"COMPARISON OF FIBRIN GLUE AND SUTURES FOR ATTACHING LIMBAL CONJUNCTIVAL AUTOGRAFT AFTER PTERYGIUM EXCISION"

By

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Dissertation Submitted to the
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In partial fulfillment
Of the requirements for the degree of

MASTER OF SURGERY
IN
OPHTHALMOLOGY

Under the Guidance of

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SRI DEVARAJ URS MEDICAL COLLEGE
TAMAKA, KOLAR (APRIL - 2017)

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Date: **Signature of the Candidate**

LIST OF ABBREVIATIONS

SL. NO.	ABBREVIATION	FULL FORM
1.	BC	Before Christ
2.	AD	Anno Domini
3.	TAC	Transient Amplifying Cells
4.	VEGF	Vascular Endothelial Growth Factor
5.	MMC	Mitomycin C
6.	TPA	Thiotepa
7.	PMC	Post Mitotic Cells
8.	TDC	Terminally Differentiated Cells
9.	SC	Stem Cells
10.	UV	Ultraviolet
11	UVR	Ultraviolet radiation
12	^{90}SR	Strontium 90
13	FU	Fluorouracil
14	MMC	Mitomycin c
15	SD	Standard deviation
16	β	Beta
17	γ	Gamma

ABSTRACT

TITLE: COMPARISON OF FIBRIN GLUE AND SUTURES FOR ATTACHING LIMBAL CONJUNCTIVAL AUTOGRAFT AFTER PTERYGIUM EXCISION.

NEED FOR THE STUDY:

Pterygium is frequently occurring ocular surface lesion with characteristic wing shaped fleshy growth, encroaching from conjunctiva upon the cornea. Pterygium excision with limbal conjunctival autograft with sutures has become a standard procedure but it is associated with disadvantages. Fibrin glue has recently emerged as major breakthrough for attaching the graft.

Limbal conjunctival transplantation has proved to be the best treatment option, as it is associated with least recurrence rate. It has been demonstrated that fibrin glue alone can be used to attach conjunctival autografts and reduce operating time and post-operative discomfort.

OBJECTIVES OF THE STUDY:

1) To compare efficacy of fibrin glue with suturing in terms of operating time, postoperative symptoms, signs and recurrences.
2) To compare safety of fibrin glue with suturing in terms of anaphylactic reaction and disease transmission (HIV, HBsAG).

MATERIAL AND METHODS:

This is a hospital based prospective randomised study conducted on 100 patients attending department of Ophthalmology, R.L.JALAPPA HOSPITAL AND RESEARCH CENTRE, hospital attached to SRI DEVARAJ URS MEDICAL COLLEGE between January 2015 and June 2016.

Written informed consent from patients fulfilling the inclusion criteria were obtained and subjected to thorough ocular examination including visual acuity, refraction, keratometry, ocular movements, fluorescein staining and slit lamp examination. Patients were randomly allocated to 2 groups, Group A (FIBRIN GROUP =50) and Group B (SUTURE GROUP =50) by using computerised random number method / table. Group A underwent pterygium excision with limbal conjunctival autograft with fibrin glue and Group B underwent pterygium excision with limbal conjunctival autograft with suture.

Various parameters like operating time as well as postoperative symptoms and signs like pain, foreign body sensation and lacrimation, subconjunctival haemorrhage, graft retraction/gaping and recurrences were noted in both the groups on postoperative day 1, day 3, day 10 and 1 month. Recurrence was noted on 1^{st}, 3^{rd} and 6^{th} postoperative month.

RESULTS:

Both groups were similar in the age and females were more in number. Mean age of limbal conjunctival autograft with suture was 52.39 years and 53.22 years in fibrin glue group. Mean operating time was 43.00 minutes in the suture group compared to fibrin glue group which was 22.78 minutes. Patients in fibrin glue group had less symptoms of pain, foreign body sensation, lacrimation, sub conjunctival hemorrhage and graft gaping compared to suture group. There were 3 & 1 recurrence seen in suture group & fibrin glue group respectively at the end of six-month follow-up period.

CONCLUSIONS:

In our study we found that fibrin glue is a safe and effective method for attaching limbal conjunctival autograft following pterygium excision. Its use results in a shorter

operating time, less post-operative discomfort and inflammation compared to suturing and there was less recurrences of pterygium when compared to sutures. Fibrin glue was also found to be safe as there is no anaphylactic reaction and disease transmission like HIV and HBsAG.

Key words: Pterygium, Fibrin glue, Sutures.

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INTRODUCTION

INTRODUCTION

Pterygium is a frequently occurring ocular surface lesion with characteristic wing shaped fleshy growth, encroaching from conjunctiva upon the cornea. Although simple to excise, high rates of recurrence make its management challenging.

There are perhaps as many ways of surgical excision of pterygium as there are theories of its aetiology, causative factors include ultraviolet light exposure, chronic inflammation, elastodysplasia, elastodystrophy, stem cell aplasia, dry eyes etc. The surgical modalities include bare sclera technique, application of antimetabolites, conjunctival autograft, amniotic membrane transplantation and limbal conjunctival autograft.[1]

Prevalence of pterygium is 5.2% worldwide but, more common in warm and dry climates with prevalence of 22% in equatorial areas and less than 2% in latitudes above 40 degrees.[2]

The prevalence of pterygium in India ranges from as low as 0.75% to as high as 10.42% in different states and an overall average in prevalence being 5.2%.

Higher incidence in males in the age group of 20-40 years. The pterygium can vary from small atrophic quiescent lesion to a large fibrovascular lesion commonly involving nasal limbus but can occur on either side of the cornea. It consists of a Head which rests over cornea, Neck and Body[3]. Pterygium is associated with decreased visual acuity due to involvement of visual axis, irregular astigmatism, extra ocular motility restriction and cosmetic intolerance.[4]

The recurrence may be due to the incomplete excision associated with fibroblastic proliferation and production of matrix metalloproteinases under the influence of inflammatory cytokines.[5]Other reason for the angiogenesis factor to occur is the surgical insult which acts as stimulus for neovascularisation.

After excision there is chemotaxis and influx of polymorphonuclear leukocytes, which then release the angiogenic factor which is the stimulus for neovascularisation and recurrence.[6]

UV light induced localised damage to limbal-conjunctival cells and thus deficiency has been the most recent concept for causation. And limbal-conjunctival transplantation has proved to be the best available treatment option in the everlasting search for ideal technique, as it is associated with least recurrence rate.[1]

Although the best technique for a successful outcome after pterygium excision is yet to be determined, in recent years, pterygium excision with limbal-conjunctival autograft with sutures has become a standard procedure, as it is associated with least recurrence rate. However it requires higher surgical expertise and is associated with disadvantages including prolonged operative time and suture related complications such as button holes, dellen ulcer, suture abscesses, symblepharon, granuloma formation, tissue necrosis and graft dehiscence.[1]

Now the attention is towards making the method more patient as well as surgeon friendly. In this direction fibrin glue has recently emerged as major breakthrough for attaching the graft.

Fibrin glues have been used in an array of ophthalmic procedures such as conjunctival closure in strabismus, vitreoretinal and glaucoma surgery[7]. Because of its biological and biodegradable properties, fibrin based adhesives may be used to attach the conjunctival autograft without inducing inflammation[8]. Tissue adhesives of different types had been used in previous studies to attach conjunctival grafts and compared with the use of sutures,were associated with a shorter operative time and reduced postoperative

complaints.[9-12]Hence we conducted this study to compare the efficacy and safety of fibrin glue versus suturing for attaching limbal-conjunctival autograft after pterygium excision.

OBJECTIVES OF STUDY

OBJECTVES OF STUDY

1. To compare efficacy of fibrin glue with suturing in terms of operating time, postoperative symptoms, signs and recurrences.
2. To compare safety of fibrin glue with suturing in terms of anaphylactic reaction and disease transmission (HBV, HIV).

REVIEW OF LITERATURE

REVIEW OF LITERATURE

The term pterygium comes from the ancient Greek word πτερυξ (pteryx) = wing and πτερυγιον (pterygion) = fin. Pterygium is characterized by a triangular portion of the bulbar conjunctiva encroaching onto the cornea, usually within the inter-palpebral fissure and most often from the nasal side. It is a fibrovascular growth originating from subconjunctival tissue and encroaches the cornea involving the bowman's layer and superficial stroma.

Histopathologically, it shows signs of elastotic degeneration of the conjunctiva. If not treated it may encroach the entire pupillary axis and thus cause a significant disturbances in the visual acuity. The contractile forces of pterygium on peripheral cornea, leads to significant flattening of the horizontal meridian (with the rule astigmatism), which is proportional to the size of the pterygium.[13]

Historical aspects

Pterygium was also mentioned by Hippocrates around 400 B.C. He treated it with eye drops made of lead, zinc, copper, iron, bile juices, urine and maternal milk. Celsus (25 BC) and Galenus (129 AD) also advocated complex topical solutions. Avicenna (1000 AD) proposed cutting the pterygium with scissors.[13]

The next recorded study is of celsus (Rome 50 AD) where he passes a needle and thread beneath the pterygium and with a sawing motion separates the tissue. It was then described by Vegabhatt (India 300 AD), Paul Aegineta (Greece 7th century), Al Rhazes (Arabia 932 AD), Avicenna (Greece 980-1036AD) and Chakradatta (India 1060 AD) [13]

Pterygium was also described by Sushrutha (India), the world's first surgeon ophthalmologist before 1000 A.D. In Sushruta Samhita he describes: "with the patient on

recumbent on an operation table, the pterygium is loosened and disturbed by sprinkling powdered salt into the eye.

With the patient looking laterally, a sharp hook is used to secure the growth at its loosened upturned part, and is held up with a toothed forceps, or a threaded needle is to be passed from below the part which would be held up with the thread. The pterygium is then scratched with a sharp round topped instrument. The root of the pterygium should be pushed as under from the black outline (cornea) of the eye to the medial canthus and then excised and removed. Any remnant of the pterygium should be removed with a scarifying ointment to prevent recurrences."[13]

In the eighteenth century, it was fashionable to treat a pterygium with copper sulphate in the XIX century with silver nitrate and lead acetate, and atropine was added to encourage the healing of the associated corneal ulcers.[14, 15]

The nineteenth century saw the advent of surgery of pterygia.

- Scarpa (1802): Removal of the head from the cornea using forceps, section of a portion of the body (3-4 mm) and subsequent concentric excision of the detached tissue as far as the limbus. [16]
- Arlt (1850): Excision of the head from the cornea and a diamond shaped portion of the body with conjunctival cross-over plastic surgery.
- Desmarres (1855): Introduced the technique of deviating the head in an attempt to change the direction of growth and induce it to atrophy. The technique was modified by Terrien who deviated the growth towards the superior fornix as opposed to the inferior fornix suggested by Desmarres.[17]

- Knapp (1869): Suggested the technique of transposition. The pterygium is cut longitudinally into two halves that are fixed below the superior and inferior conjunctiva.[18]

In The Twentieth Century, the techniques of keratoplasty and the physical treatments of pterygium were developed.

- Mc Reynolds (1902): Presented a modified Desmarres technique which placed the head of the pterygium in a conjunctival pouch.[19]
- Gifford (1909): Used a thin epidermal graft to cover the sclera that was exposed following the complete removal of the pterygium.[20]
- Morax and Magitot (1911): Used the first artificially- preserved homologous corneal grafts.[21]
- Terson (1911): Was the first to use radiation therapy with X-rays.[22]
- Fuchs (1911): Presented the first results of autologous penetrating keratoplasty for the treatment of corneal pathologies, and Terson (1913) performed this on pterygia. The technique involved replacing a full-depth corneal disc containing the head of the pterygium with a penetrating disc of the same diameter removed from the superior peripheral cornea. The results were poor because of opacity when developed in both discs, and because of tropism and infection.[22]
- Magitot (1916): Suggested lamellar auto keratoplasty using a technique which is similar to Terson's but which used lamellar discs removed from the same eye.[23]
- Elschnig (1926): In order to repair serious conjunctival defects, he performed conjunctival plastic surgery with transposition of a bridge created from the contra-

lateral limbus. So Elschnig was the first person to introduce conjunctival graft for pterygium surgery.[24]

- Amorin (1936): Suggested treatment with a diathermy coagulator.[25]
- Burnam and Neil (1941): Used a radioactive applicator (Radon).[26]
- D'Ombrain (1948): Suggested the technique of scleral baring for the first time.[27]
- Paufique (1950): Developed a lamellar keratoplasty for the optic and therapeutic treatment of the corneal pathologies; this also included the pterygium which until then considered being a minor pathology.[28]
- Haik (1957): Used topical beta-therapy with strontium 90.[29]
- Meacham (1962): Was the first to use antibiotics to prevent the recurrences.[30]
- Panzardi(1964): Used amniotic membrane to repair the conjunctival tissue loss following excision of the pterygium.[31]
- Kenyon (1985): Reported excellent results in the prevention of recurrences by grafting autologous conjunctiva to the limbus.[31]
- In a study by Uy et al to compare the efficacy and safety of fibrin glue and suturing for attaching conjunctival autografts among patients undergoing pterygium excision, the study was conducted on twenty-two patients undergoing excision of primary pterygium. A superior conjunctival autograft was harvested and transferred onto bare sclera after pterygium excision. Fibrin glue was used to attach the autograft in eleven eyes and nylon 10-0 suture was used to attach the autograft in eleven eyes. The patients were followed up for 2 months. The study concluded that fibrin glue is a safe and effective method for attaching conjunctival autografts. The

use of fibrin glue results in shorter operating times and less postoperative discomfort.[32]

- In a study by Bahar et al, to compare the short-term results of conjunctival closure in pterygium surgery using fibrin adhesive versus vicryl sutures with respect to operative time, postoperative ocular signs and symptoms, and overall patient satisfaction, a comparative prospective randomized clinical trial was performed in sixty five eyes with primary nasal pterygium. Surgery in all patients consisted of the bare sclera technique combined with intraoperative mitomycin C. Patients were randomized to undergo conjunctival closure with a fibrin tissue adhesive (Quixil; n = 39) or 8-0 Vicryl absorbable interrupted sutures (n=26).Clinical assessment was performed on days 1, 3, 10, and 21 after surgery. Patients completed a questionnaire at each follow-up visit, grading pain, discomfort, and satisfaction with the procedure. The groups were compared for operative time, ocular signs and symptoms, and overall satisfaction. The study concluded that the use of fibrin glue in pterygium surgery significantly reduces operative time and patient symptoms, pain, and discomfort.[33]

- In a cohort study by Srinivasan et al, where sixty-two patients underwent pterygium surgery with fibrin glue, two eyes had graft dehiscence. The study concluded that intense eye rubbing in the early postoperative period can lead to graft dehiscence.[34]

- A study by Ozdamar et al was done to compare clinical and histopathologic outcomes of tissue glue and vicryl suture to attach limbal conjunctival autografts in pterygium surgery. In this study twenty-four eyes of twenty-four patients were included. All eyes had primary pterygia and were treated with limbal conjunctival autograft transplantation after pterygium resection. Tissue glue (Tisseel*) was used

to attach the limbal conjunctival autograft in twelve-eyes and vicryl sutures in twelve eyes. Patients were followed for six months. Histopathologic examination was performed in both groups on postoperative days 1, 15, and 45. Main outcome measures were patient comfort, graft success, complications, histopathologic evaluation, and recurrence of pterygium. The study concluded that limbal conjunctival autografting is an effective surgical technique for the treatment of pterygium and tissue glue was efficacious in securing the limbal conjunctival autograft in pterygium surgery.[107]

- In a study by A Karalezli et al fifty patients with primary nasal pterygium were randomized to undergo pterygium surgery using either fibrin glue or 8-0 vicryl sutures for conjunctival autograft. Outcome measures were based on postoperative patient comfort, duration of surgery and recurrence of pterygium. The study concluded that use of fibrin glue in pterygium surgery with conjunctival autografting significantly reduces surgery time, improves post-operative discomfort and results in a lower recurrence rate compared to conjunctival autografting using sutures.[75]

- In a study by Pan HW et al, to evaluate the safety and clinical efficacy of fibrin glue in pterygium surgery with conjunctival autografting. The use of fibrin glue has been introduced in the treatment of pterygium. However, its role versus traditional suturing is still a matter a debate. They performed a meta-analysis to compare the safety and clinical efficacy of fibrin glue with suture for conjunctival autograft attachment in pterygium surgery. The study included 342 participants with 366 eyes in 7 studies were analysed. The methodological quality of all the included trials was assessed with the jaded score. The meta-analysis was performed with the fixed effects model for complication rate and recurrence rate and random effects

model for operating time (weighted mean difference -17.61 minutes 95% confidence interval, -26.03 to -9.18, P<0.0001) and was more effective in reducing the recurrence rate (0.33, 95% CI, 0.15-0.75 P=0.004) compared with suture.

- There were no significant differences in the complication rate (1.82, 95% CI, 0.63-5.27, P=0.27) between the 2 groups. They concluded that meta-analysis supports the superiority of fibrin glue to suture in pterygium surgery with conjunctival autografting in that the use of fibrin glue can significantly reduce the recurrence rate without increasing the risk of complications.[35]

- In a study by Cha DM et al, to compare the effect of using fibrin glue or 10-0 nylon sutures on the clinical outcome of patients undergoing pterygium excision and conjunctival autografting. The study included 52 eyes from 46 patients who underwent pterygium excision and conjunctival autografting and were followed up for more than 3 months.

The operation duration, postoperative inflammation, complications and recurrence rates were compared between groups of 20 patients (22 eyes) for whom fibrin glue was used and 26 patients (30 eyes) for whom suturing was performed with 10-0 nylon in pterygium excision and conjunctival autografting. The operation duration was 27.71 (5.52) minutes in the fibrin glue group and 43.30 (8.18) minutes in the suture group (P=0.000). seven days after the operation, the fibrin glue group showed milder conjunctival inflammation than the suture group (P=0.000). Postoperative complications and corneal recurrence rates were not statistically different between the two groups. They concluded that the use of fibrin glue in pterygium excision with conjunctival autografting is likely to be more effective, safer procedure than suturing.[36]

For more than thirty centuries, man has tried to conquer this little growth. It has been incised, removed, split, transplanted, excised, cauterized, galvanized, heated, inverted, dissected, rotated, coagulated, repositioned, irradiated, excimerlasered, stripped and grafted. Despite the best techniques in the hands of the greatest surgeons there have been recurrences and when the pterygium recurs it is much more aggressive.

ANATOMY OF CONJUNCTIVA[37, 38, 39]

The conjunctiva is a thin, translucent mucous membrane which derives its name from the fact that it attaches the eyeball to the lids. It lines the posterior surface of the lids and is then reflected forwards on to the globe of the eye. The epithelium becomes continuous anteriorly with the epithelium of the cornea. Thus it forms a barrier which prevents ingress to the orbit from outside.

Conjunctiva is divided for purpose of description into three parts -palpebral, fornix, and bulbar parts.

