysfunction theory:

Chen and Tseng [58](1990) stated that the basal limbal epithelium of the cornea contains stem cells which contribute in the maintenance of the demarcation between cornea and conjunctival epithelia.

It was reported that the primary abnormality in pterygium is the abnormal stem cells. Immunohistochemical techniques have demonstrated altered limbal epithelial stem cells at the leading edge of pterygia along the normal corneal epithelial membrane.

Based on this, Dushku and Reid[59] (1994) proposed that the pathogenesis of pterygia is due to altered limbal epithelial basal cells which give rise to a zone of motile daughter cells, the pterygium cells. These migrate from the limbal region centripetally along the corneal basement membrane dissolving Bowman's layer.

Grimmett and Holland[60] (1997) stated that conjunctivalization of the cornea is prevented by a healthy population of limbal stem cells that acts as a stable barrier at the junction. So, pterygium formation may ultimately represent a focal limbal stem cell dysfunction state.

DIFFERENTIAL DIAGNOSIS:[39,40]

1. Pseudopterygium: It can be located anywhere on the limbus unlike true pterygium. Corneal trauma history like marginal keratitis, corneal ulcer and lime injuries is mostly present and a probe can be passed with ease beneath the neck.

2. Pinguecula: Usually does not invade the cornea and becomes difficult to differentiate when it is big.

3. Epithelioma: In this, the surface is more irregular, the subconjunctival connective tissue of the caruncle is not heaped and blood vessels are not oriented into any specific shape.

4. Bowen's tumor: A tumor with features similar to that of epithelioma with rare occurrence.

5. Epithelial hyperplasia: They demonstrate thickening of the subconjunctival connective tissue and greyish or whitish plaques with surrounding congestion.

6. Squamous cell carcinoma of the limbus: Probably due to chronic ultraviolet radiation exposure. Commonly occurs in the inferotemporal zone of the limbus and diagnosis is confirmed by histopathological analysis.

7. Conjunctival papilloma: It is highly vascular and bleeds easily. Mainly viral in origin and diagnosis is histological.

8. The limbaldermoid: A congenital, rare lesion which has a rounded reddish yellow appearance situated between the limbus and cornea.

9. Phlyctenularkeratoconjunctivitis: It is a circumscribed, minute gel-like conjunctival lesion with coiled capillaries around it and conjunctival congestion. Pathogenesis is delayed hypersensitivity to microbial or diet proteins. Occurs commonly in infants and children.

10 .Lymphoma of the conjunctiva: A very rare lesion occurring in the inferior and nasal bulbar conjunctiva. This is a salmon pink, flat subconjunctival lesion which is not much vascularized.

Signs and symptoms[17, 61]:

•Discomfort

•Foreign body sensation

•Congestion

•Irritation

•Lacrimation

•Obstruction of the visual axis (Decreased visual acuity).

•Diplopia on lateral gaze.

•Acquired irregular astigmatism.

•Painless area of elevated vascularized white tissue on the inner and outer edges of the cornea.

MANAGEMENT OF PTERYGIUM

MEDICAL MANAGEMENT: [62]

Mild symptoms of photophobia and injection from a small pterygium can often be managed by avoiding smoke and dust-filled environments. Topical, preservative-free lubricants, vasoconstrictors and a mild non penetrating corticosteroid can safely relieve symptoms when used judiciously. Ultraviolet light blocking spectacles have been recommended to prevent progression.

SURGICAL MANAGEMENT:

Indications for surgical treatment of pterygium include [63]:

- Proximity to the visual axis resulting in diminution of vision
- Encroachment of visual axis
- Significant astigmatism leading to visual problems
- Restriction of ocular movements causing diplopia
- Atypical appearance such as possible dysplasia
- Symptomatic growth
- Cosmetic concerns

Recurrence is the most troublesome outcome and different surgical techniques have been invented to prevent it.

Anesthesia: If additional surgery such as a conjunctivalautografting is planned, retrobulbar or peribulbaranesthesia would be required.

SURGICAL TECHNIQUES:

Excision (Bare Sclera):

This was first described by D'Ombrain in 1948.Excision of all parts of pterygium is done exposing the bare sclera underneath. It can be done by incising from corneal apex or the pterygium body.

Castroviejo recommended the simultaneous removal of superficial corneal layers while removing the pterygium. He described a smooth dissection that should not be unnecessarily deep to remove the pterygium and any corneal opacity when present .Authorities recommend that maximum cornea should be left intact to avoid the perforation or weakening of cornea.[64]

Youngson[65] made a report on the outcome of 100 bare sclera operations and proved that more than one-third of cases had recurrences. He was of the view that the conjunctival epithelium with adhesion to sclera in contact with corneal epithelium and the pterygium became the advancing edge of a new, rapidly growing extracornealpterygium .

Simple conjunctival closure:

This is the simplest method which consists of complete removal of all the fibrovascular proliferation and suturing the upper and lower cut edges of the

conjunctiva. Czermack recommended that stabilization of the conjunctiva was achieved by suturing through the topmost layers of cornea.

Excision with Primary Closure

A sliding conjunctival flap is prepared by lifting the superior horizontal edge of the conjunctiva with a fine-toothed forceps and separated from the Tenon's capsule lying below with Westcott scissors. The conjunctiva is incised parallel to the limbus; the length of the incision is almost equivalent to that of the horizontal conjunctival defect. The incision is extended peripherally to the approximate length of the vertical conjunctival defect left by the pterygium excision. The flap is then brought inferiorly to cover the conjunctival defect. A one year recurrence rate of only 5% has been established.

In a 5 year study, 800 patients with primary pterygium underwent "merest sclera" surgery. In this, the damaged limbo-conjunctival area is covered completely with superior and inferior conjunctival flaps so that the tear film can be reestablished. After a 1-year follow-up, 17 recurrences were found (2.1%). All these resulted from premature wound dehiscence and/or postoperative infection.[66]

Transplantation of the head of the pterygium:

Desmarres[24] first suggested that a pterygium would atrophy if the pterygium head was dissected and transposed to a new position away from the cornea. Knapp[30] dissected the pterygium, split it into two halves and sutured them to the conjunctiva.

The Mc.Reynold's[25] operation comprised of separating the head, neck and portion of the body of the pterygium from its bed. It was brought down into a pocket of bulbar conjunctiva dissected at 6 o'clock inferiorly by suturing through the head.

Then it was attached at 6 o'clock position to the superficial sclera. This flap was then swept over the pterygium body and then pushed down to the body of the pterygium.

Conjunctival Autograft:

It acts as a barrier following the limbus and migration of nasal conjunctiva after excision of pterygium by bare sclera technique is prevented.

- Kenyon and associates[12] described a transplantation technique where excision of recurrent or advanced pterygium was done followed by harvesting grafts from supero-temporal bulbar conjunctiva to cover the wounds.

- The study included 54 patients and 57 eyes, out of which 80% were recurrent. In the mean follow-up of 2 years, only three (5.3%) recurrences occurred were noted after 2 years of follow up. Minimal subconjunctival tissue has to be taken to avoid graft retraction and scar formation.

