“THE EFFICACY OF FIBRIN GLUE VS SUTURES FOR ATTACHING CONJUNCTIVAL AUTOGRAFTS AFTER PTERYGIUM EXCISION – A RANDOMIZED CLINICAL TRIAL”

REG NO. BK0110005

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

MASTER OF SURGERY (M.S.)
in
OPHTHALMOLOGY

DEPARTMENT OF OPHTHALMOLOGY,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
BELGAUM, KARNATAKA

APRIL - 2013

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ENDORSEMENT

This is to certify that the dissertation entitled **"THE EFFICACY OF FIBRIN GLUE VS SUTURES FOR ATTACHING CONJUNCTIVAL AUTOGRAFTS AFTER PTERYGIUM EXCISION – A RANDOMIZED CLINICAL TRIAL"** is a bonafide research work done by **CANDIDATE REG NO. BK0110005**

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LIST OF ABBREVIATIONS USED

°C	-	degree celcius
°F	-	degree Fahrenheit
^{90}Sr	-	Strontium -90
AD	-	After Death
B.C.	-	Before Christ
BAX	-	Bcl-2–associated X
BCL	-	B-cell lymphoma
bFGF	-	Basic fibroblast growth factor
BUT	-	Break up time
CI	-	Confidence interval
cm	-	Centimeter
DNA	-	Deoxyribonucleic acid
EGF	-	Epidermal growth factor
FU	-	Fluorouracil
HES	-	Henan Eye Survey
HPV	-	Human papilloma virus
HSV	-	Herpes simplex virus
IL	-	Interleukin
IU	-	International units
kiu	-	Kallikrein inhibitor units
Mg	-	Milligram
ml	-	Millileter
mm	-	millimeter
MMC	-	Mitomycin C

MMP	-	Matrix metalloproteinase
Nm	-	Nanometer
No	-	Number
OR	-	Odds ratio
PCR	-	Polymerase chain reaction
PLD	-	Phospholipase D
RT	-	Reverse transcription
s	-	Seconds
SD	-	Standard deviation
TNF	-	Tumor necrosis factor
UV	-	Ultra violet
UVR	-	Ultraviolet radiation
VEGF	-	Vascular endothelial growth factor
Vs	-	Versus
ZES	-	Zeku Eye Study
B	-	Beta
γ	-	gamma

ABSTRACT

Background and Objective

Fibrin glues have been used in an array of ophthalmic procedures such as conjunctival closure in strabismus, vitreoretinal and glaucoma surgery. The present study was undertaken to assess the efficacy of fibrin glue versus suture in patients undergoing conjunctival autografting and also to compare operative time and post operative complications

Methods

This one year randomized controlled trial on 44 patients with primary pterygium was conducted at Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2011 to December 2011. Based on the computer generated randomization, these patients were divided into two groups namely, Group 1 (Fibrin glue group: n= 22) and Group 2 (Suture group: n=22).

Results

In the present study equal distribution of sex (50%) was seen in group 1 and in group 2, female preponderance was seen with male to female ratio of 1:214. The mean age in group 1 was 51.74 ± 13.65 years and in group 2, it was 45.74 ± 13.75 years. All the patients in both groups presented with fleshy mass. Most of the patients (77.27%) in both the groups had grade 2. Majority of the patients (95.45% in group 1 and 100% in group 2) had progressive type of pterygium. Among the majority of patients (86.36%) in group 1 the surgical time was significantly less (21 to 30 minutes) compared to group 2, where 86.36%

required 31 to 40 minutes. The mean surgical time in group 1 was significantly less compared to group 2 (25.83 ± 6.23 vs 34.70 ± 7.96 minutes).

Conclusion and interpretation

The present study showed better efficacy of fibrin glue in conjunctival autografting among the patients undergoing pterygium excision, in terms of pain, foreign body sensation, lacrimation and discomfort during blinking. Also, it significantly reduced the surgical time with fewer post operative complications.

Key Words:

Conjunctival autograft; Fibrin glue; Pterygium; Suture.

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Chapter 1

Introduction

INTRODUCTION

Pterygium has been described as a triangular wing shaped encroachment of the bulbar conjuctival tissue onto the cornea.[1] It can vary from small, atrophic quiescent to large, aggressive, rapidly growing fibrovascular degenerative lesions that can distort the corneal topography. In advanced cases, it can obscure the optical center of the cornea causing visual disturbances.[2]

Pterygium is a common disorder in many parts of the world, with reported prevalence rates ranging from 0.3 to 29%.[3] Epidemiological studies[4,5] suggest an association with chronic exposure to sunlight, with an increased geographical prevalence within a peri-equatorial 'pterygium belt' of latitudes of 378 north and south of the equator.