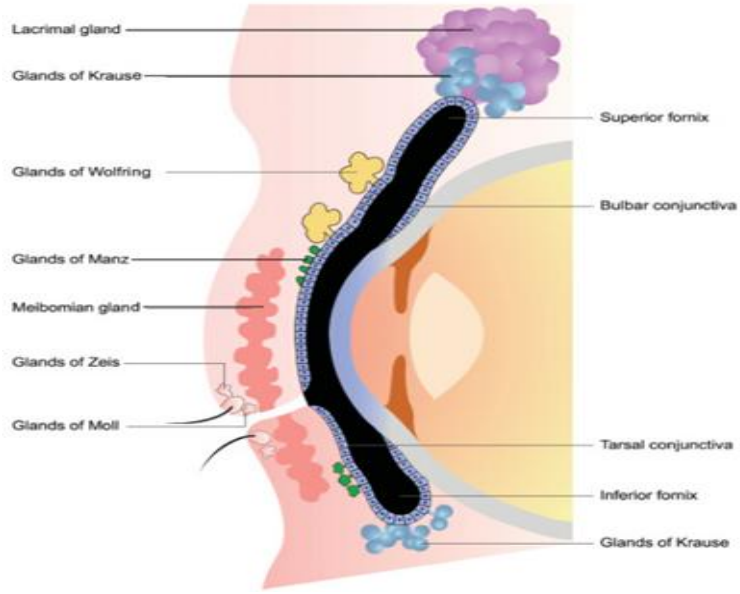


Figure 1: Anatomy of Conjunctiva

The palpebral part is sub-dived into two zones. The marginal zone extends from the opening of the glands at the lid margin, far as the sub-tarsal furrow, which is about 2 mm up on the back of the eye lid. At this point, the tarsal glands and the lacrimal punctum emerge. This region is covered with tissue which can withstand much wear.

The tissues are not smooth and they have minor ridges or elevations. These provide slight depression over the cornea and the tears liquid can run across the depression between the ridges.

The tarsal zone is thin, vascular and is light red in colour. It has a good attachment to the underlying tissues being transparent so that the Meibomian glands can be seen from the rear as yellow streaks unlike the upper tarsal conjunctiva which is closely adherent to the tarsus. The orbital zone is loosely attached to the tissues below lying in a horizontal fold. The conjunctival fornix is a linear sac folded above, below and laterally and extending along the margin of the orbit. This fold prevents stretching when the eye moves medially. The plica semilunaris has a corresponding function. In order to avoid collapse of the fornix as the globe rotates; there are appropriate connections of the tissues with the superior, inferior and lateral recti. Thus the fornix follows movements of these muscles. The plica semilunaris have corresponding connections with the medial rectus.

In the intertendinous interval, which is in the diagonal regions of the fornix, the conjunctiva may extend to the cornea. The fornix is well supplied with vessels and a rich venous network can be especially well seen in the inferior fornix, where also the whitish aponeurotic expansion from the inferior rectus and inferior oblique shows through the conjunctiva.

The bulbar conjunctiva is thin and transparent so that white sclera is seen through it giving rise to the white of the eye. It is attached loosely to the tissues beneath, except around the limbus which is a 3 mm wide zone, where it is fastened firmly.

The bulbar conjunctiva is at first in contact with the tendons of the recti muscles covered by the Tenon’s capsule. Thus in exposing these tendons, for instance in tenotomy we must divide the conjunctiva, then the capsule of tenon before they are reached.

In front of the insertion of recti tendons the bulbar conjunctiva lies on the anterior portion of the Tenon's capsule, up to a point 3 mm from the cornea. The conjunctiva is separated from the capsule of tenon by loose areolar tissue, in which we find the sub- conjunctival vessels. In between conjunctiva and the sclera, there is the loose episcleral tissue in the anterior portion of the Tenon's space. In this space, we find the anterior ciliary arteries which form the pericorneal plexus and the tendons of the insertion of the recti muscles. At about 3 mm from the cornea, the conjunctiva, Tenon's capsule and the sclera become much closely united. For this reason, although it is difficult to raise a fold of conjunctiva close to the cornea, a much firmer hold of conjunctiva and episcleral tissues can be obtained here with the forceps than elsewhere.

The palisades of Vogt are found in the limbal conjunctiva as little raised ridges, about 0.55 mm wide and 1 or 2 mm long. They are light elevations, often with pigment in the furrows and are more distant at the lower limbal area.

CONJUNCTIVAL EPITHELIUM

The epithelium of the tarsal region consists of two or three layers of columnar cells. Because it forms a very thin, uneven layer, with ridges and grooves, it reduces friction, but simultaneously ensures a useful collection area of debris and bacteria.

The epithelium of the fornix consists of 3 or 4 layers of cubical cells, increasing in number from bulbar conjunctiva. Around the limbus a stratified layer appears between 8 and 10 cells thick, with additional squamous epithelium which is very robust. The surface layer cells of conjunctiva have microvilli similar to those of the cornea.

The stroma consists of the two portions a superficial adenoid layer and a deeper fibrous layer. At the limbus, neither layer passes over the cornea.

The adenoid layer is not present at birth, but if formed first in the region of the fornix 3-4 months after birth. The adenoid layer is thin but most developed in the fornix, being here 50-70 μm in thickness. It consists of a fine connectivity tissue reticulum in the meshes of which the lymphatics lie, it is absent at marginal and tarsal zones.

The fibrous layer is generally thicker than the adenoid, but is almost nonexistent over the tarsus with which it is continuous. In it are found the vessels and nerves to the conjunctiva, the unstriped muscle of Muller, and Krause's gland, which are as it were encapsulated by it.

THE CONJUNCTIVAL GLANDS

Goblet cells are present as mono cellular mucous producing glands, which are found in the basal epithelial layer. They rise within the layer to discharge their secretion on the surface although it is uncertain whether, after secreting mucous the cells are able to replenish their supplies. About 1.5 million cells are found in each conjunctival sac, most authorities suggest that the distribution is greatest near fornices, with fewer in the tarsal conjunctiva.

The number from these cells contributes greatly to the content of the tears liquid, which in turn is helpful for moistening and protecting the conjunctiva and cornea so that even extirpation of lacrimal gland becomes innocuous, while on the other hand, xerosis of the conjunctiva involving their destruction leads to desiccation in spite of copious flow of tears.

THE CONJUNCTIVAL BLOOD VESSELS

The arterial supply of conjunctiva comes from three sources:

1. The peripheral arterial arcades

2. Marginal arterial arcades

3. The anterior ciliary arcades

Bulbar conjunctiva is supplied by 2 sets of vessels. The posterior conjunctival arteries are branches from the arterial arcades of eye lids and anterior conjunctival arteries which are branches of anterior ciliary arteries. Terminal branches of posterior conjunctival arteries anastomose with anterior ciliary arteries to form the pericorneal plexus. Conjunctival veins accompany the corresponding arteries but are more numerous than the corresponding arteries. The major portion of the bulbar conjunctiva, tarsal-conjunctiva and fornix drain into the palpebral veins.

LYMPHATICS

The conjunctival lymphatics are arranged in two plexus: A superficial, composed of small vessels, placed just beneath the vascular capillaries and a deep, consisting of larger vessels situated in the fibrous layer of the conjunctiva and receiving the lymph from the superficial plexus. They drain towards commissures, where they join the lymphatics of the lid, to lymph gland, pre auricular, and submandibular.

NERVE SUPPLY OF THE CONJUNCTIVA

Sensory innervation for the bulbar conjunctiva is from the long ciliary nerves which are branches of the nasociliary nerves. The upper fornix and the palpebral conjunctiva are served by the frontal and trochlear divisions of the ophthalmic nerve, while the lacrimal nerve covers the region of the outer canthus. The conjunctiva of the lower eyelid is innervated by the infra orbital nerve. Short ciliary nerves supply the cornea and the corneal circumzone of conjunctiva.

ANATOMY OF LIMBUS[40]

Anatomically the limbus is a transitional zone of the conjunctivocorneal and corneoscleral junction. The limbus is the junctional zone, about 1.5 mm wide in the horizontal plane and 2 mm in the vertical, between the cornea and the sclera, its internal edge being called the corneal limbus and its external edge the scleral limbus. The corneal limbus is demonstrated by a line joining the termination of Bowman's layer to the termination of Descemet's membrane. The termination of Bowman's layer is indicated on biomicroscopy by the internal limit of the marginal arcade of corneal vessels, seen best at the upper and lower limbus. The termination of Descemet's layer is visible on gonioscopy as the most anterior landmark of the drainage angle, Schwalbe's line, which may at times be hypertrophied (anterior embryotoxon) as a congenital anomaly and is then visible on gonioscopy as a fine internal ridge. The scleral limbus is less clearly defined by a line perpendicular to the surface, passing through the scleral spur.

Within the limbal zone, the orderly packing of the corneal collagen gives way to the coarse interweaving of scleral fibres, and the fibril diameter increases markedly from the narrow range of fine fibril diameters in the cornea to the broad range found in the sclera. Collagen fibrils are said to run a circular course at the limbus, which is the weakest region in the corneoscleral envelope as assessed by bursting pressure.

Centrally, the corneolimbal junction is demarcated by a line joining the termination of Bowman's layer to the termination of Descemet's membrane. Peripherally, the sclerolimbal junction is demarcated by a parallel line passing through the scleral spur. Cornea epithelium is subject to constant trauma and shedding of the surface epithelium, and replenishment is from epithelial cells beneath and peripheral to the central desquamating epithelium.

The origin of the corneal epithelium appears to reside in the crypts of Vogt, where a population of immortal stem cells resides, and possessing enormous potential for clonogenic cell division. These cells [stem cells and transient amplifying cells (TAC)] are located exclusively in the limbal region, with the stem cells in the basal epithelium and TAC occurring in the basal and suprabasal levels, extending up to the superficial layers.

The absence or malfunction of corneal stem cells is characterized by the loss of proliferative capacity of corneal epithelium, resulting in surfacing of the cornea with transdifferentiated conjunctivally-derived epithelium or, in the worst case, failure to resurface at all in the presence of a persistent epithelial defect, with corneal neovascularisation and scarring. Such disorders include primary dysfunctions such as aniridia and congenital erythrokeratoderma, and secondary ones (the most common, in which limbal stem cells are destroyed, either traumatically (e.g., alkali burns) or immunologically (e.g., Stevens Johnson syndrome).The limbus has two important functions with regards to the corneal epithelium. Firstly, the corneal epithelium is renewed by stem cells located at the limbus, the so-called limbal stem cells. Secondly, the limbus also acts as a barrier preventing the conjunctival epithelium and its blood vessels from encroaching on to the corneal surface. When the limbal stem cells become deficient or dysfunctional, the disease of limbal stem cell deficiency results.

The limbus can be divided into three zones:

1. The deep limbus, which contains the trabecular meshwork and Schlemm's canal.
2. The mid limbus containing the transitional corneoscleral stroma which projects, with a conoid profile, into the scleral limbus. It also contains the intrascleral venous plexus.
3.The superficial limbus, which consists of the episclera, Tenon's capsule, the conjunctival stroma and the limbal conjunctival epithelium with its specialized anatomical features.

LIMBAL STEM CELLS

Evidence for the limbal location of corneal epithelial stem cells comes from almost 40 years of both clinical observations and basic science research. The migration of limbal pigment during corneal epithelial wound healing in guinea pig eyes first suggested the important role of the limbus with regard to the corneal epithelium. This was confirmed by clinical observations in patients with corneal epithelial wounds, where it was seen that the corneal epithelium healed from the peripheral aspects of the cornea. Such observations led to the X, Y and Z hypothesis of corneal epithelial homeostasis, which suggested that the movement of cells from the basal layers of the corneal epithelium (X) and the movement of cells from the periphery of the cornea (Y) replace those cells that are lost from the corneal surface through natural shedding (Z).

Basic science research has further localized the limbal stem cells to the basal layer of the limbal epithelium. DNA labelling studies of mouse corneas have identified a subset of epithelial cells in the basal layer of the limbal epithelium that move slowly through the cell cycle and in fact are often found in a quiescent state but that have the potential during wounding to cycle rapidly to replace the lost cell. This quiescent yet agile potential to cell cycle is an important property of adult stem cells. Indeed, this potential can be seen during in vitro culture, where it has been shown that the limbus has a higher cell expansion potential than the cornea.

It is not surprising that corneal epithelial stem cells are found to reside in the basal layer of the limbus. The cellular microenvironment is important in maintaining the stem cell state of stem cells. This is known as the stem cell niche. The basal layer of the limbus provides the stem cells closeness to stromal vasculature, which brings important growth factors to the stem cells.

The cornea, being a clear tissue, is avascular and so cannot provide this environment to its epithelial stem cells. To increase the contact of limbal stem cells with their microenvironment, the basement membrane of the limbus undulates to increase the surface area. These undulations can be seen clinically on the surface of the limbus, giving it a corrugated appearance. These visible corrugations are referred to as the palisades of Vogt and are more prominent at the superior and inferior limbus where the upper and lower eyelids, respectively, provide protection to the limbal stem cells. Stem cells are a small subpopulation of specialized undifferentiated, self-renewing cells, which are capable of indefinite proliferation of large number of differentiated progeny, responsible for the cellular replacement and regeneration in all the self-renewing tissues.[42]All the cells in a self-renewing tissue can be placed into two compartments as Proliferative and Non proliferative[41, 42] . The cells in proliferative compartment are stem cells (SC) and transient amplifying cells (TAC) that are derived from mitotic division of stem cells.

Cells in non proliferative compartment are post mitotic cells (PMC) which are in different stages of maturation by differentiation into the terminally differentiated cells (TDC). Thus the cellular hierarchy of these self-renewing is comprised of different cell population in the order of SC-TAC-PMC-TDC. Stem cells are produced more when the limbal epithelium is damaged, a pathological state known as Limbal stem cell deficiency develops in a number of corneal diseases.[43]

There has been recent controversy regarding the possibility of corneal epithelial stem cells residing in the corneal epithelium, as well the limbal epithelium. Despite this, there are many decades of both clinical and scientific evidence of the limbal location of the true corneal epithelial stem cell. They have therefore more commonly come to be known as limbal stem cells.

CONJUNCTIVAL TRANSDIFFERENTIATION

When cornea is denuded of its epithelium, the denuded corneal surface is healed by ingrowth of surrounding conjunctival epithelium. Healing takes place in 2 ways:-

a) With extensive vascularisation

b) With either no vascularisation or with vascularisation limited to peripheral cornea

In the latter group it is first seen that the epithelium first shows conjunctival epithelium like morphology with goblet cells, which later on transforms into corneal epithelium without goblet cells. This process is called transdifferentiation. In the former group with extensive vascularisation the epithelium remains that of the conjunctiva hence called conjunctivilisation.

Stages of transdifferentiation

Shapiro et al identified 5 distinct stages of morphological transdifferentiation during corneal re-epithelisation from conjunctiva.

Stage 1- There is high mitotic rate and cell sliding to fill in the defect, with few recognizable goblet cells. The epithelium is 3-4 cell layers, immediately after healing.

Stage 2- Decreased rate of mitosis epithelium with appearance of goblet cells at limbus.

Stage 3- Mitotic rate of epithelium is below that of normal corneal epithelium, with goblet cells reaching uniform distribution across the cornea.

Stage 4- Disappearance of goblet cells associated with another burst of mitotic activity of the cells.

Stage 5- Epithelium is morphologically that of corneal type with mitotic rate equivalent to corneal epithelium.

PTERYGIUM

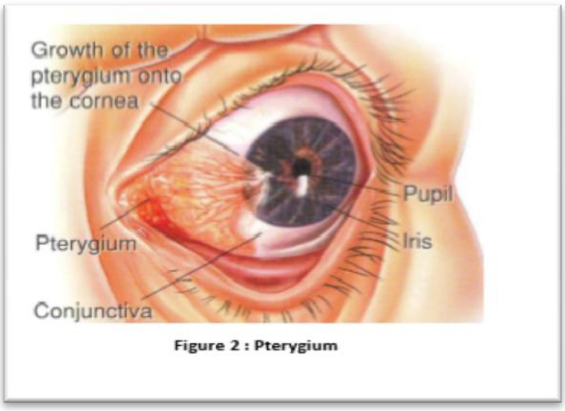


Figure 2 : Pterygium

DEFINITION

Pterygium is defined as a triangular fibrovascular growth of the bulbar conjunctiva encroaching on top the cornea in the interpalpebral fissure. It is a horizontally oriented triangular growth of abnormal tissue that invades the cornea from the central region of the bulbar conjunctiva.

Winter (1556) differentiated 2 forms of Pterygium

True Pterygium:is an elastotic degenerative condition of sub-conjunctival tissue which proliferates as vascularised granulation tissue encroaching and destroying the superficial layers of stroma and Bowman's membrane of the cornea.

Pseudo Pterygium: It is the result of an inflammatory process in which a fibro vascular scar of the bulbar conjunctiva becomes adherent to a raw area on the cornea and is passively dragged across the cornea. Hence a glass rod can be passed beneath the pseudo pterygium

CLASSIFICATION[44, 45]

a) Dohety's Morphological Classification

1) Progressive
2) Regressive.

b) JooselBaraquen Classification

1) Conjunctival stage
2) Corneal stage or true pterygium stage

c) Fuch'sClassification: On basis of vascularity, colour thickness and clinical aggressiveness.

1) Pterygium Crassum
2) Pterygium Vasculasum,
3) Pterygium Carnosum,
4) Pterygium Sarcomatosum,
5) Pterygium Membranosum

d) William M. Town Classification

1) Actively growing pterygium
2) Fleshy or malignant pterygium
3) Slow growing pterygium
4) Stationary pterygium
5) Atrophic Pterygium

e) Modified Roherty's Classification

1) **Primary pterygium** which is divided into
    i. **Progressive**: It is a fleshy vascular pterygium in which the neck is hyperaemic, head is voluminous and has a gelatinous appearance.

The cap is very serrated with its borders infiltrating the healthy corneal tissue and in front of it are numerous riders (infiltrations).

ii. **Stationary or Mildly Progressive**: Presents a thin pale and sparsely vascularised head with the cap of a smooth border and seldom presenting outside.

iii. **Regressive or Atrophic Pterygium**: In the halo of opacity in front of the head and stops advancing and gradually becomes absorbed and atrophy of pterygium follows with the vessels tending to disappear.

2) **Recurrent Pterygium**: In which cornea is reinvaded by vessels and a conjunctiva like tissue to varying extent of the surgical removal.

GRADES OF PTERYGIUM: It is graded depending on its extent of corneal encroachment.

Grade I Less than 2mm

Grade II between 2 – 3mm

Grade III More than 3mm

OR

Grade I Less than 1.5 mm

Grade II Less than ½ radius of cornea

Grade III More than ½ radius of cornea

Grade IV Almost to the centre of cornea

EPIDEMIOLOGY

World wide prevalence of pterygium varies from 1 to 25 percent, depending on the population studied. Internationally, the relationship between decreased incidence in the upper latitudes and relatively increased incidence in lower latitudes persists. [46]

Occurrence within the United States varies with geographical location. Within the continental United States, prevalence rates vary from less than 2% above the 40^{th} parallel to 5-15% in latitudes between $28\text{-}36^{O}$. A relationship is thought to exist between increased prevalence and elevated levels of ultraviolet light exposure in the lower latitudes.[47, 48]

Previously reported prevalence rates of pterygium vary widely with geography, race, age and gender. The epidemiological studies around the world have shown that the prevalence rates range from 0.3% to 37.46%[49, 50]. The earliest estimate was from a survey[51] in New South Wales, Australia, which reported 9.6% prevalence. In the Blue Mountains Eye Study, Panchapakesan[52] found 266 subjects had pterygium (or had a history of pterygium surgery) out of 3564 paticipants aged 49yrs or older; the prevalence was 7.4%. Another study[49] in 1984 reported the prevalence of pterygium was only 0.3%. The prevalence of pterygium from a number of populations in urban Caucasians in Victoria, Australia was 1.2%.[53]

A population based study[54] by Marcus Ang in 2012 at Singapore studied the prevalence and risk factors of pterygium on a multiethnic Asian population and reported that Malays (15.5%) have a higher prevalence of pterygium as compared with Indians (7%) and Chinese (7.0%).

The 5.2% prevalence of pterygium in people aged 50 and older in Wardha. India has been reported.[55] Prevalence of pterygium in South Indian population as studied by the Chennai Glaucoma Study was found out to be 9.5%. [56]A study of prevalence of pterygium in Karnataka (1957) is 1.29%. In India its prevalence is high in Maharastra, Assam and Andhra Pradesh.