- Size of the graft is greater than the bare sclera left after excision. The estimated area of conjunctiva to be excised is delineated by using cautery.

- The head of the pterygium is excised starting from the cornea to the limbus by superficial and sharp dissection. Blunt and careful dissection of the conjunctiva and Tenon's capsule is performed to separate from the horizontal rectus muscle and the bare sclera and rectus muscle are left behind.

- The size of conjunctival graft is measured with the help of calipers.

- Care has to be taken to include minimal subconjunctival tissue in the graft while dissecting it. The conjunctival margins can be adhered to the limbus by means of two interrupted sutures.

- Interrupted sutures of 8-0 Vicryl are used for graft transplantion to the recipient bed and for the limbal margin of the graft, 10-0 nylon is used.

Lamellar Keratoplasty:

When significant corneal thinning is present due to previous pterygium surgery, a lamellar keratoplasty may be indicated to restore the normal ocular surface integrity. Many authors have suggested that a lamellar keratoplasty acts as a barrier to pterygium regrowth.

Recurrence rates after lamellar keratoplasties using lyophilized donor tissue have been reported between 0% and 60%. In severe cases where the visual axis is involved by thinning and scarring, a penetrating keratoplasty may be indicated for visual rehabilitation.[67]

Amniotic membrane transplantation:

I P Luanratanakorn et al conducted a study where the method of Kim and Tseng[58]was used to prepare and preserve human amniotic membrane. It was taken following elective caesarean section and human immunodeficiency virus , hepatitis B and C viruses and syphilis were screened by serological testing. The amnion and the chorion were separated using blunt dissection and harvested amniotic membrane was flattened using nitrocellulose paper. 364cm^2 discs were cut and stored in a sterile vial containing glycerol and Dulbecco modified Eagle's medium in a volume of 1:1 ratio at 280 degrees C.

The study included 346 eyes of 346 patients. The total recurrence rate in the amniotic membrane group at 6 months was 28.1% and 13.3% in the conjunctival group.

Cut and Paste technique using Fibrin glue:

Procedure as described by Koranyi et al [8] -

It is a novel, sutureless minimal incision pterygium surgery, using biological tissue adhesive glue.

- Tisseel Duo Quick is a tissue adhesive with dual components mimicking fibrin formation occurring in the body. One component consists of fibrinogen mixed with factor XIII and aprotinin and the other is thrombin-$CaCl_2$. Both components are mixed together in equal quantities. The fibrin peptides are broken down to fibrin monomers by the action of thrombin. Cross linking of monomers occurs resulting in fibrin clot formation.

- Excision of pterygium was done. Scraping of the wound area was done to clean cornea and sclera and cautery was applied to bleeding vessels. A conjunctival graft of same size as the defect of nasal conjunctiva was prepared at the limbus on superotemporal part of same eye.

- The graft was transferred over the nasal area and glue was used for graft attachment. Epithelial side was oriented upwards and limbal edge approximated to the limbus.

- A drop of thrombin was applied on scleral bed and another drop of protein solution put on the graft. After this, flipping of graft was done over the sclera and creases were flattened.

- Fibrin glue as a method of graft fixation in pterygium surgery is fast and safe without any side effects. The post-operative pain and surgery time are reduced.

Fibrin glue: A tissue adhesive

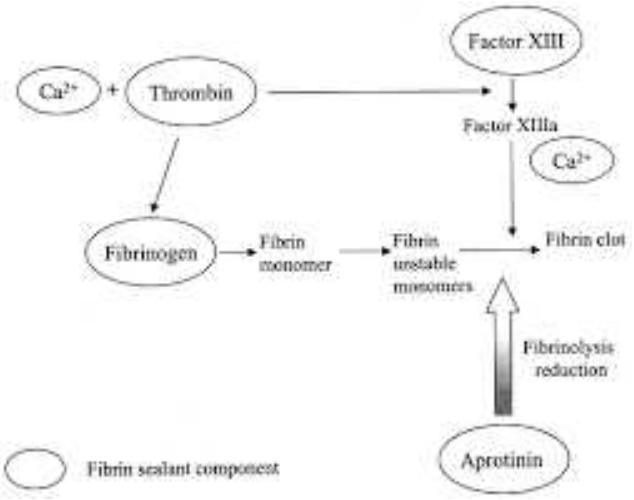
Tissue adhesives are classified into biologic adhesives like fibrin-based adhesives and synthetic adhesives like cyanoacrylate derivatives.

- Fibrin glue is a product derived from blood which is completely absorbed, comparatively simple to use and stored either in a refrigerator or at room temperature [13].
- In 1944, Tidrick et al. used fibrin glue for the first time for skin graft fixation.
- Introduced in ophthalmology in the 1940s to perform penetrating keratoplasty in rabbits[69].
- It simulates the final steps in coagulation cascade where the fibrinogen component is acted upon by thrombin component.[70,71]

Mechanism of action:

- When injury occurs to human tissues, a blood clot is formed to control the bleeding that occurs.
- This resembles the final common pathway of blood coagulation. The adhesive capability of fibrin glue is due to similar pathway.
- Once there is a trigger of the coagulation pathway, activated factor X convertsprothrombin to thrombin and fibrinogen is hydrolysed to fibrin. Factor XIII, present in the fibrinogen component of the glue is activated by thrombin. The clot is stabilized by the process of cross linking and polymerization of the fibrin chains with the help of calcium ions.

- Proliferation of fibroblasts occurs with resultant granulation tissue formation within hours of polymerization of .Within two weeks after application, this process is completed.



The commercially available fibrin sealant kit contains separate vials of these:

1. Freeze Dried Human Fibrinogen (40 mg/ml)

2. Freeze Dried Human Thrombin (500 IU/ml)

3. No antimicrobial preservative is added in any of the components

4. Aprotinin solution (Bovine) as a sterile solution in a composition of 3000 kiu/ml

5.1 x 5 ml ampoule of sterile water for injection

6. Applicator with two mixing chambers and one plunger guide

Storage

The lyophilised powder is to be stored between +2°C and +8°C (35°F and 46°F)

In India, it is available as Tisseel Fibrin Sealant (Baxter Vienna, Austria) and as Reliseal (from Reliance life-sciences).[72]

Advantages

The total surgical time is decreased when suturing the graft is avoided. Its use decreases the risk of postoperative wound infection. Mucous and debris collected in sutures may act as a source of infection.

It is well tolerated, non-toxic and has additional antimicrobial activity. The smooth seal along the entire length of the wound edge gives a higher tensile strength, with the bond being resistant to greater shearing stress. Allergic reactions are rare. Reports of anaphylactic reactions have been attributed to the bovine aprotinin component of fibrin glue.[13]

Disadvantages:

The major drawback is the risk of transmission of diseases from single and pooled blood donors. This may be minimized by screening the donors. The best method is to use the patient's own blood for fibrin glue preparation but it needs at least 24 hours for processing and expensive.[13]

The commonly used method of viral inactivation is the solvent/detergent method which inactivates lipid coated viruses. Additional means of reducing viral transmission risk are a combination of γ-radiation, cryoprecipitation, adsorption, vapor heating, pasteurization and nanofiltration.