The risk factors for pterygium include areas with more ultraviolet radiation,[6] hot, dry, windy, dusty, and smoky environments.[4,7] There is also a hereditary factor.[8]

Limbal stem cells are indispensable for maintenance of healthy ocular surface and are thought to create a barrier against the growth of conjunctival fibrovascular tissue into the cornea and thus play a role in pathogenesis of pterygium. When deeper parts of the limbal epithelium is damaged or removed, an abnormal corneal surface is produced. The characteristic changes are conjunctival epithelial in growth, vascularization and inflammation as seen in pterygia.[9]

Anti-inflammatory drugs and lubricants have an important role in minimising the patients' discomfort but do not cure the disease. Hence, surgical removal is the treatment of choice.[9]

The various treatments for pterygium are aimed at reducing recurrence of the lesion. Over the years, many surgical procedures to excise this recurrent disorder have been described.[10]

Earlier methods of pterygium excision like bare sclera technique or Mc Reynolds operation were associated with high recurrence. Many techniques have been suggested, as adjunct therapies such as β radiation, thiotepa, 5-FU, and mitomycin C. High recurrence rates are weighted against eye threatening postoperative complications.[11]

There have been many attempts to optimise pterygium surgery. Autologous conjunctival grafting is reported to be the best method, giving both low recurrence rate and few complications.[12-14] Sutures have been used traditionally to attach the autograft. However, it requires higher surgical expertise and is associated with several disadvantages including prolonged operating time, postoperative discomfort, and potential for suture related complications such as buttonholes, dellen ulcer, suture abscesses, symblepharon, granuloma formation, tissue necrosis and graft dehiscence.[15]

Hence, it is reasonable to try to replace the use of sutures with an tissue adhesive that can be applied to the eye surface. In effect, attempts have been made to attach the autograft in pterygium surgery with a fibrin solution to avoid sutures.[16]

Fibrin glues have been used in an array of ophthalmic procedures such as conjunctival closure in strabismus, vitreoretinal and glaucoma surgery.[17] Because of its biological and biodegradable properties, fibrin-based adhesives may be used to attach the conjuctival autograft without inducing inflammation.[18] 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.[9,19-22]

To date, only few studies[17-22] have reported efficacy of fibrin glue for attaching conjunctical autograft in pterygium study in Indian context and the results are inconsistent.

Hence the present study was undertaken to assess the efficacy of fibrin glue versus suture in patients undergoing conjunctival autografting and also to compare operative time and post operative complications.

Chapter 2

Objectives

OBJECTIVES

The objectives of the present study were;

Primary

1. To study the efficacy of fibrin glue versus sutures

Secondary

1. To study the operating time in the two groups.

2. To study the post operative complications in the two groups.

Chapter 3

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,[9] usually within the interpalpebral 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.[23]

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.[23]

The next recorded study is of Celsus (Rome 50 A.D.) 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 A.D.), Paul Aegineta

(Greece – 7th century), Al Rhazes (Arabia – 932 A.D.), Avicenna (Greece 980-1036 A.D.) and Chakradatta (India -1060 A.D.).[23]

Pterygium was also described by Sushruta (India), the world's first surgeon ophthalmologist before 1000 A.D. In Sushruta Samhita he describes: "With the patient 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".[23]

In the nineteenth century Scarpa, Travers, Desmarres, Knapp, Klein, Prince, Boeckman, Wright, Hobby, Alt, Mackenzie and others have all suggested various methods for the treatment of pterygium.[23]

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, excimer lasered, 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.[23]

Epidemiology

Prevalence

Worldwide prevalence of pterygium varies from 1 to 25 percent, depending on the population studied.[24] Internationally, the relationship between decreased incidence in the upper latitudes and relatively increased incidence in lower latitudes persists.

Occurrence within the United States varies with geographical location. Within the continental United States, prevalence rates vary from less than 2% above the 40th parallel to 5-15% in latitudes between 28-36°. A relationship is thought to exist between increased prevalence and elevated levels of ultraviolet light exposure in the lower latitudes.[25,26]

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%.[4,27] The earliest estimate was from a survey[28] in New South Wales, Australia, which reported 9.6% prevalence. In the Blue Mountains Eye Study, Panchapakesan[29] found 266 subjects had pterygium (or had a history of pterygium surgery) out of 3564 participants aged 49 years or older; the prevalence was 7.4%. Another study[4] in 1984 reported the prevalence of pterygium was only 0.3%. The prevalence of pterygium obtained from a number of populations in urban Caucasians in Victoria, Australia was 1.2%.[30]

A population-based study[31] by Marcus Ang in 2012 at Singapore studied the prevalence and risk factors of pterygium in a multiethnic Asian population and reported that Malays (15.5%) have a higher prevalence of pterygium as compared with Indians (7.0%) and Chinese (7.0%).