OCCURRENCE

Occurrence of pterygium is more common on nasal conjunctiva than the temporal conjunctiva. It may occur in both sides actively (Double pterygium) Occasionally Nasal and temporal pterygia can occur in the same eye but isolated temporal pterygia are rare. Both eyes are frequently involved but often asymmetrically. At times 4 pterygia may be present in an individual.

Various explanations have been put forward for greater prediction on nasal side:

1. The normal flow of tears is from temporal to nasal side towards puncti and carries dust particles of the conjunctival sac and accumulates it on sulcus lacrimalis. These concentrated dust particles may cause greater irritation of nasal conjunctiva.
2. There are 2 anterior ciliary arteries on the nasal side and only one on the temporal side. It is considered that due to this fact, any irritant will lead to greater hyperemia on the nasal side and results in pterygium on nasal side.
3. Greater exposure of nasal inter palpebral conjunctiva to ultra violet radiation.
4. Greater curvature of nasal fibres of orbicularis oculi, causing a greater squeezing effect upon nasal subconjunctival tissue.
5. Greater sloping of lateral 1/3rd of upper lid and consequent protection of longer lashes.
6. Excess of sub conjunctival tissue nasally.
7. Sun light is reflected by the nose on to the nasal bulbar conjunctiva.

8. Transcameral light focusing on the nasal limbus may expose limbal basal stem cells to increased amounts of UVR (ultra violet radiation) and be associated with molecular genetic alterations to these cells, eventually leading to pterygium formation.[57]

AGE: Highest age incidence is between 20 – 40 years. Prevalence increases with age and reach their peak in age group of years and older. Pterygia are rare among children.

SEX: Male predominance with M/F ratio of 2:1. Males and females who work indoors are equally affected.

ENVIRONMENT:More common among inhabitants of region where the weather is dusty and hot with bright sun rays. Significant association exists betweenthe presence of pterygium and annual mean UV radiation, annualmaximum temperature and rates.

OCCUPATION: More common among people who work outdoor like fisherman, farmers, stone cutters, sailors, Surfers. Such individuals are exposed to highlevelsof UV radiation and long standing conjunctival irritation. It is also common in indoor workers with exposure to irritants.[58]

ETIOLOGY

There are several reviews explaining the aetiology of pterygium

1. **Radiation Factors**: It is perhaps the most obvious of the opthalmoheliosis (sun related conditions). Strong circumstantial evidence shows that exposure to UV light is important in the aetiology of pterygium. UV radiations are absorbed by the cornea and the conjunctiva while visible spectrum is transmitted. Infrared rays cause damage to tissues by their thermal effect and UV rays by their abiotic effect[59]. The UV theory of pterygium causation is also supported by various other studies. Another study suggested that there was a strong protective element in wearing of regular sunglasses or hat.[2]

2. **Environmental Factors**: Environmental irritant factors such as heat, dry atmosphere, high winds and abundance of dust are most frequently associated with this condition.[60]
3. **Tear film Abnormality**: The uneven spreading of tear film gives rise to dellen formation, when the cornea becomes dry and thin, the epithelium desquamates and the Bowman's Membrane along with the superficial stroma gets affected causing the pterygium to progress.[61]
4. **Inflammation and Infection factors**: The evidence for its inflammatory origin is the following findings.
    a) The presence of round cell infiltration in front of the advancing head and in the subepithelial tissue in progressive pterygium.
    b) The marked increase in goblet cell in the epithelium.
    c) The presence of hypertrophy of epithelium, epithelial downgrowth and cysts.
    d) The deposition of dense fibrovascular tissue in the submucosa of conjunctiva and corneal replacement by fibrous tissue is a consequence of chronic inflammation.
5. **Degenerative factor**: Fuchs (1891) brought out the fact that it was essentially an age related change. Pinguecula is seen to be the precursor of pterygium. Both pinguecula and pterygium show a common finding of hyaline and elastotic degenerative changes in deeper part of the tissues.
6. **Allergic factor**: Hilgers (1960) postulated that prolonged exposure of bulbar conjunctiva to solar radiation produces degenerative changes with formation of denatured protein. These proteins may cause antigen- antibody reaction.
7. **Neoplastic Factor**: Pterygium shows a progressive growth invasion of normal tissue and recurrence after its removal.

8. **Hereditary factor**: Autosomal dominance with a low penetrance but it would appear that it is not the actual lesion which is transmitted but rather the tendency of the eye to react in this way to environmental stimuli.
9. **Neurotropic Factor**: Neurotropic conditions of conjunctiva where conjunctiva reacts aggressively to the external stimulus suggested by Sappupo (1953).
10. **Other Factors**: Trophic changes leading to hypoplasia deficiency of choline, malnutrition, and increased blood cholesterol altered pigment metabolism have all been considered as possible causative factors.

PATHOLOGY

PATHOGENESIS:

The earliest changes occurring in the cornea are the appearance of vesicle like formation at the points in the basement membrane where the corneal nerves pass. The vesicles like formation were made by migrating keratoblasts corresponding to the island of opacity seen clinically. At these points basement membrane is destroyed and under the epithelium there appears a mass of dense tissue. This insinuates itself between basal membrane and basement membrane. The process is seen continuing at the head of the rowing pterygium. The superficial corneal lamella is penetrated by the tissue of the pterygium. Clefts appear between the lamellae; they become finer and waxy and may suffer a round celled infiltration. A fully developed pterygium is covered by conjunctival epithelial stratified with flat cells on the surface of the head and neck, but cylindrical on the numerous folds, furrows and at the base.

In the depressions there are numerous goblet cells and in the body of the pterygium, tubular downs growth of cylindrical cells from glands which may develop into cysts. At the apex, the transition from conjunctival to corneal epithelium is sharp and here the latter is frequently heaped up. But 2 types of epithelium may merge imperceptible into each other. Usually the apex itself is covered by the epithelium of the corneal type, but sometimes the conjunctiva type may extent on to the cornea throughout the epithelial layer.

Pigmentation may be pronounced. Stroma differs little from the corneal subepithelial tissue with elastotic and hyaline degenerative changes.[62]

HISTOLOGIC CHARACTERISTICS:

The term elastotic degeneration was originally used to describe the fibres within pterygia that stained with elastic tissue stains elastotic material is primarily derived from degenerated collagen and also from pre-existing elastic fibres and from abnormal fibroblastic activity. Pterygium also shows changes of actinic degeneration that represents degenerative changes resulting from radiation activated fibroblasts that secrete elastic tissue precursors.

Histologically and ultra-structurally, pterygium, pinguecula and actinic degeneration of the skin are very similar. A study[63]described the histological characteristics of pterygium as:

- Hyalinization of the subepithelial connective tissue of the substantia propria.
- Diffuse or lobular collections of eosinophilic granular material with an associated increase in the number of fibroblasts and other cells.
- An increased number of thickened and tortuous fibers that stain strongly with elastic stains (elastotic material).
- Concretions within the hyalinized and granular areas that may show either eosinophilia or basophilia.

The body of the growth is made up of vascular, areolar tissue, which is compact in old case and is loose in the early stages in which there is rapid growth. In the neck of the growth the blood vessels are connective tissue. Also present are newly formed tubular glands and larger spaces lined with epithelium, both of which may result in formation of cysts.

Histopathologically, the growth of pterygium can be easily divided into 3 phases.

1) Proliferative papillomatous corresponding to progressive form.
2) Fibromatous in which the connective tissue is more prominent but vascularity is less evident, corresponding to stationary form.
3) Atrophic sclerotic phase in which there is no further growth.

SYMPTOMS AND SIGNS[64]

1) Discomfort
2) Foreign body sensation
3) Congestion
4) Irritation
5) Dryness
6) Tearing (Lacrimation)
7) Occlusion of the visual axis (Decreased visual acuity).
8) Diplopia on lateral gaze.
9) Acquired irregular astigmatism.
10) Painless elevated vascularised white tissue on the inner and out edge of the cornea.
11) Impaired vision when growth extends into the papillary area of the cornea.

Parts[65]

A fully developed pterygium consists of three parts:

i. Head (apical part present on the cornea)
ii. Neck (limbal part)
iii. Body (scleral part) extending between limbus and the canthus.

Figure 3: Parts of pterygium

Types

Depending upon the progression it may be progressive or regressive pterygium.

1) **Progressive pterygium** is thick, fleshy and vascular with a few infiltrates in the cornea, in front of the head of the pterygium (called cap of pterygium).
2) **Regressive pterygium** is thin, atrophic, attenuated with very little vascularity. There is no cap. Ultimately it becomes membranous but never disappears.

Complications

1. Cystic degeneration
2. Infection
3. Rarely, neoplastic change to epithelioma, fibrosarcoma or malignant melanoma, may occur.

Differential diagnosis

Pseudopterygium is a fold of bulbar conjunctiva attached to the cornea. It is formed due to adhesions of chemosed bulbar conjunctiva to the marginal corneal ulcer. It usually occurs following chemical burns of the eye.

DIFFERENCES BETWEEN PTERYGIUM AND PSEUDOPTERYGIUM

FACTORS	PTERYGIUM	PSEUDOPTERYGIUM
Etiology	Degenerative process	Inflammatory process
Age	Elderly persons	Can occur at any age
Site	Situated in the palpebral aperture	Any site
Stages	Progressive, regressive or stationary	stationary
Probe test	Probe cannot be passed underneath	Can be passed under the neck

INDICATIONS FOR TREATMENT [66]

1. Defective vision from proximity to visual axis
2. Threatening the visual axis
3. Defective vision from astigmatism
4. Eye movement restriction
5. Atypical appearance such as possible dysplasia
6. Observed growth by ophthalmologist
7. Reported growth by patient
8. Symptoms of irritation
9. Cosmetic concerns

Pterygium surgery today still varies from the simplest procedure of bare sclera excision to complex surgery such as sclerokeratoplasty and amniotic membrane transplantation with or without tissue adhesive.[6]

TECHNIQUES

1. Avulsion
2. Bare scleral closure
3. Simple conjunctival closure
4. Transplantation of head of pterygium
5. Conjunctival flap and Autograft
6. Limbal conjunctival Autografts
7. Conjunctival Rotation Autograft
8. Amniotic membrane Transplantation
9. Cultivated Conjunctival Transplantation
10. Lamellar Keratoplasty
11. Adjunctive Therapy
12. Chemotherapy

Historically, there has been a common understanding that surgery is the only way to cure the disease. Medical treatments, chemical cauterization and laser therapies have all been used and abandoned. However, recently anti-VEGF therapy[47]has been tried with some success.

Many different methods of pterygium surgery have been advocated and used; some with unpredictable and poor results, due to the propensity to recur.[67]Proper reconstructive surgery began in the nineteenth century with Scarpa, Arlt (use of conjunctival graft), Desmarres and Knapp. Elschnig (1926) performed advanced conjunctival plastic surgery. β-irradiation[68] began to be used in the 1950s and the use of Mitomycin C (MMC) as adjunct therapy[69] began in Japan in the 1960s.

Amniotic membrane to substitute the conjunctiva[70] was used as early as in 1946 but the idea was developed and popularized by Tseng in the 1990s.

The surgical options available include the use of conjunctival autograft, limbal and limbal–conjunctival transplant, conjunctival flap and conjunctival rotation autograft surgery, amniotic membrane transplant, cultivated conjunctival transplant, lamellar keratoplasty and use of fibrin glue.[71]

Early pterygium removal included simple excision (detachment) of pterygium head from the anterior corneal surface. However, the realization of the potential for recurrence, often more aggressive clinically than the original lesion, soon lead to modifications of simple excision.

AVULSION TECHNIQUE

In the seventh century, Paluus and Aegeneta described the avulsion technique. With a small hook the pterygium is seized; a needle with a horse hair and a strong thread in its eye is transfixed through the middle. With the thread, the growth is raised, and with the horse hair, it is sawed off the globe centrally. At the medial canthus it is cut off with a scalpel.

BARE SCLERAL CLOSURE

Bare scleral closure as a technique generally implies the removal of the pterygium with excision of some of the bulbar conjunctiva nasally, leaving the defect to heal from the surrounding conjunctiva. Occasionally the conjunctiva is actually sutured to the sclera, leaving the defect, and other times the conjunctiva is left free to adhere to the underlying sclera. It is by far the quickest method of removal with the least surgical intervention.

The rationale for the ‘bare sclera’ technique was that the area left uncovered would be epithelialised from epithelial cells from the anchored conjunctival rim which could then

act as a barrier against pterygium re-growth from pathological tissue remnants inevitably left in situ.

However, it is the least satisfactory method with respect to recurrence rates, which mayrange as high as 80%. This procedure is now regarded as unethical and is relegated to the history of treatment options for pterygium.[57]

SIMPLE CONJUNCTIVAL CLOSURE

It generally involves the removal of the pterygium with minimal conjunctival excision and then closure of the conjunctiva with sutures leaving very little or no bare sclera. This is the simplestmethod and consists of extirpation of allthe fibrovascular proliferation and suturing the upper and lower cut edges of the conjunctiva. Czemark recommends passing suture through the superficial layers of cornea.

TRANSPLANTATION OF HEAD OF PTERYGIUM (McReynold operation)

In this procedure, head of the pterygium is dissected and transplanted under the conjunctiva away from the limbus so that any future growth is innocuous. Desmarres (1851) detached the pterygium and fastened it inferiorly making an opening in the conjunctiva in this region.

McReynold conceived the idea of passing the head of the pterygium beneath the conjunctiva without cutting it and fastening it with suture near the insertion of the inferior rectus, beneath lower bulbar conjunctiva. Unfortunately recurrence rates of 30 to 75% were reported with these techniques. Such transplantation procedures thus have been largely abandoned secondary to high recurrence rate and unsatisfactory postoperative cosmetic results.[72]

CONJUNCTIVAL FLAP AND AUTOGRAFT

Two reports[73, 74]have described the use of sliding conjunctival flaps harvested from the inferior or the superior bulbar conjunctiva to close the scleral defect, with reported recurrence rates ranging from 1 to 5%.

There is widespread acceptance of conjunctival autografting, since its introduction by Thoft in 1977 and application to pterygium. However, no single autograft technique is completely effective in preventing recurrence. Most reports also advocate a thin graft devoid of Tenon's fascia but one which is large enough to completely cover the bare scleral defect.[75]

Conjunctival autograft surgery is generally regarded as the procedure of choice for the treatment of primary and recurrent pterygium, because of its efficacy and long term safety. A free conjunctival graft is harvested from the superior bulbar conjunctiva and is attached in place over the bare scleral defect. The conjunctival autograft can be attached with sutures, fibrin glue, electrocautery or autologous blood.[71]

While attaching the graft with sutures the 10-0 nylon or 8-0 vicryl interrupted sutures are used to anchor the graft first at the limbus and then on the nasal aspect.[76]

Use of sutures to secure graft is associated with several disadvantages including complicated surgical technique, prolonged operation time, prolonged postoperative discomfort and suture related complications like dellen formation, abscess etc[10]

Another method of securing the graft is by using the tissue adhesive that is the fibrin glue, which is applied in the dried surface of the bare sclera and the graft is placed over it. The graft adheres to the sclera with formation of fibrin clot.[77]

The autograft can also be attached with the electrocautery pen. The autograft is placed on the bare sclera after excision of the pterygium and the tissue junction is welded directly using electrocautery pen. The whole circumference is welded to the surrounding conjunctiva at appropriate intervals. Each weld takes approximately 0.5 seconds until coagulation is complete. A minimum of 8 welds and maximum of 10 welds are required.[78]

The latest method of securing the conjunctival graft in place is with use of autologous blood. After pterygium excision and fashioning of the autologous conjunctival graft, the recipient bed is encouraged to achieve natural hemostasis and then the conjunctival graft is placed over the scleral defect created after the pterygium excision. The autograft attaches to the sclera with the help of the fibrin clot formed by the oozing blood from the scleral vessels.[79]

Variations in conjunctival autograft surgery include the use of narrow strip conjunctival autograft, limbal–conjunctival autografts, limbal epithelial autografts, conjunctival flaps or conjunctival rotation autografts.[71]

LIMBAL–CONJUNCTIVAL AUTOGRAFTS

It has been suggested that including limbal stem cells in the conjunctival autograft (limbal–conjunctival graft) may act as a barrier to conjunctival cells migrating onto the corneal surface and help prevent recurrence. The limbal–conjunctival graft includes approximately 0.5mm of the limbus and peripheral cornea.

The recurrence rates after limbal–conjunctival autograft surgery (ranging from 0 to 15%) are similar to that of conjunctival autograft surgery, while some authors suggest that limbal–conjunctival autografts are more effective than conjunctival autografts.[71] A

study[80]demonstrated an overall recurrence rate of 9.52% with limbal conjunctival mini autografting performed in 63 eyes.

One of the drawbacks for limbal–conjunctival autograft transplantation is that it is technically more demanding and time-consuming to perform. To date, however, it should be noted that no conclusive evidence regarding the superiority of limbal–conjunctival autografts over conventional conjunctival autografts exists, and the added risk of limbal damage at the donor site deserves consideration.[71]

CONJUNCTIVAL ROTATION AUTOGRAFT SURGERY

Conjunctival rotation autografting involves removal of the pterygium and reversal of the removed conjunctiva so that the most nasal aspect is sutured at the limbus and vice versa. This is a useful technique for cases in which it is not possible or desirable to use the superior conjunctiva as a donor source, such as with excision of extensive pterygium, which leaves insufficient conjunctival tissue for the autograft.[71]

Pterygium Extended Removal Followed by Extended Conjunctival Transplantation (P.E.R.F.E.C.T.) has been reported to have virtually no recurrences in a series of primary and recurrent pterygia removal.[81]

AMNIOTIC MEMBRANE TRANSPLANTATION

In cases with very large conjunctival defects created following pterygium excision, or if a proper autologous conjunctival graft cannot be harvested, an alternative technique is the use of preserved amniotic membrane, which is readily commercially available and provides an excellent substrate for epithelial regrowth.[57]

Amniotic membrane possesses antiscarring, antiangiogenic and antiinflammatory properties, which may be useful for treating pterygium. A study[82]compared the excision of

recurrent pterygia followed by amniotic membrane alone and amniotic membrane graft combined with intraoperative mitomycin C, and found no significant difference in the recurrence rates between the two groups.

Besides the conventional epithelised cryopreserved human amniotic membrane, the efficacy of membranes that are alternatively prepared such as the de-epithelised or freeze dried sterilized ones have also been studied. An additional advantage is that it removes the need for harvesting large autografts, thereby minimizing iatrogenic injury to the rest of the conjunctiva surface.[71] In a randomized prospective study[83], 63 amniotic membrane transplants are associated with an unacceptably high recurrence rate compared with conjunctival autograft. This result is also supported by another study.[84]

CULTIVATED CONJUNCTIVAL TRANSPLANTATION

A novel method of closing the surgical defect involves the use of an ex-vivo expanded conjunctival epithelial sheet on an amniotic membrane substrate. Although the preliminary study[85] demonstrated no significant difference in the recurrence rate compared with denuded amniotic membrane transplantation, operated eyes achieved almost immediate reepithelialisation of the ocular surface, reduced postoperative inflammation and faster ocular rehabilitation.

This procedure may be particularly useful for closing large surgical defects following excision of extensive pterygium.

LAMELLAR KERATOPLASTY

Lamellar keratoplasty may also be required, especially in cases of recurrent pterygia with firm adhesion to the corneal stroma. It has been used to act as a barrier against pterygium recurrence and to replace thinned and scared corneal tissue after pterygium excision.[71]

It does not appear to offer any special advantage in preventing pterygium recurrence, with recurrence rates ranging from 6 to 100%. As such this is not a favoured procedure for treating primary pterygium. It has mostly been used to treat recurrent pterygium to restore corneal thickness in thinned, scarred corneas. The main limitations are the need for donor corneal tissue with the attendant risks of graft rejection and transmission of infection, as well as the increased complexity of the procedure.[71]

ADJUNCTIVE THERAPY

Since the description of the use of radon for the treatment of pterygium in 1940 by Burnam and Neil, adjuncts to surgery such as radiotherapy, chemotherapy and argon laser have been advocated to decrease the rate of recurrence. Beta irradiation as a treatment modality for pterygium was first developed by King in 1950. Mecham in 1962 tried instillation of antimitotics for pterygium. Argon Laser Photocoagulation was used in pterygium by Caldwell in 1985.