Fibrin Glue in pterygium surgery:[73]

Uy et al (Ophthalmology 2005; 112(4):667-71) included 22 patients undergoing pterygium excision in a study to compare the safety and efficacy of fibrin glue and suturing in conjunctival autograft surgery. Fibrin glue was used for grafting in 11 eyes and 10-0 nylon suture was for graft attachment in 11 eyes. There was successful attachment of conjunctivalautografts in both groups and even after 2 months they were intact. The average operating time was comparatively shorter ($P<0.001$) in the fibrin glue group. The patients in the fibrin glue group had fewer postoperative symptoms compared to the suture group.

Adjunctive Therapy:

Adjuncts to surgery like radiotherapy, chemotherapy and argon laser have been suggested to reduce the rate of recurrences.

Chemotherapy:

Thiotepa:

The nitrogen mustard triethylene-thiophosphoramide is an alkylating agent with active antimitotic properties. It acts by inhibition of vascular endothelial proliferation. It was introduced by Meacham in 1962. From the third postoperative day, Thiotepaeyedrops were instilled five times daily over four weeks. Thiotepa (1:2000) was prepared from 15 mg of triethylenethiophosphoramide dissolved in water to make a volume of 15 ml. [74]

Complications:

Irritation,profoundconjunctival congestion, sclerokeratitis and depigmentation of eyelids which may be permanent, especially in darkly pigmented patients.

Mitomycin-C (MMC):

MMC inhibits DNA synthesis and is an alkylating product. It acts on cells in all phases of cell cycle and those not synthesizing DNA too. The number of mitoses is reduced, particularly in the late G1 and early S phases of the cell cycle. When injected directly on the pterygium, it has protective effect on the corneal endothelium and epithelium.[75]

When MMC was used in 0.002% to 0.04%, concentrations for 3 to 5 minutes, the recurrence was reduced significantly (P less than 0.0045) when compared to excision with bare sclera.[76,77]

The recurrence rate varies from 6.7% to 22.5% with the use of MMC intraoperatively in primary pterygium surgery.[78]

The complications are necrotizing scleritis, ulceration, corneal edema, iritis, cataract, glaucoma, hypotony due to injury of the ciliary body and damage to corneal epithelium and endothelium.

Postoperatively, MMC has been used in the form of eye drops at 0.005% to 0.04%, administered four times daily for 1–2 weeks. Recurrence rates were found to be between 0% and 38%.

Donnenfeld reported decreased vascularization and inflammation with injection of 0.1 mL (0.15 mg/mL) of MMC in the body of pterygium one month before the surgery

for pterygium recurrence. There was a 6% recurrence after a 2 year follow up period.[79]

Beta irradiation:

In 1950, the Strontium-90 ophthalmic applicator was introduced. It became popular as it was devoid of gamma rays.

Strontium-90 is produced by nuclear fission of Uranium-235. It has a half-life of 28.1 years and decays to Yttrium-90 with a half-life of 64 hours. [80]

Three weekly 800 cGy fractions beginning within 8 hours of surgery was administered for better cosmesis and reduced recurrences.[81]

Recurrence of pterygium after surgery and beta radiation ranges from 0% to 16% as reported in multiple studies.

Cataract formation after beta radiation is quite common. Other complications include conjunctival congestion, formation of symblepharon, ptosis, atrophy of iris, ulceration of cornea, and panophthalmitis.

Argon Laser:

The laser settings were a spot size of 50 microns, time exposure of 0.1 - 0.2 seconds and a power of 0.2 - 0.3 watts and the number of shots varied from 300 - 550 per sitting. The shots were arranged in 4 rows parallel to the limbus with around 1.5 mm distance between each row.

Argon laser emits a coherent blue-green light of around 488-515 nm wavelength. Therapeutic thermo ablative effect is produced when laser is converted into heat energy.Complications noted include scleral necrosis, cataract and iritis.[82]

Growth Factor inhibitors:

Anti-vascular endothelial growth factor monoclonal antibodies have been widely used in Ophthalmology for suppressing various forms of intraocular neovascular growth, such as exudative age-related macular degeneration and sub-retinal neovascular membranes, proliferative diabetic retinopathy, or neovascular glaucoma.[83]

They include pegaptanib, an oligonucleotide aptamer that binds exclusively to the 165 amino acid isoform of VEGF and recombinant monoclonal antibody bevacizumab and its fragment ranibizumab, which act against all isoforms of VEGF.[83]

Use of bevacizumab is associated with serious side effects like significant cardiovascular toxicity

MATERIALS AND METHODOLOGY

STUDY POPULATION: Patients with pterygium that attend the OPD and fulfill the inclusion and exclusion criteria.

STUDY DESIGN:A prospective, randomized clinical trial.

SAMPLE SIZE: The sample size was calculated based on the following formula:

$$n = \frac{(z_\alpha + z_\beta)^2(s_1^2 + s_2^2)}{(\bar{X}_1 - \bar{X}_2)^2}$$

where zα is linked with the level of significance and zβ is linked with the power of the test. For 5% level of the significance zα =1.96 and zβ =0.84 for 80% power of the test. $\bar{X}_1$ Is the mean of the first group (14.2) and $\bar{X}_2$ is the mean of the second group (12.25).s1 is the standard deviation of the first group (2.98) and s2 is the standard deviation of the second group (1.88).

Larger standard deviation of the two groups shall be considered (2.98).By taking 2.98 SD, sample size should be 60 + 10% of 60=66,i.e.33 subjects in each group.

STATISTICAL ANALYSIS:

The data was compiled and analysed using Microsoft Excel.For continuous variables, mean and standard deviation were used. For categorical data, rates, ratios and percentages were used.

A Chi-square ($\chi 2$) test was employed to determine the significance of differences between groups for categorical data. If p-value is < 0.05 then results would be considered to be statistically significant.

STUDY PERIOD: 1st January 2018 to 31st December 2018.

INCLUSION CRITERIA:

Patients with primary pterygium willing to be enrolled in the study and available for all subsequent follow-ups.

EXCLUSION CRITERIA:

1. Immune system, eyelid or ocular surface diseases (e.g., blepharitis, Sjogren syndrome and dry eye)
2. Hypersensitivity to any component of fibrin glue.
3. Use of anticoagulants or antiplatelet agents.
4. Bleeding or coagulation disorder.

PREOPERATIVE EVALUATION:

Patients were instructed to instill antibiotic eye drops 4 times a day one day prior to the surgery.

Detailed history was taken including the chief complaints and duration of symptoms. Ocular examination including visual acuity, sac syringing, keratometry, subjective refraction, intraocular pressure, slit lamp examination and direct ophthalmoscopy was done.

Using slit lamp examination, the pterygium was graded as:

Grade 0: Pinguecula

Grade 1: <2mm across the limbus onto the cornea

Grade 2: 2-4mm onto the cornea across the limbus

Grade 3: >4mm onto the cornea across the limbus

Grade 4: crossing the pupillary margin

Investigations like routine blood examination, random blood sugar, HIV, HBsAg were done. Medical fitness was taken when required.

Surgical technique:

Reconstitution of fibrin glue:

The fibrin sealant was prepared according to the manufacturer's instructions. The vials containing Fibrinogen, Thrombin solution and Aprotinin were placed in a water bath heated to 32 degrees for 2-3 minutes.

The first component containing fibrinogen is reconstituted by adding Aprotinin to it.The second component containing thrombin solution is reconstituted by mixing with sterile distilled water provided in the kit.

Both the components are withdrawn into separate syringes and mounted onto the duploject injector. A mixing chamber connected to a blunt applicator needle is attached to the 2-syringe nozzle to facilitate mixing of the components. When the plunger is pressed, the components are combined in the mixing chamber in equal

proportions to form the resultant fibrin sealant which can be applied directly to the desired sites.

Steps:

Group 1:

Pterygium excision with conjunctivalautografting using fibrin glue.

After peribulbaranesthesia, the eye to be operated was painted and draped.Universal eyelid speculum was applied and superior rectus bridle suture was taken with 4-0 silk suture material. Head of pterygium was dissected from cornea by holding the apex with fine forceps and scraped with Bard-Parker blade. The body of pterygium with underlying tenon's was excised using Westcott scissors.

All the bleeders over the scleral bed were then cauterized. An approximately same sized conjunctival autograft was measured using Castroviejo calipers and harvested from the superotemporal conjunctiva. The graft should be devoid of tenon's capsule and buttonholing of the graft was avoided.

Then the freshly constituted fibrin glue was applied using a duploject system with a common plunger, over the cauterized scleral bed and the graft was placed over the excised area. Gentle pressure was applied over the graft for 3 to 5 minutes. The eye was patched.

Group 2

Pterygium excision with conjunctivalautografting using autologous blood.After peribulbaranesthesia, the eye to be operated was painted and draped .Universal eyelid speculum was applied and superior rectus bridle suture was applied with 4-0 silk suture material.Head of pterygium was dissected from cornea by holding the apex with fine forceps and scraped with Bard-Parker blade. The body of pterygium with underlying tenon's was excised using Westcott scissors.

The scleral bed is allowed to bleed for around 6-7 minutes.

Dimensions of the desired conjunctival graft were measured using Castroviejo calipers and separated from the underlying Tenon's using scissors. Lateral edges were incised and limbal conjunctiva was incised last. The graft should be devoid of any tenon's capsule and buttonholing of the graft was avoided. The dissected graft was flipped over cornea and placed over the area of bare sclera left by excision of pterygium. Proper orientation is ensured with the epithelial side up and limbal edge towards limbus. The donor site is allowed to heal on its own. The eye was patched.

Post operatively, all the patients were instructed not to remove the eye patch till the next day and not to rub the eyes. On first postoperative day, patients were examined and started on steroid antibiotic eye drops 6 times a day for 1 week, tapered 1 drop each week for 6 weeks and lubricating eye drops 4 times a day for a month.

FOLLOW UP:

Patients in both groups were examined on postoperative day 1,first week, third week and sixth week. At each visit, following outcome variables were assessed:

- Pain
- Foreign body sensation
- Lacrimation
- Discomfort during blinking

It was done according to a questionnaire and the responses were graded as:

1-Absent: No symptoms

2-Mild: Patient has tolerable symptoms and present occasionally

3-Moderate: Tolerable symptoms present throughout the day or intolerable symptoms present occasionally

4-Severe: Intolerable symptoms present throughout the day.

The presence or absence of subconjunctival hemorrhage and displacement of graft was also looked for. The overall appearance of the eye was noted as red or quiet. Any complications like graft edema, graft extrusion, graft dehiscence were noted.

DISCUSSION

This was a prospective, randomized clinical trial conducted atKLES Dr. Prabhakar Kore Hospital and Medical research centre, Belagavi. It compared the efficacy of conjunctival autograft surgery with fibrin glue and autologous blood.

In a 1 year period,64 patients with primary pterygium fulfilling inclusion and exclusion criteria underwent surgery and were followed up on postoperative day 1,one week, three weeks and six weeks.

Conjunctival autografting was performed with fibrin glue in 32 patients and using autologous blood in 32 patients.

The estimated sample size was 66 but it could not be completed as there was non-availability of fibrin glue in the last part of study period and follow up could not be completed.

Age:

The patients in this study were of 21-75 years of age. The average age of patients in group 1 i.e. fibrin glue was 21-75 years(mean 49.13±15.54) while that of group 2 i.e. autologous blood was 27-79 years(mean 47.22±10.23). According to Hilghers et al, the highest incidence is found between 20 and 49 years. [22]

Gender:

In group 1(fibrin glue), 68.7 % were female patients and 31.3% were male patients. In group 2(autologous blood) 78.1 % of patients were females and 21.8 % were males. Hence, a female preponderance was found in this study. Hilgers[22]

demonstrated a higher prevalence of pterygium among males while Sharma[84] et al proved a female preponderance in their study.Pandey et al in 1984[85]conducted a studyin which there was preponderance of male patients (males 1051, 75.1%; females, 349; 24.9%). This led to the speculation that exposure to external environment is more among males than females, indicating the role of environmental factors in pterygium formation.

Site of pterygium:

According to this study, 90.6% of the cases had nasal pterygium,7.8% had both nasal and temporal and only 1.6% of cases had temporal pterygium. Greater incidence of nasal pterygium was believed to be due to drainage of tears towards medial canthus along with sand and dust particles. In a study conducted in 51 patients by Srinivas K Rao[87], nasal pterygium was found in 46 (86.8%) eyes, temporal in 4 (7.5%) eyes and both nasal and temporal in 3 (5.7%) eyes.

Presenting Symptoms:

Most of the patients in this study presented with the complaint of a fleshy mass over the black part of the eye associated with foreign body sensation, redness and watering. Some of the patients wished to get operated for cosmetic reasons.None of the patients had diplopia. Most of these findings correlate with many authors who found that most of the patients are asymptomatic in the initial stages and usually approach for cosmetic reasons or when they start experiencing foreign body sensation. Generally pterygium excision is indicated if it encroaches the visual axis or if there is unbearable irritation.[39]

Diminution of vision can be due to astigmatism produced by pull exerted over the cornea in the initial stages and later because of covering of pupillary area and corneal opacity at the head of pterygium. Pull exerted by the pterygium on the cornea leads to flattening of the horizontal meridian in corneal curvature as demonstrated by Ponico E. Carreras and Bedrossian, Robert M.[87]

Postoperative signs and complications:

On the first postoperative day, lesser number of patients in group 1 complained of pain(mild-28.1 %) as compared to patients in group 2(mild pain-34.4 %).By the first postoperative week, pain had subsided completely in group 1 whereas in group 2,mild pain was present in 9.4% patients.