CHEMOTHERAPY

Thiotepa

The nitrogen mustard N, N', N" triethylene – thiophosphoramide (Thiotepa or TPA) is an alkylating agent with active antimitotic properties. Its mode of action is by inhibition of vascular endothelial proliferation. It was introduced by Mecham in 1962 as an adjunct topical therapy. Concentration of 1:2000 (15mg in 30 ml of Ringer's solution) is given every three hours in day time for 6 weeks.

While no systemic toxicity of topical thiotepa therapy has been reported, complications reported include early and late onset poliosis and periorbital skin depigmentation that can

be permanent (especially in darkly pigmented patients), prolonged conjunctival injection, irritation, epithelial toxicity leading to delayed epithelialisation of the cornea, conjunctival deposition of black pigment, allergic reactions and scleral perforation.

Sun exposure during therapy was suggested as a contributing factor in the skin and lash depigmentation. The periorbital skin depigmentation has been cited, as the major reason thiotepa has not gained widespread acceptance in the postoperative treatment of pterygia.

Mitomycin-C (MMC)

MMC is an antibiotic, a product of Streptomyces caesiptosus, capable of alkylating DNA double helix and blocking both transcription and translation. Thus MMC is also a potent antimetabolite used in suppressing tumour cells.[57]

In the case of pterygium surgery MMC is used in concentrations of 0.2-0.4 mg/ml applied episclerally for various intervals (usually not more than 2 min). The recurrence rate with the adjunctive intraoperative use of MMC is reported to be <10%. Apart from the intraoperative use, MMC has also been used as postoperative eye drops.Other agents include the alkylating agent 5- fluorouracil (5-FU), a pyrimidine analogue used either intraoperatively or as postoperative subconjunctival injections.[57]

Although very effective in reducing recurrence rates, antimetabolite use is, nevertheless, associated with serious and potentially sight-threatening complications, such as delayed healing or even scleral melt, sometimes threatening vision or requiring further surgery for their management. The thin or necrotic sclera resulting from antimetabolites may also be treated with theuse of hyperbaric oxygen which induces hyperoxia, angiogenesis and episcleral fibroblast proliferation.[57]

Beta irradiation

Historically, irradiation has been one of the first attempts of modern surgery to suppress the potential for recurrence in pterygium management. ß-irradiation, delivered through strontium/yttrium-90 sources, effectively reduces cellular populations responsible for pterygium recurrence. The mechanism of action is through the inhibition of mitosis in rapidly dividing vascular endothelial cells.[57]

With the introduction of a Strontium applicator for ophthalmological use in 1950, Strontium -90 has become the standard source of beta radiation. The 90Sr plaque is a concave metal disc about 1-1.5cm in diameter which is hollow and filled with an insoluble strontium salt. The dose of radiation to the conjunctiva is controlled by the time that the plaque is left in contact with the surface. The maximum radiation occurs within a 2.0mm radius from the tip of the applicator.If a dose of 1800-2200 rad is given to the pterygium bed, the anterior surface of the lens receives 70-90 rad, while the posterior retina receives 4-8 rad.[57]

Recurrence rate is 3 - 11%.However, its use is not innocuous and may be associated with serious complications including vision threatening endophthalmitis.[57]

Complications

- Chronic pain,
- Photophobia,
- Scleral necrosis,
- Secondary cataract and
- Scleral infectious ulceration and endophthalmitis.

A study[86] reported delayed scleral necrosis and ulceration which led to pseudomonas endophthalmitis and eviscerstion.

Conjunctival autografting are associated with recurrence rates (ranging from 2 to 39%) that are comparable to that of mitomycin c and beta-irradiation, without the attendant risk of sight-threatening complications associated with mitomycin c or betairradion usage.[71]

A study[87] demonstrated that there was no statistically significant difference in the recurrence rates between conjunctival autografting and mitomycin c use. Compared with the use mitomycin c and beta-irradiation, conjunctival autografting is more technically demanding and more time consuming to perform.

Argon Laser

Following surgical excision, any early evidence or recurrent pterygium is treated with 50 micrometer of laser burns to the neovascular fronds. Spot size of 50 micrometer is applied at the limbus in a pattern of 4 parallel rows.

Conversion of laser light into heat energy produces a thermo ablative effect. The power is adjusted to limit conjunctival epithelial burning and shrinkage. The recurrence rate is 12%.

Complications

- Scleral necrosis
- Scleromalacia
- Secondary iritis
- Cataract

Growth factor inhibitors

Anti- vascular endothelial growth factor monoclonal antibodies have become widely available in ophthalmic practice mainly because of their success in 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.[57]

Such factors include Pegaptinib, an oligonucleotide aptamer that binds exclusively to the 165 amino acid form of VEGF, and recombinant monoclonal antibody Bevacizumab as well as its fragment Ranibizumab, both directed against VEGF.[57]

Previous studies have already evaluated the potential use of Bevacizumab in pterygium management.[88, 89] However, Bevacizumab is also associated with potential serious side effects, including significant cardiovascular toxicity. The study of VEGF expression in individual lesions may therefore allow for selective Bevacizumab or other anti-VEGF administration, potentially reducing the risk of recurrence or aggressive clinical behaviour without taking unnecessary systemic risks.[57]

FIBRIN GLUE

TYPES

The two basic categories of tissue adhesives are - synthetic (commonest is nbutyl-2-cyanoacrylate) and biological (fibrin glue).[90]

In addition to these two tissue adhesives, newer adhesives available for surgeons are:

1. Gelatin and thrombin products

2. Albumin and glutaraldehyde products

3. Polyethylene glycol polymers

Each of these products is unique in terms of advantages and limitations and consequently used for different indications. Of all tissue adhesives, more reports available in world literature are about cyanoacrylate and fibrin glue.[7]

CYANOACRYLATE

Cyanoacrylate-based glues have traditionally been the most widely used glues for ophthalmic surgery[7]. Cyanoacrylate requires minimal hydration to polymerise and set. They can only be used externally because they induce inflammation. The tensile strength of the bonding is one of the highest of all glues. The major drawback of cyanoacrylate glue is that they form a solid,impermeable mass in situ. This persists as a foreign body causing inflammatory reactions like giant papillary conjunctivitis and corneal neovascularisation. They are also impermeable to fluids and metabolites. Though these disadvantages preclude its intraocular use, they are not very significant if the glue is applied superficially.[91]

FIBRIN SEALANTS

Fibrin glue is a blood-derived product that is absorbable, relatively easy to use, and can be kept at room temperature or in a refrigerator. Although the use of fibrin as a biologic adhesive was first introduced in 1909, it was not until 1944 that Tidrick et al. used fibrin for skin graft fixation.[92] Fibrin glue is a biological tissue adhesive which imitates the final stages of the coagulation cascade when a solution of human fibrinogen is activated by thrombin (the two components of fibrin glue).[93]

Fibrin glue includes a fibrinogen component and a thrombin component, both prepared by processing plasma. It can be prepared at a blood transfusion centre or from patients own blood[94] or obtained as a commercially available preparation[95]. When it is derived from individual volunteer donations, it may have a low concentration of fibrinogen[96]. The commercially available products are produced from pools of plasma, usually contain high yields of fibrinogen and, consequently, produce firm coagulum. Unlike cyanoacrylate glue, fibrin glue forms a smooth seal along the entire length of the wound edge and thereby provides greater postoperative comfort to the patient with fewer complications.

MECHANISMS OF ACTION

When human tissue is injured, bleeding ensues and then ceases due to formation of a blood clot. This is the initial mechanism of natural wound closure. Clot is formed as a product of the final common pathway of blood coagulation. Fibrin glue mimics this coagulation cascade resulting in its adhesive capability[93].

Once the coagulation cascade is triggered, activated factor X selectively hydrolyses prothrombin to thrombin.

In the presence of thrombin, fibrinogen is converted to fibrin. Thrombin also activates factor XIII (present in the fibrinogen component of the glue), which stabilizes the clot, by promoting polymerization and cross linking of the fibrin chains to form long fibrin strands in the presence of calcium ions. This is the final common pathway for both the extrinsic and intrinsic pathways of coagulation in vivo, which is mimicked by fibrin glue to induce tissue adhesion.

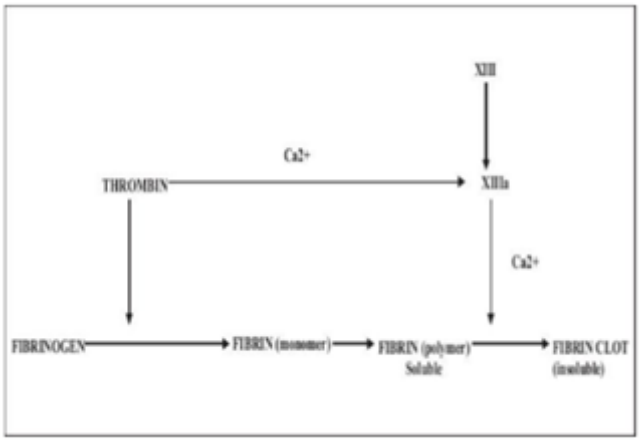


Fig 4: Mechanism of action of fibrin glue

There is subsequent proliferation of fibroblasts and formation of granulation tissue within hours of clot polymerization. Clot organization is complete two weeks after application. The resultant fibrin clot degrades physiologically.

METHODS OF PREPARATION

Numerous techniques have been used to prepare fibrin glue; either from homologous or autologous plasma. The autologous source avoids any possible risk of viral transmission. Homologous fibrin glue is prepared from donors screened like other blood products, followed by inactivation of viruses by solvent / detergent treatment.

The plasma is centrifuged to produce a precipitate containing fibrinogen and a supernatant containing the thrombin. The precipitate is resuspended in a small volume of the

supernatant and used as the fibrinogen component. The supernatant is further treated by clotting to convert residual fibrinogen to fibrin followed by its filtration to isolate the fibrin. The resulting serum is used as the thrombin component.

The various methods of preparation are:

- Fibrinogen: Modified Hartman's Procedure[95]
- Thrombin: Armand J Quick method[97]
- Fibrinogen rich concentrate[98]
- Preparation during emergency need[99]

LARGE-SCALE PREPARATION OF THROMBIN FROM HUMAN PLASMA:

Aizawa et al have discussed the preparation of thrombin for large scale use[100]. Similarly Alston et al described another cost effective method of autologous fibrin sealant from protamine precipitated fibrinogen concentrate[101]. De somer et al have demonstrated the mechanical and chemical characteristics of autologous surgical glue made by mixing ultra filtered plasma with gluteraldehyde.[102]

COMMERCIALLY AVAILABLE FIBRIN GLUE

Tisseel* VH Fibrin sealant (Baxter AG, Vienna, Austria) is a commercially available fibrin adhesive approved by the US Food and Drug Administration as an adjunct to hemostasis. The kit contains the following in separate vials.

1. Large Blue Bottle: Sealer protein concentrate (Human), Freeze dried, vapour treated, containing:

- Clottable protein - 75 to 115mg

- Fibrinogen - 70 to 110mg
- Plasma fibronectin - 2 to 9 mg
- Factor XIII - 10 to 50 IU
- Plasminogen - 40 to 120 µg (microgram)

2. Small Blue Bottle: Aprotinin solution, bovine 3000 KIU /ml

3. White Bottle: Thrombin 4 (bovine), freeze dried reconstituted contains 4IU/ml

4. Large Black Bottle: Thrombin 500 (bovine), freeze dried reconstituted contains 500 IU/ml

5. Small Black Bottle: Calcium chloride solution, 40mmol/L

1+2 (Fibrin component)

3+5 (Thrombin component)- Used for slow release

4+5 (Thrombin component)- Used for rapid release

It is advisable to maintain the cold chain, i.e., to keep the temperature well regulated constantly from the time after preparation till use. Before use, the syringes containing two components of fibrin glue, namely, Thrombin (Black) and Fibrinogen (Blue) are taken out from the deep freeze and thawed to room temperature.

The fibrin sealant (Tisseel* VH, Baxter Healthcare Corp, Deerfield, IL) is prepared according to the manufacturer's directions. In brief, colour-coded vials (colour code-Black and Blue) are warmed for several minutes in a patented fibrotherm device. The procedure requires the addition of the fibrinolysis inhibitor, Aprotinin, to the sealer protein concentrate vial followed by warming. While this solution is being stirred, the second component is prepared by injecting the contents of calcium chloride vial into the Thrombin vial (Thrombin 500 or Thrombin 4, depending upon whether an early or a delayed clot is

required) which is then warmed. Only a small amount of the thrombin-calcium chloride solution is required to drive thereaction to fibrin formation. To slow the process of fibrin formation, only 0.1ml of the thrombin-calcium chloride solution is withdrawn into a disposable syringe to which 0.9ml of balanced salt solution (Acorn Inc, Decatur, IL, USA) is added to achieve a 1:10 dilution. This syringe is placed into the Duploject injector along with a parallel disposable syringe containing the fibrin sealer protein and fibrinolysis inhibitor. A mixer nosecone, topped by a blunt applicator needle, is attached to the 2-syringe nozzle to facilitate mixing of the two syringe components. When the common plunger is depressed, the fibrin sealer solution and the thrombin solution are combined in the nosecone, in equal volumes, to form the resulting fibrin sealant that is directly applied to the designated tissues.

An indigenous preparation Reliseal (Reliance Industries, India) is also available with similar components. All fibrin sealants in use have two major ingredients, purified fibrinogen (a protein) and purified thrombin (an enzyme) derived from human or bovine (cattle) blood. Many sealants have two additional ingredients, human blood factor XIII and a substance called aprotonin, of which is derived from cow's lungs. Factor XIII is a compound that strengthens blood clots by promoting cross linkage of fibrin strands. Aprotoninis a protein that inhibits the enzymes that break down blood clots.is a protein that inhibits the enzymes that break down blood clots.

TECHNIQUE FOR APPLICATION

- The two components of fibrin glue can either be applied simultaneously or sequentially, depending on the surgeon's preference.

- When simultaneous application is preferred, both the components are loaded into two syringes with tips forming a common port (Duplojject syringe). When injected, the two components meet in equal volumes at the point of delivery.
- The thrombin converts the fibrinogen to fibrin by enzymatic action at a rate determined by the concentration of thrombin. The more concentrated thrombin solution, thrombin 500, produces a fibrin clot in about 10 seconds and the more dilute thrombin solution, thrombin 4, results in a clot in about 60 seconds after glue application to the surgical field.
- As mentioned earlier, both the extrinsic and the intrinsic mechanisms of blood coagulation are bypassed but the physiological final common pathway of coagulation is replicated.
- Factor XIII (present in the fibrinogen component of the glue) cross links and stabilizes the clot's fibrin monomers while aprotinin inhibits fibrinolytic enzymes, consequently resulting in a stable clot.
- For sequential application, thrombin is first applied on to the area of interest, followed by a thin layer of fibrinogen. In a minute or two, coagulation starts and by two or three minutes, polymerization is complete.
- Alternatively, when apposition is required between opposing surfaces, thrombin solution may be applied to one and fibrinogen to the other surface.
- In all of these cases, prior to application of the glue, the surgical field must be dried meticulously. After application, the tissue is pressed gently over the glue for 3 minutes for firm adhesion. At the end of the procedure, pad and bandage is applied after instillation of antibiotic drops.

SAFETY OF FIBRIN GLUE

Fibrin glue prepared from donor is as safe as other tested blood products[92]. Most but not all viruses can be inactivated by solvent / detergent treatment. The alternative approach to ensure that fibrin glue is virus free is by preparing it from homologous fresh frozen plasma from donors in whom current tests for viral markers are negative for at least six months after the donation. This simple accreditation measure excludes the theoretical possibility of the donors having been in the window period when they donated blood or plasma.

To further ensure its safety, most of the proteinaceous products are sterilized by gamma irradiation.

ADVANTAGES OF FIBRIN GLUE

Fibrin glue reduces the total surgical time because time required to place sutures is saved[92]. The use of glue has been found to lower the risk of postoperative wound infection, contrary to conventional suturing[103]. This can be attributed to accumulation of mucous and debris in sutures which may act as a nidus for infection.

However, there is no data available to substantiate the low incidence of postoperative reaction and infection. Mixtures of fibrin glue and antibiotics are being used for local delivery of antimicrobial activity. It is well tolerated, nontoxic to the tissue wherever it is applied and has some antimicrobial activity.

The smooth seal along the entire length of the wound edge results in a higher tensile strength, with the bond being resistant to greater shearing stress. Fibrin glue is also a useful adjunct to control bleeding in selected surgical patients. It has a low incidence of allergic reactions. However, anaphylactic reactions following its application have been reported.[104]This reaction has been attributed to the presence of aprotinin in fibrin glue.

Fibrin glue encourages the formation of adhesions when applied to contaminated tissues. Its use in infected wounds [105] has been reported by two authors. This could be possible due to presence of aprotinin which possesses some antimicrobial activity[106].

DISADVANTAGES OF FIBRIN GLUE

The major drawback to its use is the risk of transmitted disease from pooled and single-donor blood donors. The same can be minimized to a great extent by obtaining the blood from screened healthy donors.

The safest preparation is by using the patient's own blood to prepare fibrin glue. It is expensive and autologous donation requires at least 24 hours for processing. The resultant product often has variable concentrations thereby resulting in an unpredictable performance. Moreover, tensile strength of fibrin glue has not been adequately determined and precludes quantification, being dependent on various extraneous factors also.

Ever since the introduction of fibrin glue in ophthalmology, its major use has been in pterygium surgery. It is a safe and effective method for attaching conjunctival autografts for wound closure following pterygium surgery. Its use results in a shorter operating time, less postoperative discomfort and inflammation. Fibrin glue also provides a more even attachment of the graft to the scleral bed. Most cases performed with fibrin adhesive healed with minimal inflammation and there were only sporadic cases of graft dislodgment or loss.

MATERIAL AND METHODS

MATERIALS AND METHODS

SOURCE OF DATA:

This prospective randomised study will included 100 patients attending department of Ophthalmology, R.L.JALAPPA HOSPITAL AND RESEARCH CENTRE, hospital attached to SRI DEVARAJ URS MEDICAL COLLEGE between January 2015 and June 2016.

INCLUSION CRITERIA:

Nasal primary pterygium (progressive) encroaching more than 2mm of cornea.

EXCLUSION CRITERIA:

- Recurrent pterygium
- Temporal pterygium
- Pre-existing glaucoma
- Patients on anticoagulants
- History suggestive of any hypersensitivity to human blood products
- Immune system disease, eyelid or ocular surface diseases eg- blepharitis, sjogren syndrome and dry eye.
- History of previous ocular trauma.

METHOD OF COLLECTION OF DATA

Hundred patients fulfilling the criteria framed included in this study. Informed consent obtained from all patients. After detailed ocular and systemic history, a thorough ocular examination including visual acuity, refraction, keratometry, ocular movements, fluorescein staining and slit lamp examination is done.

The patients randomly allocated to 2 groups, Group A (50) and Group B (50) by using computerised random number method / table.

Group A underwent pterygium excision followed by autologous limbal conjunctival graft attachment by fibrin glue

Group B underwent pterygium excision followed by autologous limbal conjunctival graft attachment by nylon 10-0 sutures.

OPERATION TECHNIQUE

Under local anaesthesia (peribulbar block), eye is painted and draped, lid speculum applied and pterygium excised. Limbal conjunctival autograft taken from supero temporal aspect of same eye, taken to the exposed scleral bed for attachment.