43.8 % of patients in group 1 complained of mild foreign body sensation and 3.1 % moderate foreign body sensation on postoperative day 1 as compared to 68.8% patients in group 2 complained of mild foreign body sensation and 6.3% moderate foreign body sensation. At the end of first week, this reduced to 9.4 % in group 1 and 28.8% in group 2.At the sixth week, only one patient had foreign body sensation in group 2 and none complained in group 1.

Lacrimation was absent in 59.4%,mild in 37.5 % and moderate in 3.1 % of patients in group 1 and it was the same in group 2 patients on postoperative day one.6.3% of patients in group 2 had mild lacrimation at the first postoperative week.

In a study conducted by Ratnalingam et al, the immediate postoperative pain scores were definitely lower in the fibrin adhesive group ($p<0.05$).[88]

Uy et al[89] in his study proved that postoperative symptoms like pain, foreign body sensation, lacrimation and discomfort were lesser and disappeared more rapidly in the fibrin glue group($p<0.01$).

Subconjunctival hemorrhage was present in one patient in fibrin glue group while three patients in autologous blood group had subconjunctival hemorrhage which disappeared in two patients by the end of six weeks. Uy et al [89] noted subconjunctival hemorrhage under the graft in one patient in fibrin glue group which diminished in 3 weeks.

The graft was partially displaced in 12.5% of patients in fibrin glue group. Displacement of graft was not seen in any case in autologous blood group.

Visual acuity in both groups lesser than 6/18 were mostly due to cataractous changes in lens.

In both the groups, the overall appearance of the eye was quiet at all follow ups. At the end of six weeks of follow up, all the grafts were stable and no complications were seen like graft edema, retraction and papilloma.

CONCLUSION

This study showed that the incidence of postoperative symptoms like pain, foreign body sensation and lacrimation were seen among fewer patients in the fibrin glue as compared to the autologous blood group.Though the displacement of graft was higher in fibrin glue.

The main disadvantage of fibrin glue is its high cost.

Autologous blood is a cost effective alternative and is the most commonly used

SUMMARY

This study is a prospective, randomized clinical trial to compare the efficacy of fibrin glue and autologous blood in attaching the conjunctival autograft following pterygium excision in management of primary pterygium.

- Sixty four eyes were randomized into 2 groups (32 in each group) after a detailed ocular examination.
- All the patients were randomly assigned into the two groups, since around 3-4 patients were pooled in group I for cost effectiveness.
- Cases of primary pterygium were included in the study.
- Mean age in Group I was 49.13 years and 47.22 years in Group II.
- In this study it was observed that 5.4% belonged to grade I,63% to grade II and 2.3% to grade III.
- Maximum incidence of pterygium was seen in the age group of 41– 50 years. Majority of them were females (73.4%).
- Most of the patients presented with the complaints of a fleshy mass growing over the nasal part of the cornea and associated with foreign body sensation,redness,watering and in some cases, diminution of vision. Few patients got operated only for cosmetic disfigurement.
- At the first postoperative day, pain was seen in 28% of patients in group I and 34% in group II which reduced to 0% in group I and 9% in group II at the end of first postoperative week.
- At the first postoperative day, foreign body sensation was seen in 44% of patients in group I and 69% in group II which reduced to 10% in group I and 28% in group II at the end of first postoperative week.

- Subconjunctival hemorrhage was present in one patient in group I and in three patients in group II.
- Displacement of graft was present in three patients in group I.

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CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr. / Mrs. / Ms. _____

You are invited to participate in our research study titled "A one year randomized clinical trial to evaluate the efficacy of conjunctivalautograft with fibrin glue and autologous blood in pterygium surgery at KLES Dr.Prabhakar Kore hospital and MRC, Belagavi" conducted by Dr._____ . Post Graduate student in M.S. Ophthalmology under the guidance ofDr _____, Professor, Department of Ophthalmology, J.N. Medical College, Belagavi.

Respected Sir/Madam we request you to enroll yourself in our study as you are eligible for participation. Your participation in research is voluntary. If you decide to participate you are free to withdraw at any time.

Purpose of the study:To evaluate the efficacy of conjunctivalautograft with fibrin glue and autologous blood in pterygium surgery

Procedure Involved: If you agree to enroll yourself in this study you will be asked your present, past and family history. You will be clinically examined and relevant investigations will be done. Then the mass in your eye known as pterygium would be excised and conjunctival autograft would be placed using either fibrin glue or autologous blood. Selection of the procedure will be based on randomisation chart, so you can be selected in either of the groups. You would be asked to come for follow up on specified dates when your progress would be monitored, documented and photographed.

Risks and Benefits: There are no major risks involved with the use of either fibrin glue or autologous blood. As fibrin glue does not express antigens and initiates a natural coagulation process in the body therefore it reduces the risk of immune response. However you can have some discomfort. For which all necessary precautions would be taken. Your participation may benefit you and others by establishing certain facts about the study.

Alternatives: If you are not willing to participate you will be treated according to the existing protocol and it will not affect your relationship with this hospital.

Cost for participating in this research: There will not be any extra cost incurred by you. You will however have to pay for the investigations which are part of the existing management protocol for the condition. There is no commitment for any reimbursement or any other compensation.

Privacy and Confidentiality: Your privacy is guaranteed. However your medical records can be directly accessed and reviewed by authorised individuals or by the ethics committee. Records which could reveal your identity will be kept confidential. Personal data will remain anonymous if data is being published or written as a dissertation.

Authorisation to publish results: When the results of the research are published or discussed in a conference no information will be displayed that would disclose your identity.

Compensation: In the event of injury related to the study, treatment will be made available through KLEs Dr.Prabhakar Kore Hospital and MRC, Belagavi. There is no compensation or payment for such medical treatment by law. The doctors and the staff will provide facilities and medical attention to you.

Questions:

If you have any questions about the research you may please contact:

1. Investigator, Dr. Neha B.E. Postgraduate student, Department of Ophthalmology, JNMC Belagavi.
2. Guide, Dr.S.C.Bubanale, Professor, Department of Ophthalmology, JNMC, Belagavi.
3. Dr. RoopaBellad, Professor, JNMC, Belagavi and Chairman, Institutional Ethics Committee.

PROFORMA

PATIENTS ID NO: ☐☐

NAME: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

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AGE: ☐☐ Years

SEX: ☐ (1-Male; 2-Female)

ADDRESS: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

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CONTACT NUMBER: ☐☐☐☐☐☐☐☐☐☐

OP NUMBER: ☐☐☐☐☐☐☐☐

IP NUMBER: ☐☐☐☐☐☐☐☐

DATE OF ADMISSION: ☐☐ / ☐☐ / ☐☐☐☐

PROVISIONAL DIAGNOSIS:

DATE OF SURGERY: ☐☐ / ☐☐ / ☐☐☐☐

DATE OF DISCHARGE: ☐☐ / ☐☐ / ☐☐☐☐

CHIEF COMPLAINTS(1=yes;2=no):

Fleshy mass in the eye:

Diminution of vision:

Redness:

Pain:

Diplopia:

HISTORY OF PRESENT ILLNESS: (1=yes,2=no)	RE	LE
Fleshy mass in the eye		
Pain:		
Redness:		
Watering:		
Discharge:		
Itching:		
Ocular irritation:		
Photophobia:		
Diplopia:		
Coloured halos:		
Other complaints (if present):		

PAST HISTORY-(1=yes,2=no)

	RE	LE
INTRA OCULAR SURGERY		
TRAUMA		
OTHER		

MEDICAL HISTORY-

(1=present,2=absent)

Diabetes	
Hypertension	
Bleeding disorder	
Others	

FAMILY HISTORY-

(1=significant, 2=non-significant) ☐

If 1,specify:

PERSONAL HISTORY-

(1=significant, 2=non-significant) ☐

If 1,specify:

GENERAL PHYSICAL EXAMINATION:

VITALS-

- PR(per min):
- BLOOD PRESSURE(mm Hg):
- TEMPERATURE :
- RESPIRATORY RATE(per min):

(1=present, 2=absent)

Pallor		Clubbing	
Icterus		Lymphadenopathy	
Cyanosis		Edema	

SYSTEMIC EXAMINATION: (1=normal,2=abnormal) ☐

CVS:

If 2,specify

RS:

If 2,specify ☐

CNS: ☐

If 2,specify

P/A: ☐

If 2,specify

OCULAR EXAMINATION-

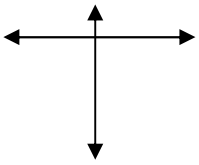
- HEAD POSTURE: (1=erect;2=tilted)
- FACIAL SYMMETRY: (1=symmetrical;2=asymmetrical)
- VISUAL AXIS: (1=parallel;2=not parallel

If 2, specify)

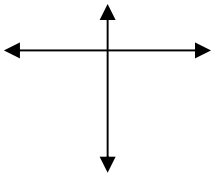
- EXTRA OCULAR MOVEMENTS :

Uniocular

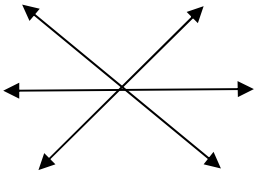
RE



LE



Binocular



- VISION:

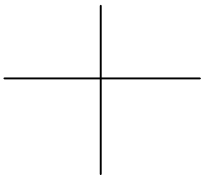
	RE	LE
Unaided		
Pin hole		
Aided		
Near Vision(without glasses)		
Near Vision(with glasses)		

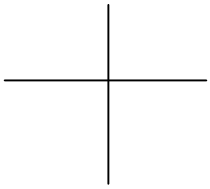
- KERATOMETRY:
-

	RIGHT EYE	LEFT EYE
K1		
K2		

- **REFRACTION**:
- RETINOSCOPY:

OD OS





- SUBJECTIVE CORRECTION:

RIGHT EYE: LEFT EYE:

SPHERE	CYLINDER	AXIS	VISION		SPHERE	CYLINDER	AXIS	VISION
				DISTANT				
				NEAR				

- ANTERIOR SEGMENT EXAMINATION :

	RIGHT EYE	LEFT EYE
ADENEXA(1=Normal;2=Abnormal) If 2,specify:		
CONJUNCTIVA(1=Normal,2=Abnormal) If 2,specify:		
SCLERA: (1=Normal;2=Abnormal)		
CORNEA: (1=Clear;2=Hazy;3=Other)		
ANTERIOR CHAMBER: (1=Normal Depth;2=Shallow;3=Deep)		
IRIS: (1=Normal;2=Atrophic patches;3=other)		
PUPIL: • SIZE: (1=Normal;2=Constricted;3=Dilated) • REACTION(Direct, Indirect): (1=Normal,2=Abnormal) If 2,specify		
LENS(1=Clear;2=Cataract)		

- FUNDUS-

	RIGHT EYE	LEFT EYE
GLOW		
MEDIA		
DISC • Size • Margin • Cup:Disc ratio • Neuroretinal Rim		
BLOOD VESSELS		
BACKGROUND		
MACULA		

- INVESTIGATIONS:

- Tonometry(air puff tonometer):
-

	RE	LE
IOP		

- Random blood sugar _____mg/dl

- DIAGNOSIS-

SURGERY-

1=pterygium excision with conjunctival autograft with fibrin glue

2= pterygium excision with conjunctivalautograft with autologous blood.

FOLLOW UP-

- KERATOMETRY:

	RIGHT EYE	LEFT EYE
K1		
K2		

- **REFRACTION:**

- RETINOSCOPY:

OD OS

- SUBJECTIVE CORRECTION:

RIGHT EYE: LEFT EYE:

SPHERE	CYLINDER	AXIS	VISION		SPHERE	CYLINDER	AXIS	VISION
				DISTANT				
				NEAR				

	1st postoperative day	1st postoperative week	3rd postoperative week	6th postoperative week
PAIN				
FOREIGN BODY SENSATION				
LACRIMATION				
DISCOMFORT DURING BLINKING				
SUBCONJUNCTIVAL HEMORRHAGE				
DISPLACEMENT OF GRAFT				
OVERALL APPEARNCE OF THE EYE				

ANNEXURE III.ETHICAL CLEARANCE.

K.L.E.UNIVERSITY'S
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
(Accredited 'A' Grade by NAAC)

Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu

Phone: (+ 91-(0)831 Office : 2471350
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 75 **Date: 22/11/2017**

To,

[redacted]
PG student in Ophthalmology,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"A ONE YEAR RANDOMIZED CLINICAL TRIAL TO EVALUATE THE EFFICACY OF CONJUNCTIVAL AUTOGRAFT WITH FIBRIN GLUE AND AUTOLOGOUS BLOOD IN PETRYGIUM SURGERY AT KLES DR PRABHAKAR KORE HOSPITAL AND MRC, BELAGAVI"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Arathi Darshan)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