Group A: FIBRIN GROUP

- The graft bed is dried and a drop of reconstituted solution of fibrin glue is put on it by the application system. Fibrin glue (Reliseal™, a fibrin sealent prepared by reliance life sciences) consists of two main components Fibrinogen (human) and Thrombin (human).
- These are loaded into two syringes with tips forming a common port. When injected the two components meet in equal volumes at the point of delivery. The thrombin converts the fibrinogen to fibrin by enzymatic action, and Factor XIII (present in the fibrinogen component of the glue) cross links and stabilizes the clots fibrin monomers].
- The graft is secured in the place immediately following this. Proper care is taken to ensure that the spatial orientation maintained and that the sides of the graft exposed to the edges of the recipient conjunctiva.

- After drying period of 5 minutes, the lid speculum removed and patient asked to blink several times to check he graft adherence and motility.

Group B(SUTURE GROUP): 5-6 interrupted nylon 10-0 sutures used to secure the graft.

Subsequently, for both the groups sub conjunctival injection of gentamycin and dexamethasone given away from the graft site. Then antibiotic ointment will be placed and a patch applied for 24 hrs.

Various parameters like operating time (starting from placement of lid speculum to its removal at the end of surgery) as well as postoperative symptoms and signs like pain, foreign body sensation and lacrimation, subconjunctival haemorrhage, graft retraction/gaping and recurrences were noted in both the groups.

Follow up done on 1^{st}, 3^{rd}, 10^{th}, 30^{th},90^{th} and 180^{th} postoperative day.Blood test for HIV and HBsAG, 3^{rd} and 6^{th} month in Group A.

The assessment of symptoms like pain, foreign body sensation and lacrimation was done using a questionnaire and the responses were graded on a scale of 0 to 3 as:

- Absent –no symptom
- Mild –Patient had tolerable symptom and present occasionally
- Moderate –Tolerable symptom present through out the day or intolerable symptom present occasionally
- Severe–Intolerable symptom present through out the day

Operated eye was evaluated for presence or absence of hemorrhage, graft retracton/gaping and recurrence.

STATISTICAL ANALYSIS

STATISTICAL ANALYSIS

Data analysed using the statistical program for social sciences (SPSS) software. Comparison of visual outcome will be done using Mann Whitney-U Test. T test was used to compare two groups in terms of operation cost and surgery time as well as recurrence rates, difference in proportions by chi-square test. A probability value (p value) <0.05 will be considered statistically significant.

OBSERVATION AND RESULTS

RESULTS

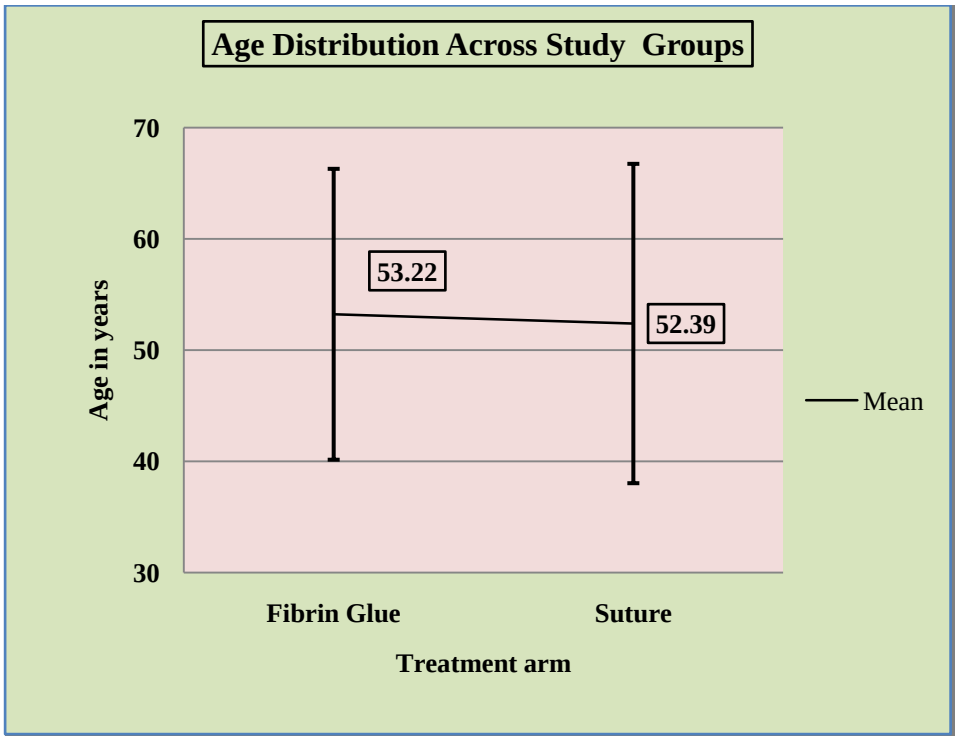
A) PATIENT CHARACTERISTICS

1. AGE

Table 2: Age distribution

Age*	Category	Mean	Standard deviation	Range
	Fibrin Glue	53.22	13.07714	25 to 73
	Suture	52.39	14.3567	23 to 84
*P = 0.76; Not significant				

Graph 1: Age distribution



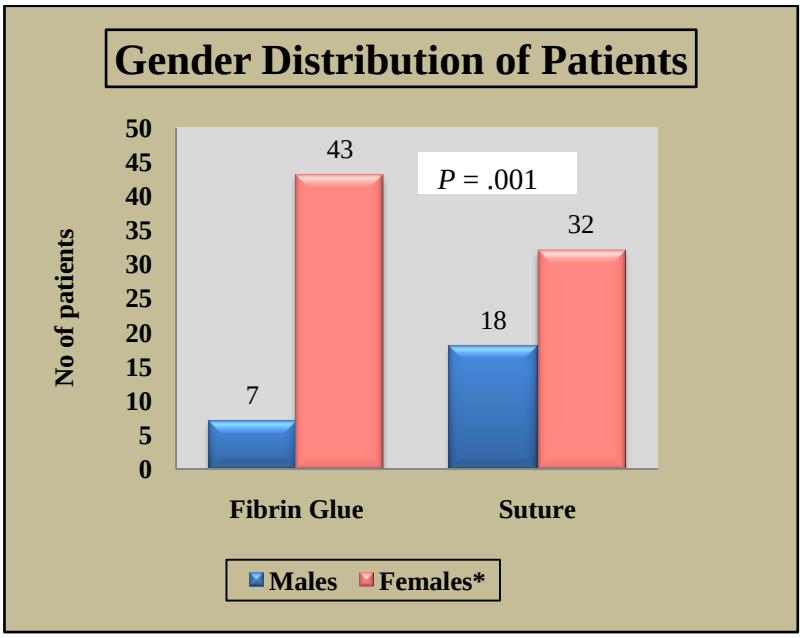
Both groups were similar in age compositions. Mean age of conjunctival autograft with fibrin glue group was 53.22 years and suture group was 52.39 years.

2. GENDER

Table 3: Sex distribution

Category	Fibrin Glue	Suture
Males	7	18
Females*	43	32
*P = .001 (McNemar test)		

Graph 2: Sex distribution



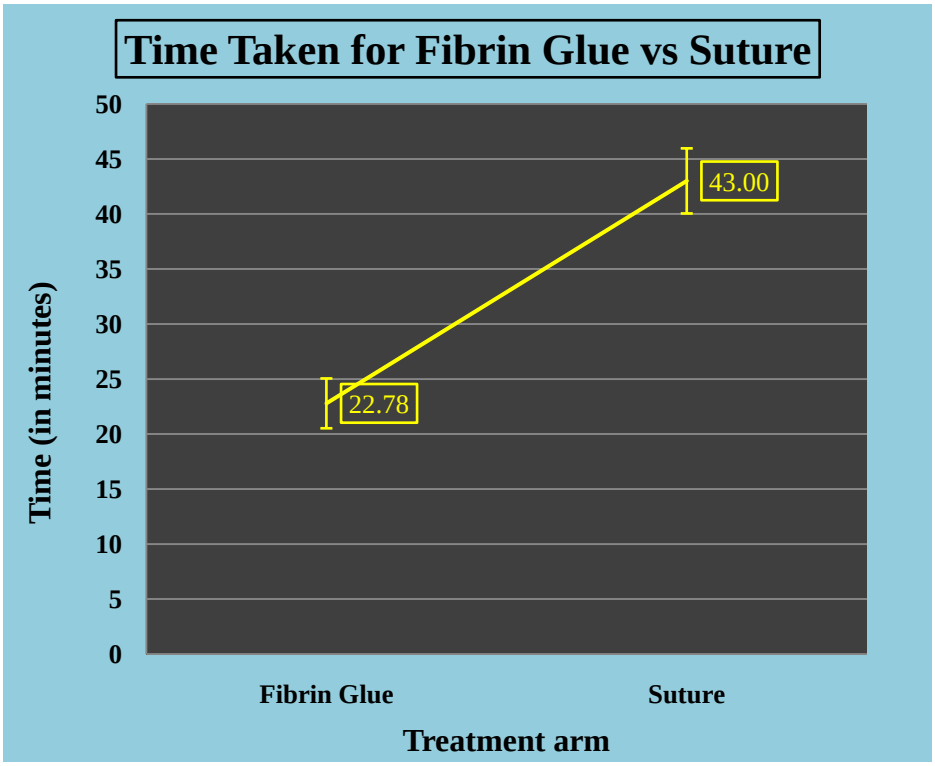
Out of 50 patients in fibrin group 7 were males and 43 were females. In suture group 18 were males and 32 were females.

B) OPERATING TIME

Table 4: Operating time between fibrin glue and suture

Category	Mean	SD
Fibrin Glue	22.78	2.27
Suture	43.00	2.96
*P<.0001		

Graph 3: Operating time between fibrin glue and suture



Mean operating time was 22.78 minutes in fibrin glue group whereas it was more in the suture group of patients which was 43.00 minutes. There was statistically significant difference between the operating times between the two groups with results favouring the fibrin glue group. (p=0.001)

C) SYMPTOMS

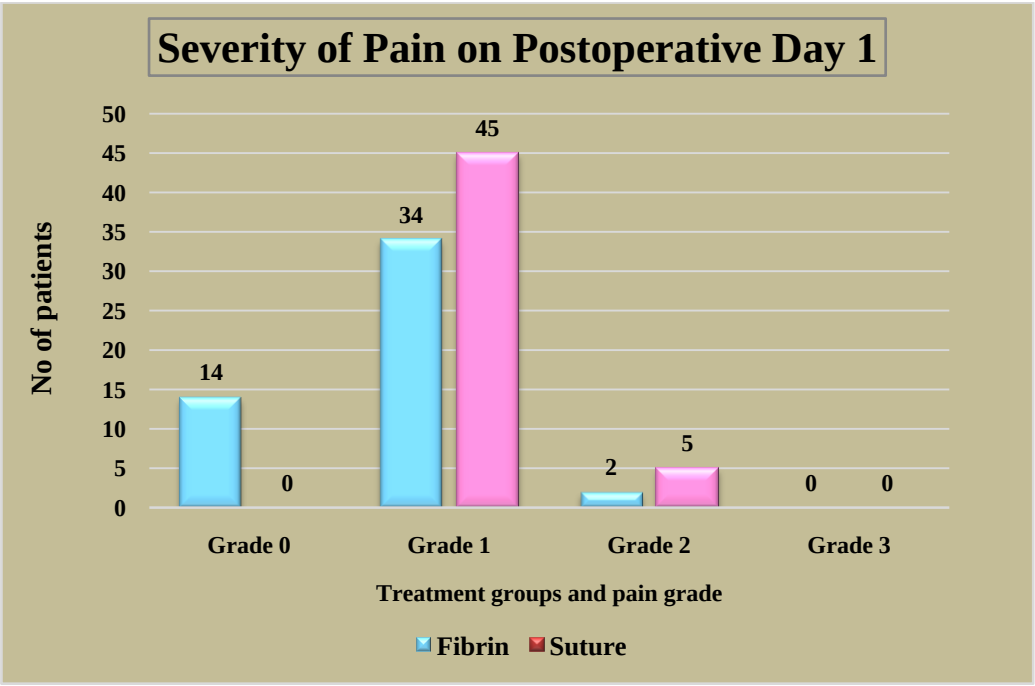
1. DAY -1

a. PAIN

Table 5: Pain grading on post operative day 1

Pain grade	Fibrin	Suture
Grade 0	14	0
Grade 1	34	45
Grade 2	2	5
Grade 3	0	0
*P<.0001		

Graph 4:Pain on postoperative day 1



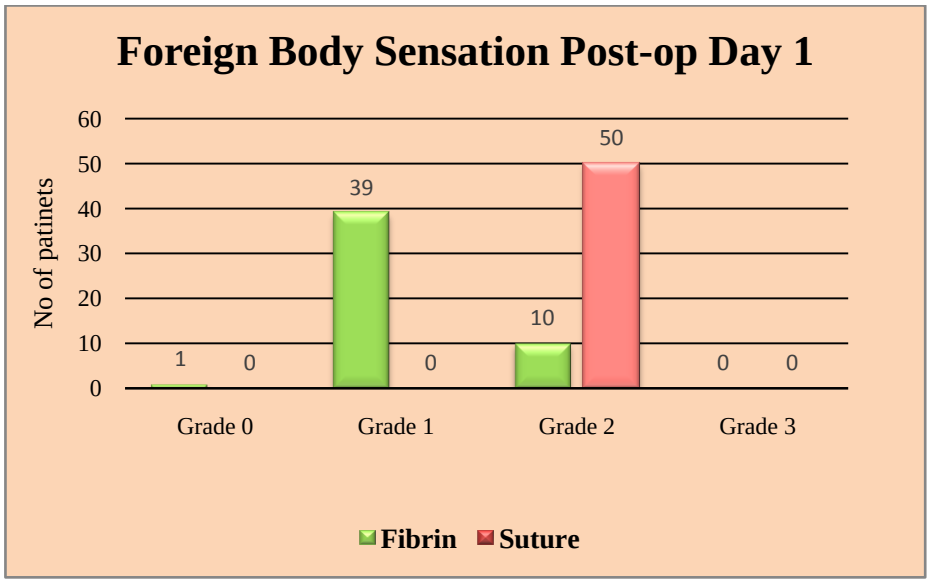
While comparing two groups, there were more patients with Grade 1 and Grade 2 pain in the suture group while the patients in the fibrin glue group had less pain. The difference in pain was statistically significant between the two groups on 1st postoperative day. (p=0.0001)

b. FOREIGN BODY SENSATION

Table 6: Foreign body sensation

Foreign Body sensation	Fibrin	Suture
Grade 0	1	0
Grade 1	39	0
Grade 2	10	50
Grade 3	0	0
P<.0001		

Graph 5: Foreign body sensation



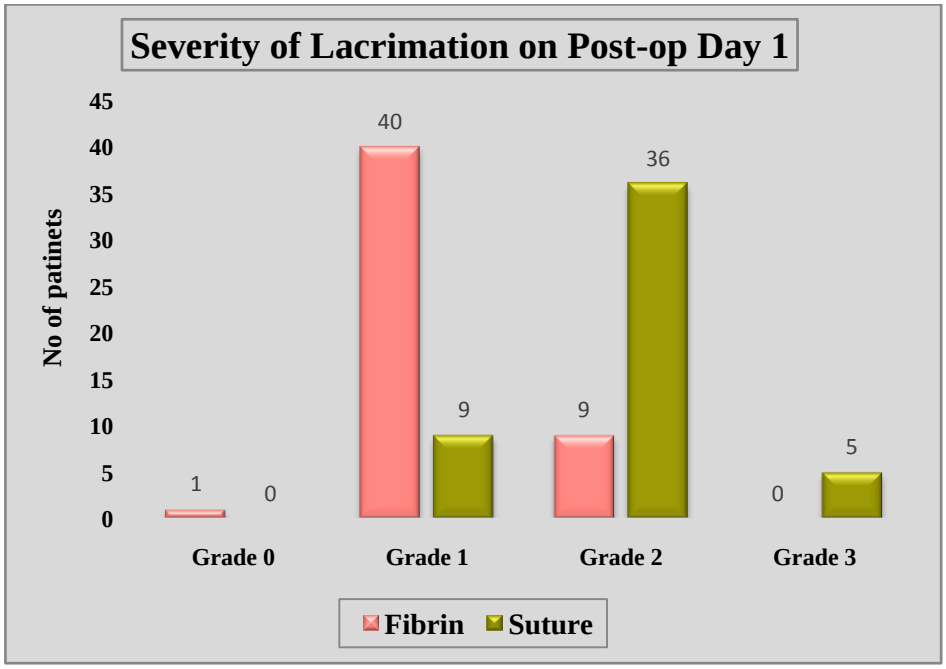
Patients in Fibrin glue group had grade 0 and grade 1 symptoms and less patients with grade 2 symptoms whereas in suture group all patients had grade 2 symptoms of foreign body sensation on postoperative day 1. The difference in foreign body sensation was statistically significant between the two groups on 1st postoperative day. (p=0.0001)

c. LACRIMATION

Table 7: Lacrimation

Lacrimation severity	Fibrin	Suture
Grade 0	1	0
Grade 1	40	9
Grade 2	9	36
Grade 3	0	5
P<.0001		

Graph 6: Lacrimation



In fibrin glue group more patients had grade 1 symptoms and less patients had grade 2 symptoms of lacrimation whereas in suture group more patients had grade 2 symptoms and few patients had grade 3 symptoms of lacrimation on postoperative day 1. The difference in lacrimation was statistically significant between the two groups on 1st postoperative day. (p=0.0001)

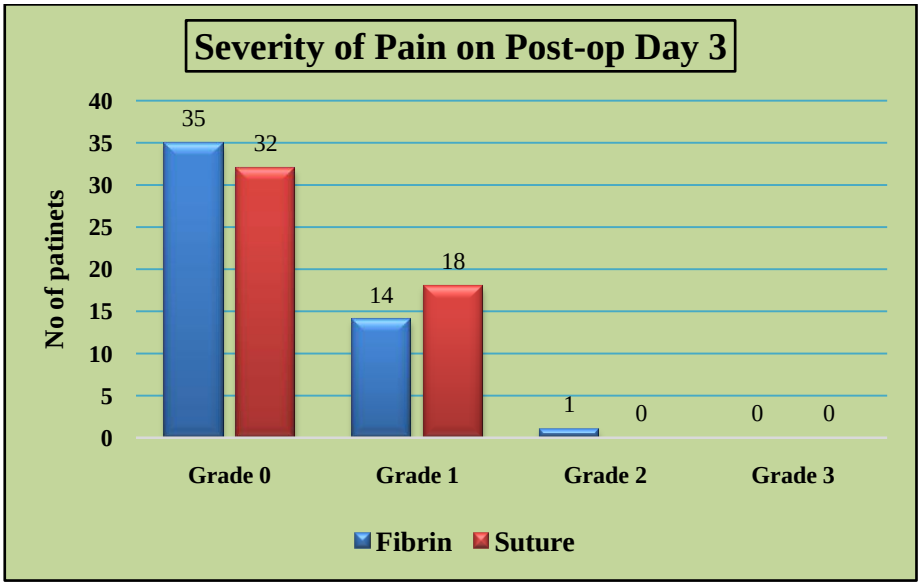
2. DAY 3

a. PAIN

Table 8: Pain on postoperative day 3

Pain grade	Fibrin	Suture
Grade 0	35	32
Grade 1	14	18
Grade 2	1	0
Grade 3	0	0
P>.05; not significant		

Graph 7: Pain on postoperative day 3



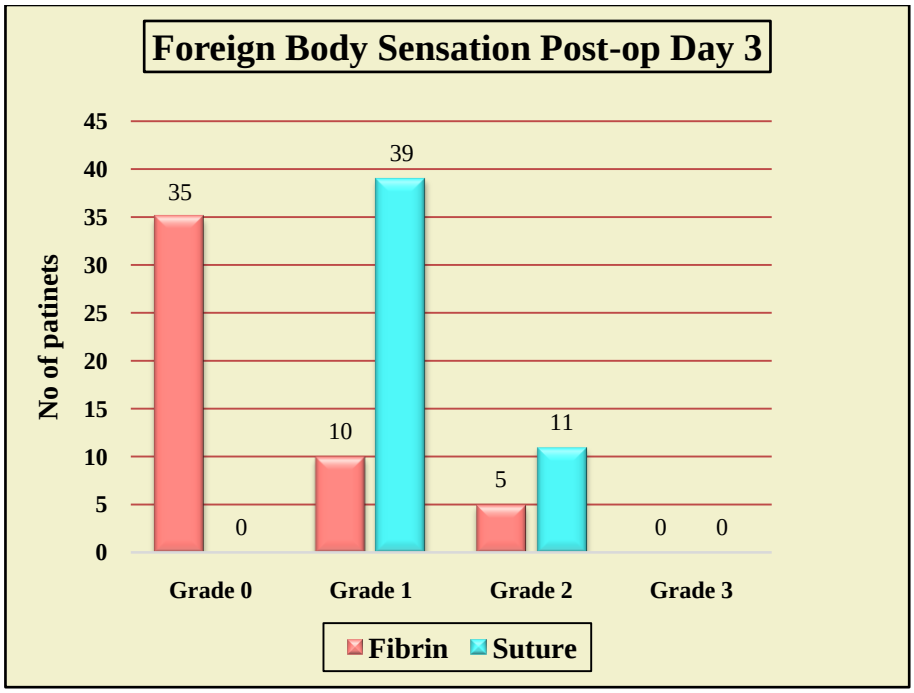
In fibrin glue group 35 patients had grade 0, 14 patients had grade 1 and 1 patient had grade 2 symptom of pain, where as in suture group 32 patients had grade 0 and 18 patients had grade 1 symptom of pain on postoperative day 3. The difference between the two groups was not statistically significant (*P*>.05).

b. FOREIGN BODY SENSATION

Table 9: Foreign body sensation on postoperative day 3

Foreign Body sensation	Fibrin	Suture
Grade 0	35	0
Grade 1	10	39
Grade 2	5	11
Grade 3	0	0
P<.0001		

Graph 8: Foreign body sensation on postoperative day 3



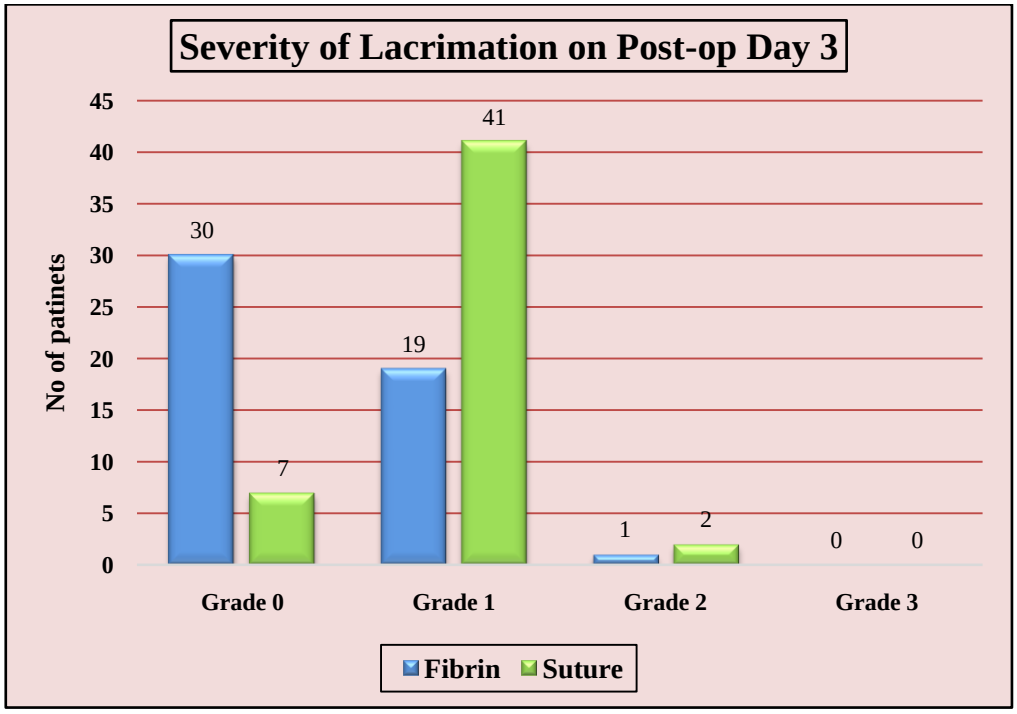
In fibrin glue group more patients had grade 0 symptom of foreign body sensation but in suture group more patients had grade 1 symptom of foreign body sensation and few patients had grade 2 symptom of foreign body sensation. The difference between the two groups is statistically significant (*P*<.0001).

c. LACRIMATION

Table 10: Lacrimation on postoperative day 3

Lacrimation severity	Fibrin	Suture
Grade 0	30	7
Grade 1	19	41
Grade 2	1	2
Grade 3	0	0
P<.0001		

Graph 9: Lacrimation on postoperative day 3



In comparison with severity of lacrimation between the two groups, there were less patients with grade 1 and grade 2 where as in suture group had more patients in grade 1 and grade 2 on postoperative day 3.The difference between the two groups is statistically significant (*P*<.0001)

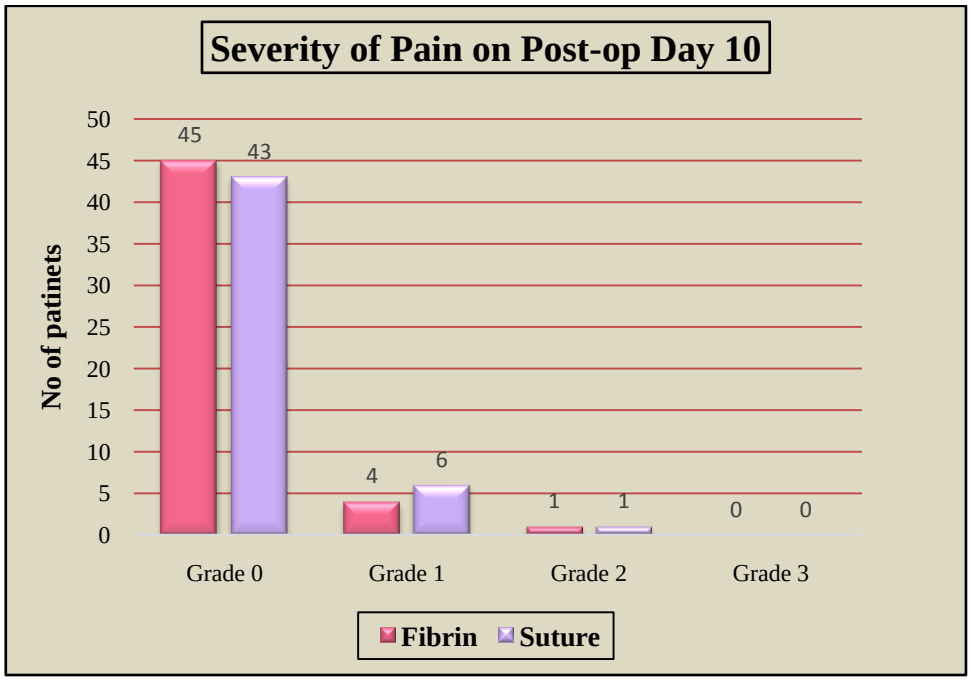
3. DAY 10

a. PAIN

Table 11: Pain on postoperative day 10

Pain grade	Fibrin	Suture
Grade 0	45	43
Grade 1	4	6
Grade 2	1	1
Grade 3	0	0
P = .46; not significant		

Graph 10: Pain on postoperative day 10



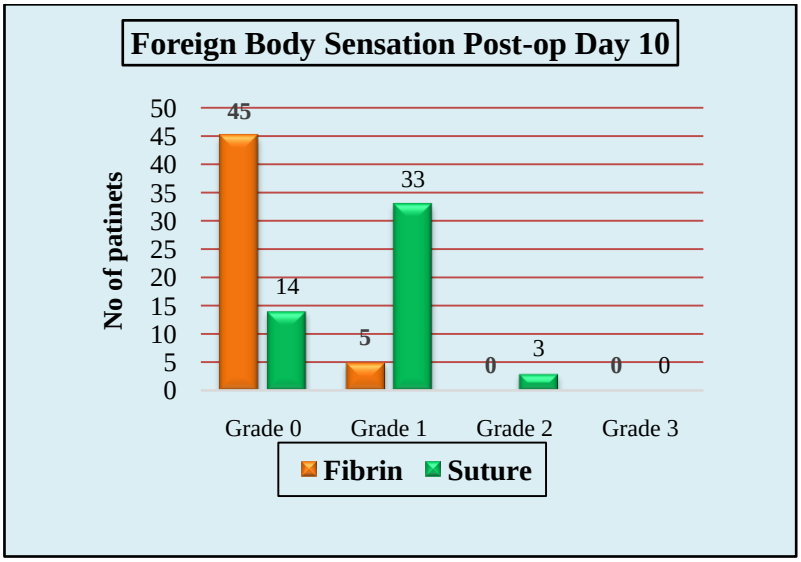
In comparison between the two groups with severity of pain on postoperative day 10, there was not much difference clinically.45 patients had grade 0 symptom, 4 patients had grade 1 symptom and 1 patient had grade 1 symptom of pain in fibrin glue group whereas in suture group 43 patients had grade 0 symptom, 6 patients had grade 1 symptom and 1 patient had grade 2 symptom. The difference was not statistically significant (*P* =0 .46)

b. FOREIGN BODY SENSATION

Table 12: Foreign body sensation on postoperative day 10

Foreign Body sensation	Fibrin	Suture
Grade 0	45	14
Grade 1	5	33
Grade 2	0	3
Grade 3	0	0
P<.0001		

Graph 11: Foreign body sensation on postoperative day 10



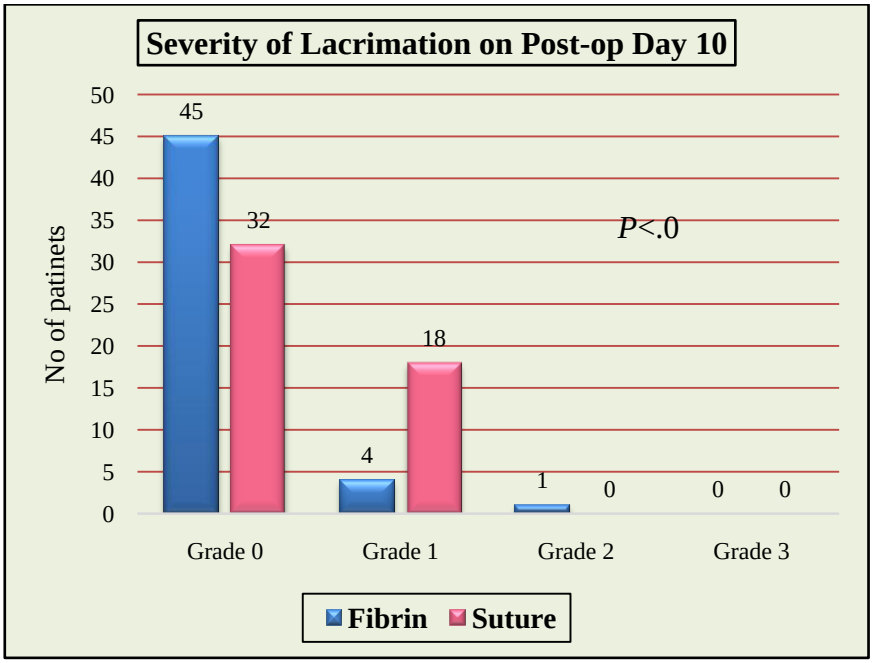
While comparing the two groups based on foreign body sensation on post-operative day 10, More patients had grade 0 symptom in fibrin glue group whereas in suture group more patients had grade 1 symptom and few patients reported with grade 2 symptom. The difference was statistically significant (*P*<.0001).

c. LACRIMATION

Table13: Lacrimation on postoperative day 10

Lacrimation severity	Fibrin	Suture
Grade 0	45	32
Grade 1	4	18
Grade 2	1	0
Grade 3	0	0
P<.05		

Graph 12: Lacrimation on postoperative day 10



In comparison with severity of lacrimation between the two groups, there were 45 patients with grade 0 and 4 patients with grade 1 where as in suture group had 32 patients in grade 1 and 18 patients in grade 2 on postoperative day 10.The difference between the two groups is statistically significant (*P*<0.05).

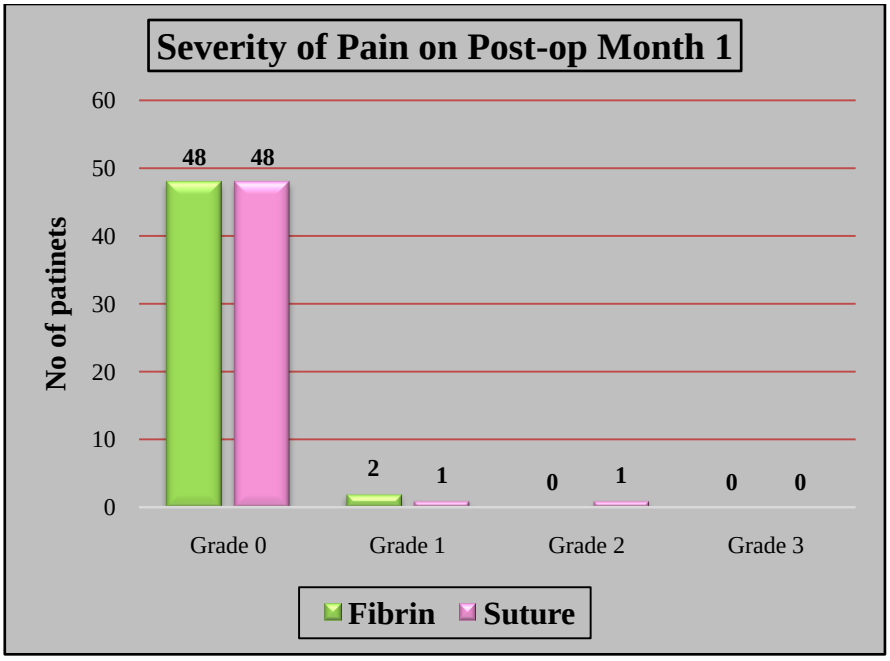
4. 1 MONTH

a. PAIN

Table 14: Pain on postoperative day 1 month

PAIN GRADE	FIBRIN	SUTURE
Grade 0	48	48
Grade 1	2	1
Grade 2	0	1
Grade 3	0	0
P = .44; not significant		

Graph 13: Pain on postoperative day 1 month



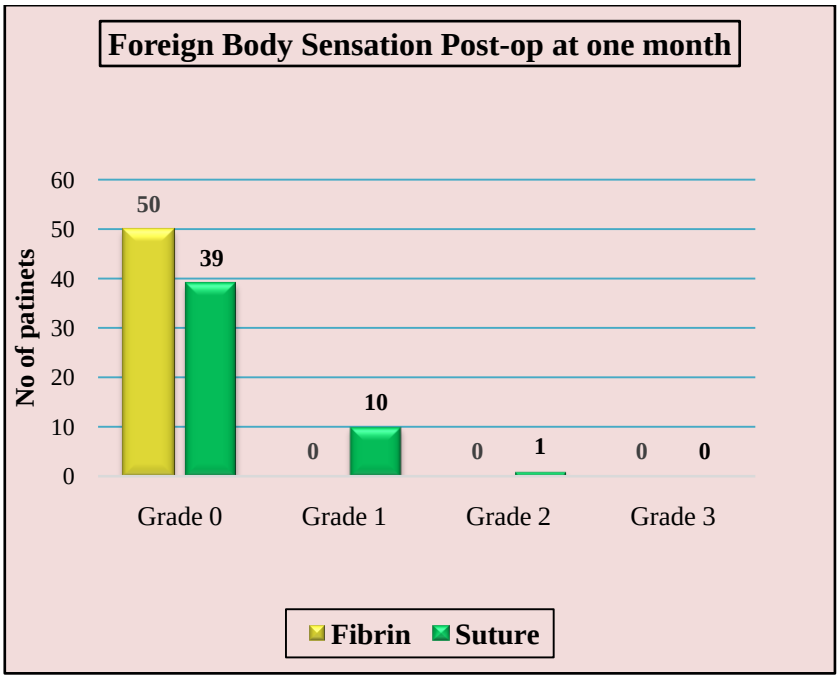
Compared to day 10 pain perception had decreased in both fibrin and suture groups. The difference between two groups is not statistically significant (*P* = 0.44).

b. FOREIGN BODY SENSATION

Table 15: Foreign body sensation on postoperative day 10

Foreign Body sensation	Fibrin	Suture
Grade 0	50	39
Grade 1	0	10
Grade 2	0	1
Grade 3	0	0
P<.001		

Graph 14: Foreign body sensation on postoperative day 1 month



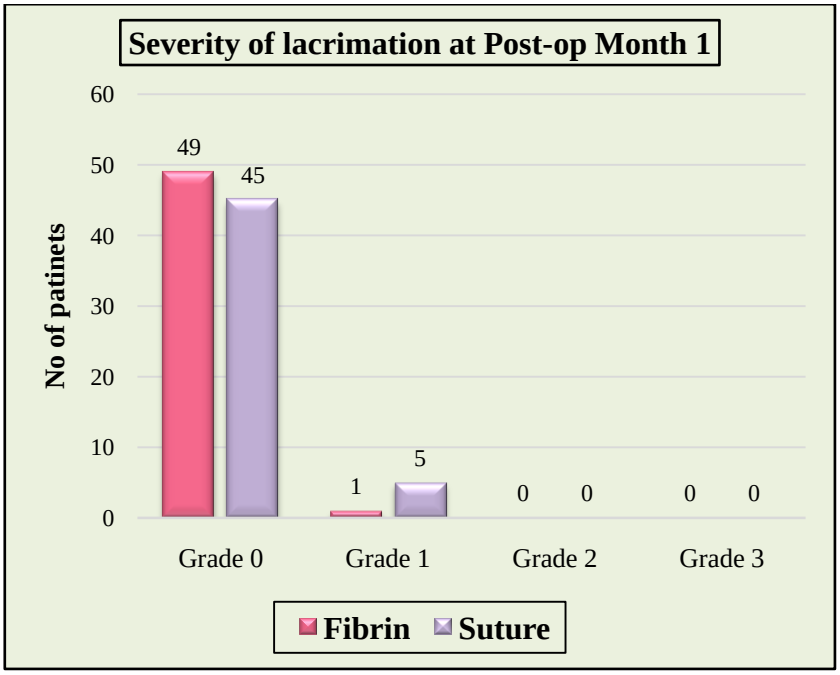
While comparing the two groups on 1 month regarding foreign body sensation, patients had grade 1 symptom in suture group compared to fibrin glue group. The difference was statistically significant (*P*<.001).

c. LACRIMATION

Table 16: Lacrimation on post-operative month 1

Lacrimation severity	Fibrin	Suture
Grade 0	49	45
Grade 1	1	5
Grade 2	0	0
Grade 3	0	0
P<.05		

Graph 15: Lacrimation on post-operative month 1



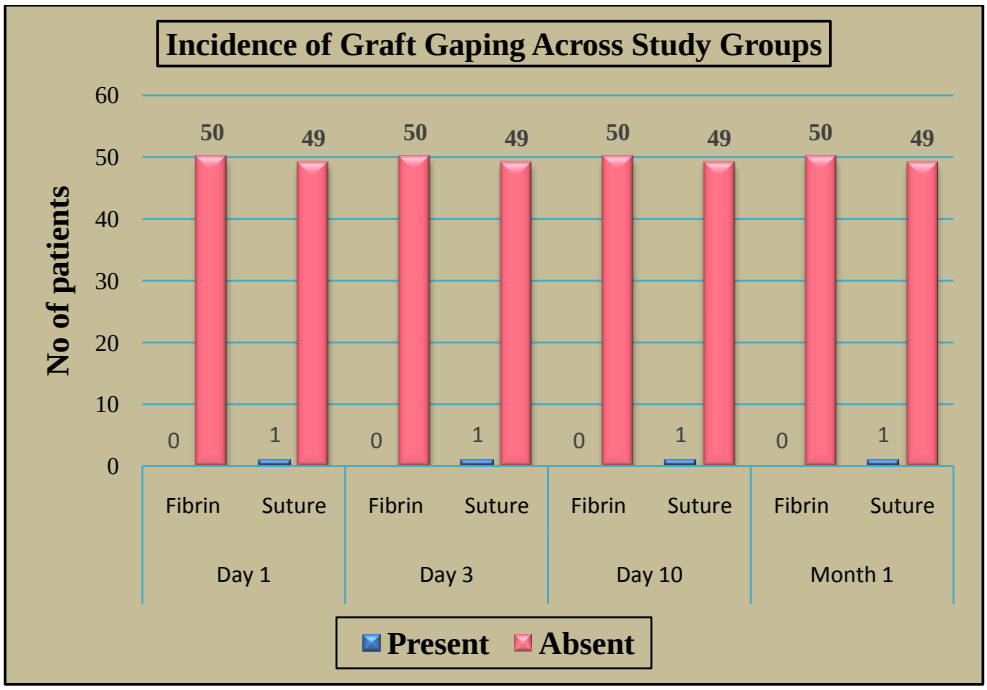
There was statistically significant difference in lacrimation between the two groups on postoperative month 1 though suture group had slightly more patients with grade 1 symptoms.*(P*<.05)

d. GRAFT GAPING

Table 17: Graftgaping on postoperative day 1, day 3, day 10 & 1st month.