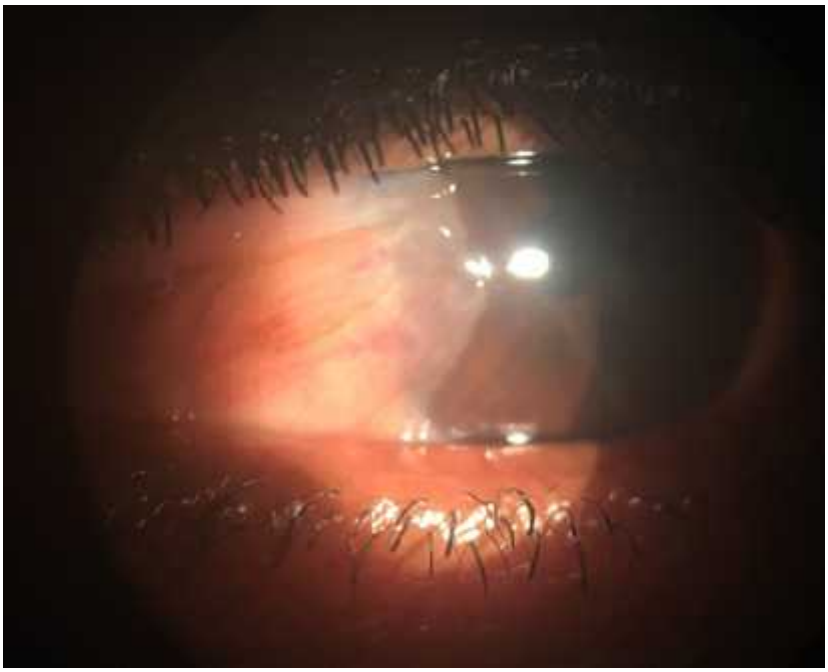
For

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

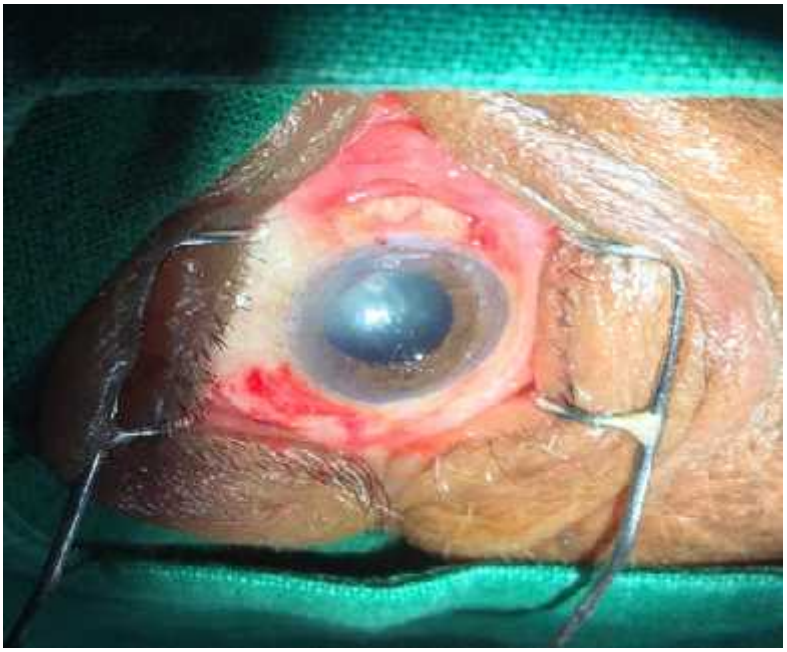
71

PHOTOGRAPHS

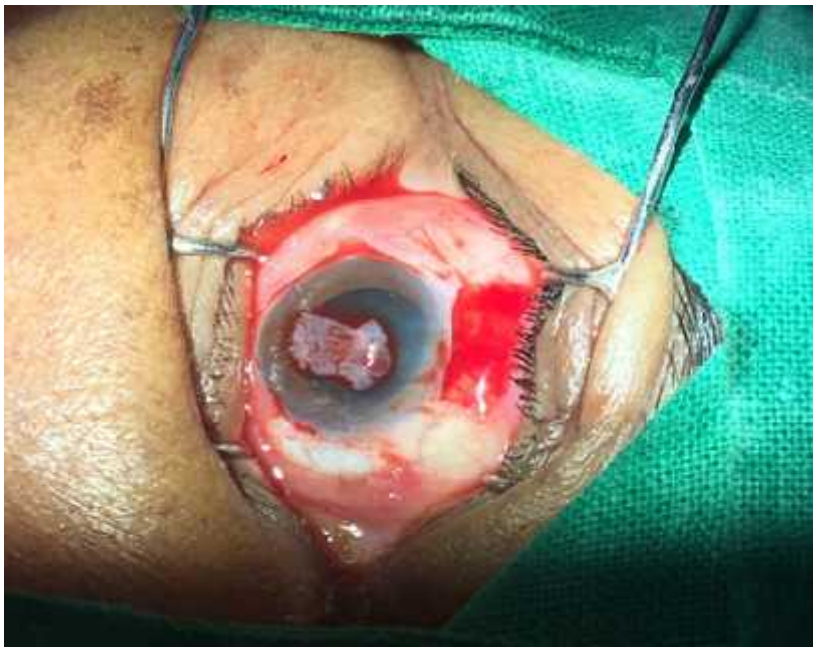
Photograph 1- Grade II nasal pterygium:



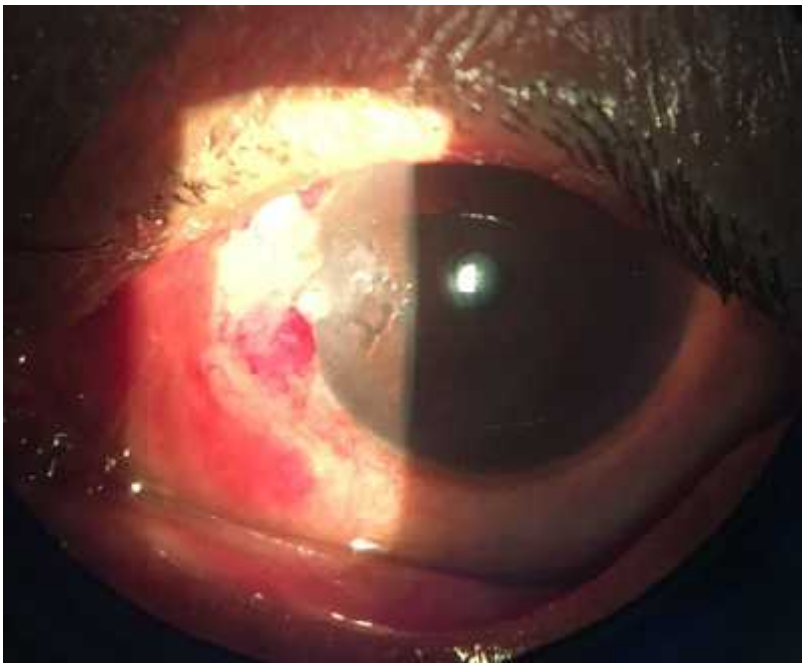
Photograph 2 - Intraoperative using fibrin glue