GRAFT GAPING	GROUP	Present	Absent	p
Day 1	Fibrin	0	50	P = .31; NS
	Suture	1	49	
Day 3	Fibrin	0	50	
	Suture	1	49	
Day 10	Fibrin	0	50	
	Suture	1	49	
Month 1	Fibrin	0	50	
	Suture	1	49	

Graph16: Graftgaping on postoperative day 1, day 3, day 10 & 1st month.



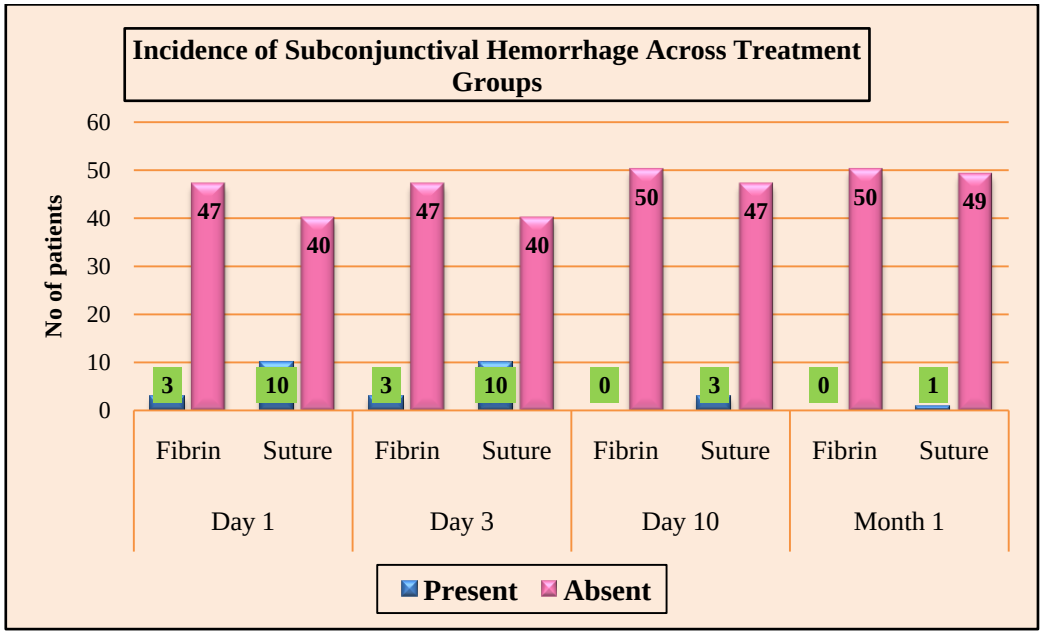
There was no statistically difference in graft gaping between two groups on postoperative day 1, day 3,day 10 and 1 month.(P = 0.31).

e. SUBCONJUNCTIVAL HEMORRHAGE

Table 18: Subconjunctival hemorrhage on postop day 1, day 3, day 10 and 1 month.

FOLLOW UP	GROUP	PRESENT	ABSENT	P VALUE
Day 1	Fibrin	3	47	*P*<.05
	Suture	10	40	
Day 3	Fibrin	3	47	*P*<.05
	Suture	10	40	
Day 10	Fibrin	0	50	P>.05; NS
	Suture	3	47	
1 month	Fibrin	0	50	P = .31; NS
	Suture	1	49	

Graph 17: Sub conjunctival Hemorrhage on postoperative day1, day 3, day 10 & 1 month.



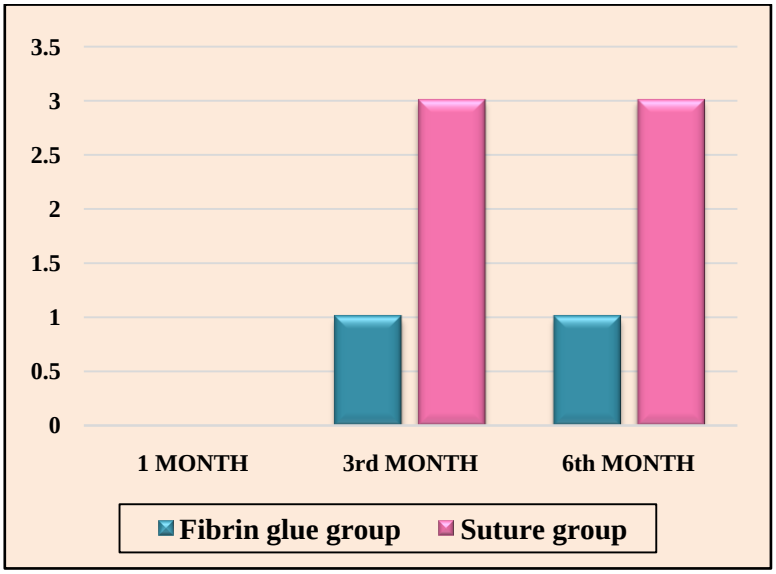
There was statistically difference between the two groups on post op day 1 and day 3 between the two groups, as there were less patients had SCH in fibrin group when compared to suture group and no statistically difference between the two groups on post op day 10 and 1 month.

f. RECURRENCE

Table 19: Recurrence on 1st month, 3rd month and 6th month

RECURRENCE	1 MONTH	3rd MONTH	6th MONTH
Fibrin glue group	0	1 (2%)	1 (2%)
Suture group	0	3 (6%)	3 (6%)

Graph 18: recurrence on 1st, 3rd, and 6th month



All 50 patients from the fibrin group and 49 patients from suture group were evaluated for any signs of recurrence, as 1 patient from suture group did not return to follow up. Recurrence was seen in 3 (6%) patients at the end of 3rd month in suture group and 1 (2%) recurrence in fibrin glue group.

At the end of 6 months, 43 patients reported to follow-up in fibrin group where as in suture group 37 patients reported to follow-up. 3 patients (6%) reported with recurrence in suture group & one (2%) in fibrin glue at the end of 6th month follow-up of our study period.

SAFETY OF FIBRIN GLUE

Anaphylactic Reaction	NO	
HIV	Negative- 3rd month	Negative-6th month
HBsAG	Negative-3rd month	Negative-6th month

Fibrin glue use was found to be safe as there is no anaphylactic reaction and disease transmission like HIV and HBsAG.

DISCUSSION

DISCUSSION

Hundred patients who underwent primary pterygium excision and limbal conjunctival auto grafting were studied. The patients were randomly divided into two groups of fifty patients each. One group underwent auto grafting with fibrin glue and the other group with 10-0 nylon suture. The two groups were compared in terms of pain, foreign body sensation, lacrimation, subconjunctival hemorrhage and graft gaping at the end of first, third, tenth and 1st month postoperative day. The patients were followed up at the end of 1st month, 3rd month and 6th month to look for recurrence of pterygium.

Both groups were similar in the **age**. Mean age of limbal conjunctival autograft with fibrin glue group was 53.22 years and suture group was 52.39 years.

Gender distribution was out of 50 patients in fibrin group 7 were males and 43 were females. In suture group 18 were males and 32 were females. Females are more in number in our study as they live in rural areas and they are out door agricultural workers.

Mean operating time was 22.78 minutes in fibrin glue group whereas it was more in the suture group of patients which was 43.00 minutes which was statistically significant. This is comparable with other studies.

MEAN OPERATING TIME			
SL NO	**STUDY**	**FIBRIN GLUE**	**SUTURE**
1	Our study	22.78 minutes	43.00 minutes
2	Koranyi et al	9.7 minutes	18.5 minutes
3	Karalezli et al	15.7 minutes	32.5 minutes
4	Cha DM et al	27.71 minutes	43.30 minutes
5	Arora et al	13-16 minutes	25-35 minutes

In the study by **Koranyi et al**, the average surgery time was 9.7 minutes (range 6-13) for fibrin glue and 18.5 minutes (range 12-30) for sutures, *P*<0.001.[6]

In a study by **Karalezli et al**, the mean duration of surgery was 15.7 minutes(range 12-18min) in fibrin glue group and 32.5 minutes(range 25-40 min) in suture group, the operation time being significantly shorter in fibrin glue group(*P*<0.001). [76]

In a study by **Cha DM et al**, the operation duration was 27.71 (5.22) minutes in the fibrin glue group and 43.30 (8.18) minutes in the suture group (***p*** = 0.000). [36]

In the study by **Arora et al**, average surgical time was 13-16 minutes in tissue glue group versus 25-35 minutes in suture group. Similar to all these studies, the operation time was found to be significantly shorter in the fibrin glue group in the present study also.[108]

In the present study on postoperative day one, significantly **lower pain** was reported by patients in the fibrin glue group, mild pain=34 (68%), moderate=2 (4%) and 14 (28%) patients did not experience pain when compared to group 2,wherein majority 45 (90%) experienced mild pain and 5 (10%) had moderate pain (**P*<.0001). However, during the follow up at day 3, day 10 and 1st month, post-operative pain reported by patients was similar in both the groups (*P*>.05). This is comparable with other studies.

Study by **Vichare N et al** noted that pain was less in fibrin glue than those with suture group (P>0.05) [10]

A similar study by **Ratnalingam et al** noted that on a 10-point numerical rating scale, both the fibrin adhesive and the suture group had low median pain scores. However, the pain scores immediately post- surgery and 1week post-surgery were significantly lesser in the fibrin adhesive group (*P*>.05). [109]

Another study from India by **Bisen et al** reported that, using fibrin glue instead of sutures while placing the conjunctival autograft in pterygium excision causes significantly less pain. **(110)**

In the present study, the outcome regard to **foreign body sensation** in fibrin glue group was significantly better on day 1, day 3, day 10 and 1st month follow-ups that is, it was absent in 1 (2%) patient on day 1, 35 (70%) patients on day 3, 45 (90%) patients on day 10 and 50 (100%) at the end of 1st month compared to suture group where all the 50 (100%) patients complained about moderate foreign body sensation on day 1 which decreased to 39 (78%) patients to mild and persisted among 11 (22%) patients at day 3. During day 10 and 1st month, among 14 (28%) and 39 (78%) patients the sensation was absent respectively (P<0.001). This is comparable with other studies.

Similar study by **Vichare N et al** noted that post-operative foreign body sensation in fibrin group were more comfortable than those in suture group. **(10)**

Study from India by **Bisen et al** reported that, in fibrin glue patients, post -operative foreign body sensation of mild and moderate grade was seen in 54.54% and 36.36% of eye respectively. At the end of 1 month, 90.91% had no foreign body sensation and 9.09% had mild sensation. Compare to this in suture group, 100% patients had severe foreign body sensation on day 1 (P<.001). **(110)**

Similar results were reported in a study by **Bahar et al** which observed foreign body sensation in 20% fibrin glue patients while in suture group 60% patients felt foreign body sensation on 1st post- operative day (P<0.001) **(33)**

Study by **Karalezli et al** reported that the intensity of the post-operative complaints including foreign-body sensation was significantly lower in patients treated with fibrin glue than in those treated with sutures at both post-operative days 1 and 10 (P<0.001).

Also the intensity of itchy sensation at the first two post-operative visits was lower among patients in the fibrin glue group than in the suture group (P<0.05). [76]

In the present study **lacrimation** was absent among 1 (2%), 30 (60%), 45(90%) and 49 (98%) during post-operative day 1, day 3, day 10 and 1st month among the patients with fibrin glue group respectively. In suture group all the patients complained about mild=9 (18%), moderate=36 (72%) and severe=5 (10%) lacrimation on day 1. Among 7(14%) at day 3, 32(64%) at day 10, 45(90%) at 1st month lacrimation was not reported. Hence the lacrimation was significantly less in fibrin glue group at day 1, day 3, day 10 and 1st month (P<0.05). This is comparable with other studies.

Similar study by **Vichare N et al** noted that symptoms of lacrimation were lower in fibrin group than suture group. [10]

A study **Uy et al** concluded that subjective symptoms of lacrimation were fewer and disappeared more rapidly in fibrin glue group than suture group. [32]

A study by **Karalezli et al** reported that lacrimation was significantly lower in patients treated with fibrin glue than those treated with sutures at both post-operative days 1 and 10 (P<0.001). [76]

Another study by **Ratnalingam et al** reported significant symptomatic relief in lacrimation amongst patients in fibrin glue group compared to suture group. [109]

In the present study, the **subconjunctival hemorrhage** was observed in 3 (6%) at day 1 and day 10 which was absent at post-operative day 10 where as in suture group it was noted among 10(20%), 10(20%), 3 (6%) and 1 (2%) patients on post-operative day 1, day 3, day 10 and 1st month. The difference between both groups was clinically significant on post-op day 1 and day 3 *(P*<0.05) and the difference was not significant on post-op day 10 and 1st month(P>0.05). This is comparable with other studies.

Similar study by **Vichare N et al** noted that subconjunctival hemorrhage was completely absent in both groups at the end of follow up period. **(10)**

A study by **Srinivasan et al** reported that no significant difference in the degree of subconjunctival hemorrhage between the two groups at any point during the follow-up period.**(77)**

Another study by **Yuksel et al** noticed hemorrhage under the graft in one case of group 1 on second post-operative day. **(111)**

In the present study one patient in the suture group had **graft gaping/retraction** of 1 mm at the nasal site of the graft due to loose suture. The patient was closely on subsequent follow-up visits, re-epithelialisation of the conjunctival defect was seen after 1st month follow-up. This is comparable with other studies.

GRAFT GAPING			
SL NO	**STUDIES**	**FIBRIN GLUE**	**SUTURE**
1	OUR STUDY	0	1
2	VICHARE N et al	3	5
3	UY et al	0	1
4	MARTICORENA	2	0

Study by **Vichare N et al** noted graft retraction was more in fibrin group than suture group.**(10)**

A study by **Ozdamar Y** et al reported graft gaping was more in fibrin glue group when compared to suture group **(107)**

Another study by **Marticorena J** et al also reported graft retraction which required no intervention for a complete secondary re-epithelialization. **(112)**

In the present study three cases in suture group and one case in fibrin glue group reported with **recurrence** at the end of third and six month follow up period. This is comparable with other studies.

RECURRENCE			
SL NO	**STUDIES**	**FIBRIN GLUE**	**SUTURE**
1	OUR STUDY	1 (2%)	3 (6%)
2	VICHARE N et al	1 (3.3%)	3 (10%)
3	RITU ARORA et al	0	2
4	KORANYI et al	2 (8%)	4 (20%)
5	KARALEZLI et al	4%	12%
6	FARID et al	3.7%	20%

Study by **Vichare N et al** noted 3 recurrences in suture group and 1 recurrence in fibrin glue group at end of six month follow up period which was not statistically significant. **(10)**

Another study by **RituArora et al** reported 2 recurrences in suture group. **(108)**

Koranyi et al reported 2 recurrences in the glue group (8%) and 4 in the suture group (20%) at 6 months' follow-up. **(6)**

Karalezli et al, in their study reported significantly lower recurrence rate in the fibrin glue group ($P<0.05$) with recurrence observed in 4% in glue group and in 12% in suture group. They further opined that more severe inflammation may cause higher recurrence rates in suture cases and that the immediate adhesion of the graft with the use of fibrin glue may result in early graft vascularization and prevent recurrence. **(76)**

Farid et al in their study reported that the recurrence rate in glue group was 3.7% compared with 20% in the sutured group, with the difference being statistically significant (p=0.035). **(113)**

In our study Fibrin glue usage was not associated with any **anaphylactic reactions** and the disease transmission **HIV and HBsAG** is negative at the end of 6th month follow up period. Hence Fibrin glue usage was found to be safe.

CONCLUSION

CONCLUSION

In our study we found that fibrin glue is a safe and effective method for attaching limbal conjunctival autograft following pterygium excision. Its use results in a shorter operating time, less post-operative discomfort and inflammation compared to suturing and there was less recurrences of pterygium in fibrin glue compared to sutures. Fibrin glue use was also found to be safe as there is no anaphylactic reaction and disease transmission like HIV and HBsAG.

SUMMARY

SUMMARY

This prospective comparative study was conducted in the Department of Ophthalmology, R L Jalappa Hospital, KOLAR, between January 2015 and June 2016.

A total of hundred patients were studied. Fifty patients underwent primary pterygium excision and limbal conjunctival autografting with fibrin glue and fifty with 10-0 monofilament polyamide suture. Both groups were similar in the age and females were more in number.

Mean age of limbal conjunctival autograft with suture was 52.39 years and fibrin glue group was 53.22 years.

Mean operating time was 43.00 minutes in the suture group whereas it was much less in the fibrin glue group of patients which was 22.78 minutes.

Symptoms such as pain, foreign body sensation and lacrimation were graded on the 1st day, 3rd day, 10th day and 1 month. Subconjunctival hemorrhage and graft gaping were assessed on days 1, day 3, day 10 and 1 month.

Patients with fibrin glue had less symptoms of pain, foreign body sensation and lacrimation on all days compared to suture group. Also patient with fibrin glue had less subconjunctival hemorrhage and graft gaping in the post-operative period.

There were 3 recurrences seen in suture groups & 1 in fibrin glue group at the end of six-month follow-up period. Fibrin glue use was also found to be safe.