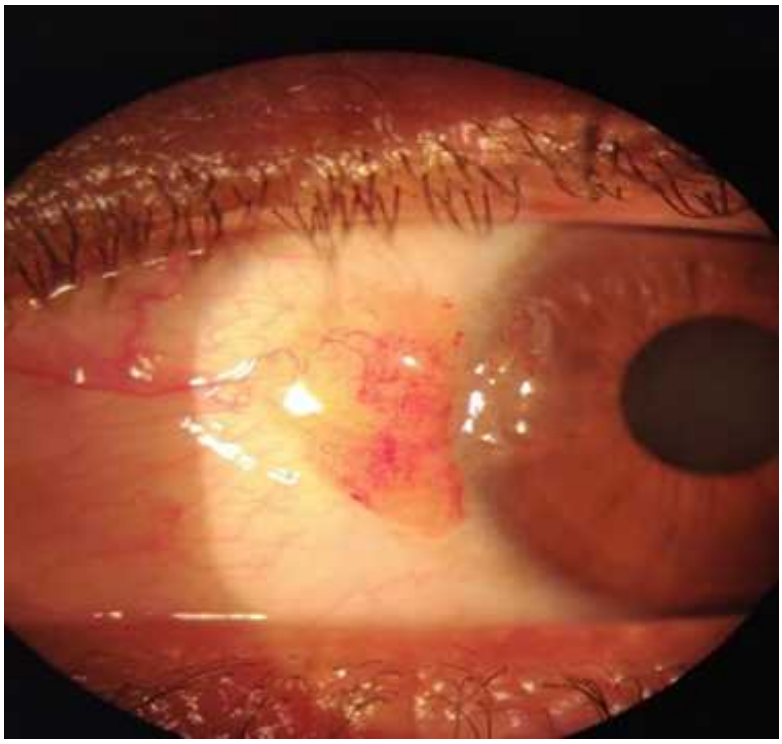
Photograph 3 - Harvesting of graft



Photograph 4 - Postoperative Day 1 with Fibrin glue

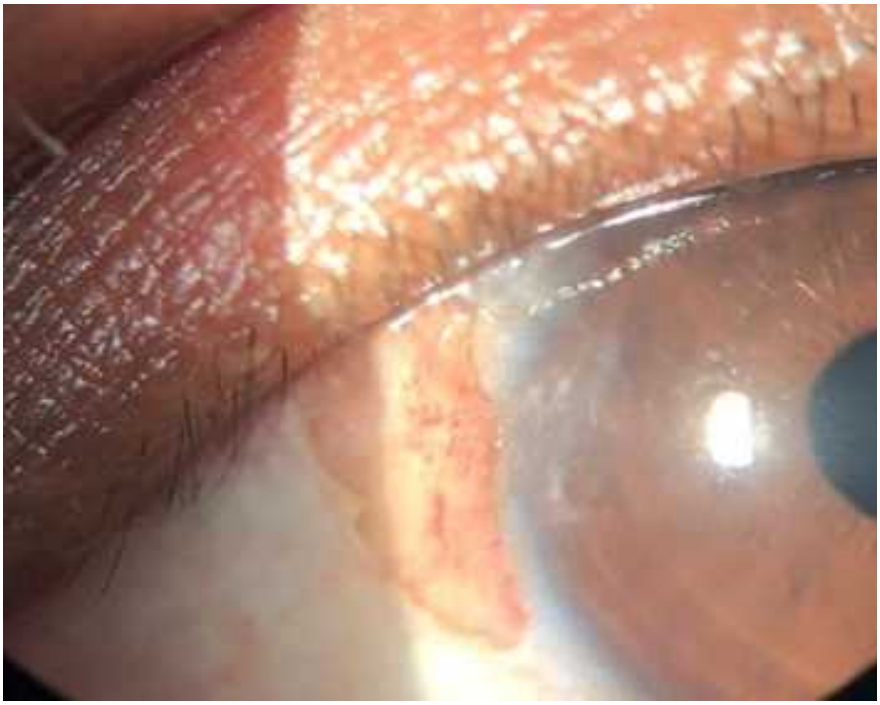


Photograph 5 - Postoperative 1st week using Fibrin glue

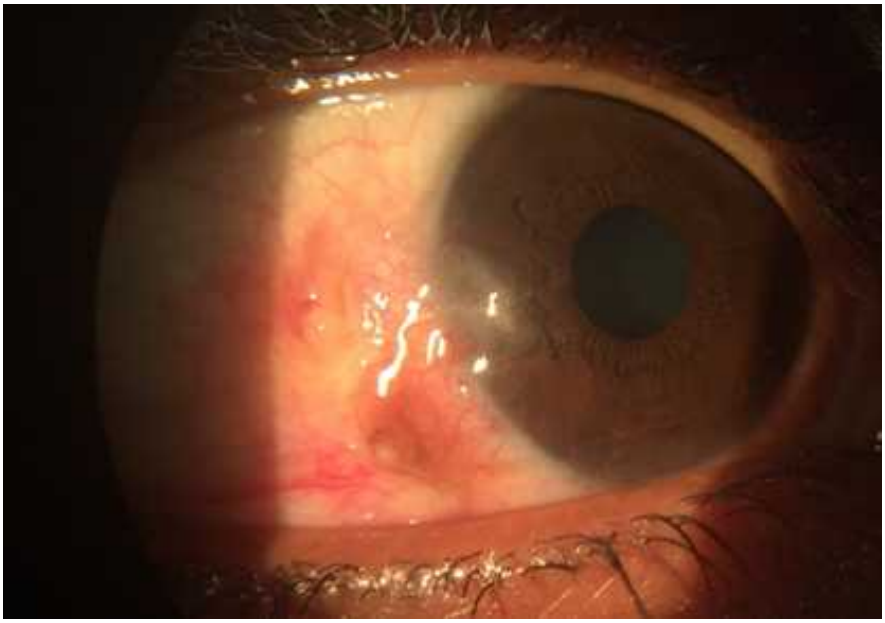


Photograph 5 - Postoperative 3rd week using Fibrin glue

Photograph 7 - Postoperative sixth week using Fibrin glue



Photograph 8 - Displacement of graft downwards in fibrin glue group



Photograph 9 - Fibrin Glue Components

Photograph 10 - Fibrin Glue Applicator

KEY TO MASTER CHART:

1. SN- serial number

2. IP-inpatient number

3. Lat-Laterality

4. FM-Fleshy mass

5. DOV-Diminution of vision

6. R-Redness

7. P-Pain

8. W-Watering

9. Dis-Discharge

10. OI-Ocular irritation

11. IOS-Intraocular Surgery

12. Tr-Trauma

13. MH-Medical History

14. RE-Right eye

15. LE-Left eye

16.OE-Operated eye

17.Pr Op VA-Pre Operative Visual Acuity

18.Po Op VA- Post Operative Visual Acuity

19.Pr Op K1,K2-Pre Operative K1,K2

20.Po Op K1,K2-Post Operative K1,K2

21.POD 1-Post Operative Day 1

22.FBS- Foreign Body Sensation

23.Lac-Lacrimation

24. DDB-Discomfort during Blinking

25.DOG-Displacement of Graft

26.Overall App-Overall appearance

Grading of outcome variables(pain, foreign body sensation, lacrimation and discomfort during blinking):

1-Absent (no symptom)

2-Mild (patient has tolerable symptoms present occasionally)

3-Moderate (patient has tolerable symptoms present throughout the day or intolerable symptom occasionally)

4-Severe(Intolerable symptoms present throughout the day)