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ANNEXURE

ANNEXURE

COMPARISON OF FIBRIN GLUE AND SUTURES FOR ATTACHING LIMBAL CONJUNCTIVAL AUTOGRAFT AFTER PTERYGIUM EXCISION"

NAME: IP NO:

AGE/SEX: DOA:

ADDRESS DOS:

DOD:

CHIEF COMPLAINTS:

H/O PRESENTING ILLNESS:

PAST HISTORY:

FAMILY HISTORY:

PERSONAL HISTORY:

GENERAL PHYSICAL EXAMINATION:

VITALS

BP: PULSE: RR: TEMP:

SYSTEMIC EXAMINATION

CARDIOVASCULAR SYSTEM:

RESPIRATORY SYSTEM:

PER ABDOMEN

CENTRAL NERVOUS SYSTEM

OCULAR EXAMINATION

HEAD POSTURE:

OCULAR POSTURE:

RE LE

VISUAL ACUITY:

DISTANT
PIN HOLE
NEAR

EYE LIDS:
LACRIMAL APPARATUS:

CONJUNCTIVA:

CORNEA:

SCLERA:

ANTERIOR CHAMBER:

IRIS:

PUPIL: Size –

Shape –

Reaction –

LENS:

OPHTHALMOSCOPY:

1. DIRECT:

2. INDIRECT:

DIAGNOSIS:

KERATOMETRY:

Horizontal:

Vertical:

LAB INVESTIGATIONS:

BLOOD SUGAR:

URINE SUGAR:

BLEEDING TIME:

CLOTTING TIME:

HIV:

HBsAg:

INTRAOPERATIVE NOTES: (OPERATING TIME)

POSTOPERATIVE MEDICATIONS

POSTOPERATIVE OUTCOME

PAIN	1st post-op day	3rd post-op day	10th post-op day	1 month
0=absent				
1=mild				
2=moderate				
3=severe				

FOREIGN BODY SENSATION	1st post-op day	3rd post-op day	10th post-op day	1 month
0=absent				
1=mild				
2=moderate				
3=severe				

LACRIMATION	1st post-op day	3rd post-op day	10th post-op day	1 month
0=absent				
1=mild				
2=moderate				
3=severe				

SUBCONJUNCTIVAL HEMORRHAGE	1st post-op day	3rd post-op day	10th post-op day	1 month
0=absent				
1=mild				
2=moderate				
3=severe				

GRAFT GAPING	1st post-op day	3rd post-op day	10th post-op day	1 month post-op
0=absent				
1=mild				
2=moderate				
3=severe				

RECURRENCE	1ST month	3rd month	6th month
Present			
Absent			

HIV & HBsAG	3rd month	6th month
POSITIVE		
NEGATIVE		

CONSENT TO PARTICIPATE

I, the undersigned, agree to participate in this study and authorize the collection and disclosure of my personal information as outlined in this consent form.

I have read or had read to me and understand the purpose of this study, the procedures that will be used, the risks and benefits associated with my involvement in the study and the confidential nature of the information that will be collected and disclosed during the study.

I have had the opportunity to ask questions regarding the various aspects of this study and my questions have been answered to my satisfaction.

I understand that I remain free to withdraw from this study at any time and this will not change my future care.

Subject's name and signature /thumb impression Date:

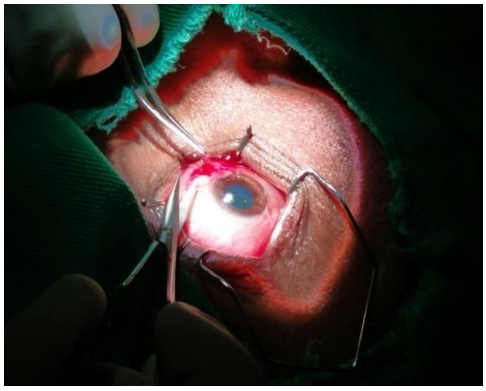
Name and signature of parent /guardian Date:

Name and signature of person obtaining consent Date:

PHOTOGRAPHS

RELISEAL KIT

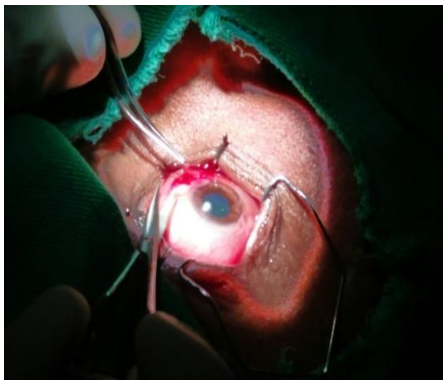
FIBRIN GLUE SYRINGE



PTERYGIUM EXCISION

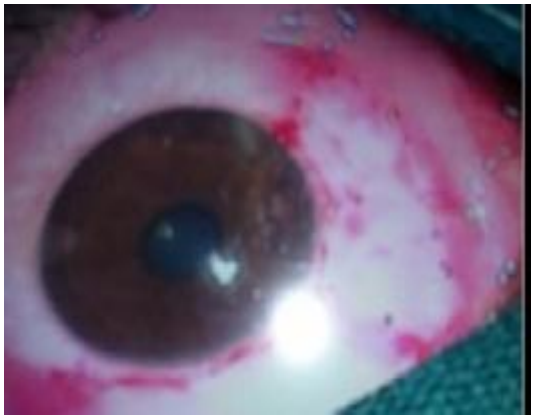
PTERYGIUM PRE-OPERATIVE

FIBRIN GLUE POST-OPERATIVE

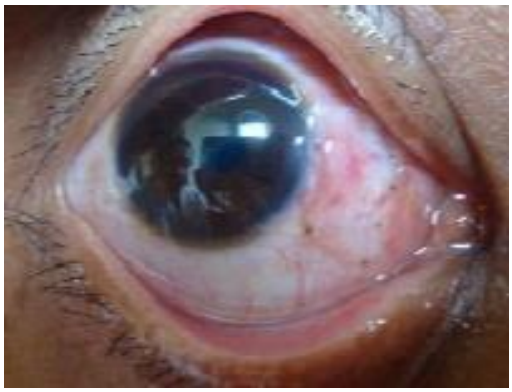


PTERYGIUM INTRA-OPERATIVE

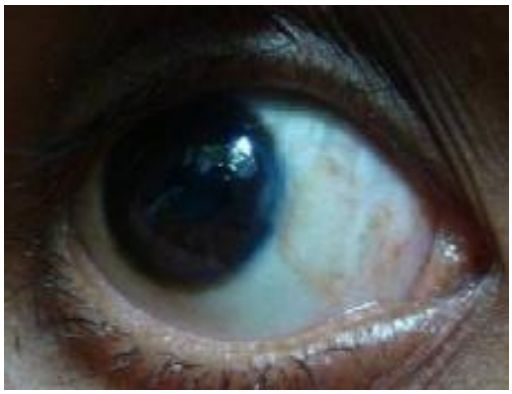
FIBRIN GLUE POST-OPERATIVE



SUTURE INTRA-OPERATIVE



SUTURE POST-OPERATIVE DAY 1



SUTURE POST-OPERATIVE 1 MONTH

Pterygium Intraoperative

MASTERCHART

KEY TO MASTER CHART

M-MALE

F- FEMALE

min- MINUTES

RE- RIGHT EYE

LE- LEFT EYE

FB- FOREIGN BODY SENSATION

LAC-LACRIMATION

GP- GRAFT GAPING

SCH- SUBCONJUNCTIVAL HAEMORRHAGE

m- MONTH

Ab-ABSENT

p- PRESENT

REC- RECURRENCE

0-ABSENT

1-MILD

2-MODERATE

3-SEVERE

Masterchart – Fibrin group

sl No	IP No	AGE	Gender	Eye	Operating time(min)	DAY 1					DAY 3					DAY 10					1 MONTH					REC			HIV and HBSAG	
						Pain	FB	Lac	SCH	GP	Pain	FB	Lac	SCH	GP	Pain	FB	Lac	SCH	GP	Pain	FB	Lac	SCH	GP	1 m	3 m	6 m	3 m	6 m
1	224233	50	F	RE	22	0	1	1	Ab	Ab	0	0	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
2	193415	49	F	LE	24	0	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
3	169977	55	F	LE	26	1	1	1	Ab	Ab	1	0	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
4	172237	55	F	RE	25	1	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
5	169987	60	F	LE	22	1	2	2	Ab	Ab	0	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO		neg	
6	173173	55	F	LE	20	1	1	1	Ab	Ab	1	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
7	173172	68	F	LE	23	1	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
8	261198	42	F	LE	21	1	1	1	Ab	Ab	1	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
9	176265	38	F	LE	27	1	1	1	Ab	Ab	1	1	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
10	175115	68	M	RE	25	1	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO		neg	
11	175103	70	M	RE	22	0	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
12	172256	60	F	LE	20	1	1	1	Ab	Ab	1	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
13	169964	65	F	RE	24	1	2	2	Ab	Ab	0	2	1	Ab	Ab	0	1	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
14	139310	60	F	RE	23	1	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO		neg	
15	133883	68	M	RE	25	0	1	1	Ab	Ab	0	0	1	Ab	Ab	0	0	1	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
16	213083	40	M	LE	26	1	1	1	Ab	Ab	1	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg

sl No	IP No	AGE	Gender	Eye	Operating time(min)	DAY 1					DAY 3					DAY 10					1 MONTH					REC			HIV and HBSAG	
						Pain	FB	Lac	SCH	GP	Pain	FB	Lac	SCH	GP	Pain	FB	Lac	SCH	GP	Pain	FB	Lac	SCH	GP	1 m	3 m	6 m	3 m	6 m
17	210164	62	F	RE	21	1	1	1	Ab	Ab	0	0	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
18	21O168	63	F	RE	22	1	2	1	P	Ab	1	1	1	P	Ab	1	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	p	p	neg	neg
19	187738	60	F	LE	27	0	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO		neg	
20	176199	65	F	LE	23	1	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
21	169985	40	F	RE	20	0	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
22	161714	60	F	RE	22	1	1	1	Ab	Ab	1	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
23	155135	72	M	RE	24	0	1	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
24	155122	73	F	RE	27	2	2	2	Ab	Ab	2	2	2	Ab	Ab	2	1	2	Ab	Ab	1	0	1	Ab	Ab	NO	NO	NO	neg	neg
25	219266	52	F	RE	24	1	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
26	227890	30	F	LE	21	1	1	1	Ab	Ab	1	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
27	134763	40	F	LE	26	1	1	1	Ab	Ab	0	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO		neg	
28	261212	65	F	RE	22	0	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
29	241534	60	F	RE	20	1	1	1	Ab	Ab	1	0	1	Ab	Ab	1	0	1	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
30	250858	26	F	RE	26	1	2	2	Ab	Ab	0	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
31	246716	27	F	RE	22	0	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
32	246726	55	M	RE	21	0	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
33	249211	50	F	LE	19	1	2	2	P	Ab	0	2	1	P	Ab	0	1	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO		neg	
34	249241	25	F	RE	23	1	1	1	Ab	Ab	1	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
35	251791	71	M	LE	23	1	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg

sl No	IP No	AGE	Gender	Eye	Operating time(min)	DAY 1					DAY 3					DAY 10					1 MONTH					REC			HIV and HBSAG	
						Pain	FB	Lac	SCH	GP	Pain	FB	Lac	SCH	GP	Pain	FB	Lac	SCH	GP	Pain	FB	Lac	SCH	GP	1 m	3 m	6 m	3 m	6 m
36	176207	65	F	RE	24	1	2	2	Ab	Ab	0	2	1	Ab	Ab	0	1	1	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
37	125757	45	F	RE	26	1	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
38	128399	50	F	LE	20	0	0	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
39	139831	50	F	RE	20	1	1	1	Ab	Ab	0	0	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
40	139310	60	F	RE	21	1	1	1	Ab	Ab	1	1	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
41	117985	50	F	LE	23	0	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO		neg	
42	116904	42	F	RE	22	0	1	1	Ab	Ab	0	0	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
43	155123	68	F	RE	22	1	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
44	145478	40	F	RE	18	2	2	2	Ab	Ab	1	1	1	Ab	Ab	1	0	1	Ab	Ab	1	0	0	Ab	Ab	NO	NO	NO	neg	neg
45	144706	60	F	RE	21	1	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
46	136386	40	F	LE	21	1	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
47	136465	60	F	LE	23	1	2	2	P	Ab	0	1	1	P	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
48	132507	35	F	RE	25	1	1	1	Ab	Ab	1	0	0	Ab	Ab	1	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
49	238394	32	F	LE	20	1	2	2	Ab	Ab	0	2	1	Ab	Ab	0	1	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg
50	176207	65	F	RE	25	0	1	1	Ab	Ab	0	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO	neg	neg

Master Chart - Suture Group:

sl No	IP No	AGE	gender	EYE	Operating time(min)	DAY 1					DAY 3					DAY 10					1 MONTH					REC		
						pain	FB	Lac	SCH	GP	pain	FB	Lac	SCH	GP	Pain	FB	Lac	SCH	GP	Pain	FB	Lac	SCH	GP	1 m	3 m	6 m
1	271989	41	F	RE	40	1	2	1	Ab	Ab	0	1	0	Ab	Ab	0	1	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
2	271128	48	M	RE	42	1	2	1	Ab	Ab	0	1	0	Ab	Ab	0	1	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	
3	231474	40	F	RE	48	1	2	2	Ab	Ab	0	1	1	Ab	Ab	0	1	1	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
4	266924	58	M	LE	48	1	2	2	p	Ab	0	1	1	p	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
5	266914	37	F	LE	40	1	2	2	p	Ab	0	1	1	p	Ab	0	1	0	p	Ab	0	0	0	Ab	Ab	NO	NO	
6	261201	70	F	RE	48	1	2	2	Ab	Ab	0	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
7	271176	34	F	RE	46	1	2	2	Ab	Ab	1	1	1	Ab	Ab	1	1	1	Ab	Ab	0	0	0	Ab	Ab	NO	NO	
8	271018	56	M	LE	43	1	2	3	Ab	Ab	0	2	1	Ab	Ab	0	1	1	Ab	Ab	0	1	1	Ab	Ab	NO	NO	NO
9	266922	58	F	RE	42	1	2	2	Ab	Ab	0	1	1	Ab	Ab	0	1	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
10	295985	40	F	LE	42	1	2	2	Ab	Ab	0	1	1	Ab	Ab	0	1	1	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
11	781971	23	M	LE	40	1	2	2	p	Ab	1	1	1	p	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	
12	94373	65	M	RE	37	1	2	2	Ab	Ab	0	1	1	Ab	Ab	0	1	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
13	120967	60	F	RE	48	1	2	2	Ab	Ab	1	1	1	Ab	Ab	2	0	0	Ab	Ab	2	0	0	Ab	Ab	NO	NO	
14	114486	65	F	LE	42	1	2	2	Ab	Ab	0	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO		
15	114512	70	M	LE	43	1	2	3	p	Ab	0	2	2	p	Ab	0	2	1	p	Ab	0	1	1	p	Ab	NO	NO	NO
16	31817	65	F	LE	40	2	2	2	Ab	Ab	1	2	1	Ab	Ab	1	1	0	Ab	Ab	0	1	0	Ab	Ab	NO	NO	NO
17	103783	46	M	RE	47	1	2	2	Ab	Ab	0	1	1	Ab	Ab	0	1	1	Ab	Ab	0	0	0	Ab	Ab	NO	NO	

sl No	IP No	AGE	gender	EYE	Operating time(min)	DAY 1					DAY 3					DAY 10					1 MONTH					REC		
						pain	FB	Lac	SCH	GP	pain	FB	Lac	SCH	GP	Pain	FB	Lac	SCH	GP	Pain	FB	Lac	SCH	GP	1 m	3 m	6 m
18	102335	44	F	LE	40	1	2	2	Ab	Ab	0	1	1	Ab	Ab	0	1	1	Ab	Ab	0	1	0	Ab	Ab	NO	NO	
19	98793	50	F	RE	46	1	2	1	Ab	Ab	1	2	0	Ab	Ab	1	1	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
20	95989	25	F	RE	48	1	2	2	Ab	Ab	1	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
21	95999	40	M	RE	43	1	2	2	p	Ab	1	1	1	p	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	
22	91153	84	M	RE	41	1	2	2	Ab	Ab	0	1	1	Ab	Ab	0	1	1	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
23	81968	27	M	LE	42	1	2	2	Ab	Ab	0	1	1	Ab	Ab	0	1	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
24	264281	60	F	RE	42	1	2	2	Ab	Ab	0	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	
25	21079	50	F	RE	42	1	2	3	Ab	Ab	1	2	1	Ab	Ab	0	1	0	Ab	Ab	0	1	0	Ab	Ab	NO	NO	
26	199099	25	F	RE	46	1	2	2	Ab	Ab	1	1	1	Ab	Ab	0	1	1	Ab	Ab	0	0	0	Ab	Ab	NO	p	p
27	204490	36	F	RE	43	1	2	2	Ab	Ab	1	2	1	Ab	Ab	0	1	1	Ab	Ab	0	1	0	Ab	Ab	NO	NO	NO
28	83736	40	M	RE	43	2	2	2	p	Ab	1	2	1	p	Ab	0	1	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	
29	222450	49	M	RE	42	1	2	3	Ab	Ab	1	2	1	Ab	Ab	1	2	1	Ab	Ab	0	2	1	Ab	Ab	NO	NO	NO
30	215496	60	M	LE	43	1	2	1	Ab	**Ab**	0	1	0	Ab	Ab	0	1	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
31	125763	48	M	RE	48	1	2	1	Ab	Ab	0	1	0	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	
32	122394	48	F	RE	44	1	2	2	Ab	p	0	1	1	Ab	p	0	1	0	Ab	p	0	0	0	Ab	p	NO	NO	NO
33	103298	60	F	RE	41	1	2	2	Ab	Ab	0	2	1	Ab	Ab	0	1	1	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
34	161719	60	F	RE	40	2	2	2	p	Ab	1	1	1	p	Ab	0	1	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
35	157881	56	F	LE	40	1	2	2	**Ab**	Ab	0	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
36	97387	66	F	LE	37	1	2	2	Ab	Ab	0	1	1	Ab	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	p	p
37	125743	30	M	RE	41	1	2	1	Ab	Ab	0	1	0	Ab	Ab	0	1	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
38	84469	34	F	RE	41	2	2	2	Ab	Ab	1	1	1	Ab	Ab	1	1	1	Ab	Ab	1	1	1	Ab	Ab	NO	NO	NO
39	95994	60	F	RE	43	2	2	2	Ab	Ab	1	1	1	Ab	Ab	0	1	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO

sl No	IP No	AGE	gender	EYE	Operating time(min)	DAY 1					DAY 3					DAY 10					1 MONTH					REC		
						pain	FB	Lac	SCH	GP	pain	FB	Lac	SCH	GP	Pain	FB	Lac	SCH	GP	Pain	FB	Lac	SCH	GP	1 m	3 m	6 m
40	102326	60	F	LE	40	1	2	2	p	Ab	0	1	1	p	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
41	94352	60	F	RE	43	1	2	2	Ab	Ab	0	1	1	Ab	Ab	0	1	1	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
42	133872	65	F	RE	41	1	2	1	Ab	Ab	0	1	0	Ab	Ab	0	1	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
43	145465	60	M	RE	48	1	2	2	Ab	Ab	0	1	1	Ab	Ab	0	1	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
44	145479	55	F	LE	43	1	2	3	Ab	Ab	0	2	2	Ab	Ab	0	2	1	Ab	Ab	0	1	0	Ab	Ab	NO	NO	NO
45	193424	65	F	RE	44	1	2	2	p	Ab	1	1	1	p	Ab	0	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
46	15886	65	F	RE	45	1	2	2	Ab	Ab	1	1	1	Ab	Ab	1	0	0	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO
47	224226	80	F	LE	45	1	2	2	Ab	Ab	1	2	1	Ab	Ab	0	1	1	Ab	Ab	0	1	1	Ab	Ab	NO	NO	NO
48	221633	7O	M	LE	40	1	2	1	Ab	Ab	0	1	1	Ab	Ab	0	1	0	Ab	Ab	0	1	0	Ab	Ab	NO	NO	NO
49	155238	69	M	LE	48	1	2	2	p	Ab	0	1	1	p	Ab	0	1	1	p	Ab	0	0	0	Ab	Ab	NO	p	P
50	185260	60	F	RE	41	1	2	1	Ab	Ab	0	1	1	Ab	Ab	0	1	1	Ab	Ab	0	0	0	Ab	Ab	NO	NO	NO