The 5.2% prevalence of pterygium in people aged 50 and older in Wardha, India has been reported.[32] Prevalence of pterygium in South Indian population as studied by the Chennai Glaucoma Study was found out to be 9.5%.[33]

Risk factors

Pterygium occurs more commonly in tropical regions, although the exact mechanisms for this are not well-known.[34] The prevalence of pterygium is associated with chronic sun exposure[26,] and specifically to ultraviolet (UV) light,[36] which may partly explain the geographic variation in prevalence.

Several population based studies have found higher rates of pterygium to be associated with older age, male sex, fewer years of education, and outdoor job location. In the Barbados Eye Study, approximately one-fourth of the black participants had pterygium, a frequency that was 2.5 to 3 times higher than among whites in this study.[37] Among black participants, lower rates of pterygium were associated with darker skin complexion.

Lower rates were also associated with always using sunglasses outdoors and using prescription glasses.[37] One study in Australia found a higher rate of

pterygium in rural areas compared to urban areas (6.7 and 1.7 percent, respectively), partly as a result of ocular sun exposure.[30]

Geographic Setting

Pterygium is most common in the so-called "pterygium belt", which is defined by a geographical latitude of 40° north and south of the equator. In this area, prevalence of up to 22% has been reported.[38,39] In countries outside of this area reported prevalence rates usually do not exceed 2% of the general population, and the lesion affects mostly patients with an extensive exposure to sunlight.[40,41]

Due to the strong sunlight, the prevalence of pterygium at the area near equator and low latitude is higher than the area of high latitude.

Sunlight and Ultraviolet Exposure

Many authors regard pterygium to be a consequence of ultraviolet induced damage with subsequent elastoid degeneration of the subepithelial connective tissue. Studies have shown that spending longer periods of time outdoors has led to an increased risk of pterygium, with cumulative exposure to

ultraviolet radiation playing a significant role; it is therefore strongly related to ocular sun exposure.[42]

A case-control study[43] of 278 patients working in outside environment was shown to be 4 to 11 times more likely to have pterygium than those working indoors.

The UV type B light in solar radiation has been found to be the most significant environmental factor in pterygium pathogenesis.[42]

A study[30] found the lifetime ocular sun exposure was an independent risk factor of pterygium (odds ratio [OR], 163) and the attributable risk of sunlight and pterygium was 43.6%. They also found that rural residence is a risk factor for pterygium (OR, 5.28) and made a conclusion that pterygium is a significant public health problem in rural areas, primarily due to ocular sun exposure.

The prevalence of pterygium was high (8.6%) in Eskimo in the south of Greenland. They believed it may be because of the ultraviolet reflection of covered snow.[44] This conclusion was consistent with Zeku Eye Study (ZES)[45] and Henan Eye Survey (HES)[46] in China.

The ZES[45] found use of sunglasses/crystal spectacles was a protective factor for pterygium (OR, 0.31; 95% CI: 0.12-0.77) as was the use of a wide brimmed hat (OR, 0.30; 95% CI:0.20-0.46). The subjects who seldom used glasses and/or wore a hat had a strong positive correlation with presence of pterygium (OR, 4-6; 95% CI: 1.9-11.3 and OR, 3.6; 95% CI: 2.4-5.4 respectively).

The HES[46] in China believed the protective mechanism is related to the ability of glasses and a hat to block UV-B wavelengths of sunlight. These results were similar to the Barbados Eye Study.[37] Further evidence for the ultraviolet theory comes from studies of ultrastructure.[42.]

A large component of pingueculae and pterygia is the result of newly synthesized elastic fiber precursors and abnormal maturation forms of elastic fibre (elastodysplasia) that undergo secondary degeneration (elastodystrophy). These structures are presumed to be elaborated by actinically damaged fibroblasts of the substantia propria and are morphologically similar to solar degeneration of the skin.

Age

Studies that were based on adult population confirm the higher prevalence of pterygium with increasing age. A prevalence study[30] in 5147 residents of Victoria over the age of 40 (range 40 to 101 years) found a weighted rate of pterygium of 2.83%, which tended to increase with age, with 6.4% of those aged 80 to 89 years found to have pterygium.

In ZES,[45] pterygium was independently associated with increasing age for persons aged 70-79 years, compared with those aged 40-49 years (OR, 2.0; 95%CI: 1.4-2.8).

In HES,[46] the prevalence increased with older age (Chi square test of trend <0.01). The prevalence of pterygium was 13.5% (95%CI: 11.2-15.9) in

participants aged 40 to 49, but 27.5% (95%CI: 15.2-39.7) for those aged 80 and above [20].

Gender

The Blue Mountains Eye study[19] found that men were at higher risk than women. The same results were found by other studies.[4,30] In HES,[46] the statistical significance was found in pterygia between men and women, similar to other reports. Reports on whether gender is related to pterygium have been debated.[42]

The ZES[45] found a statistical significance in pterygia between men and women, and found out that women had a higher risk level than men (OR, 1.5; 95% CI: 1.2-2.0).

Education Level and Socioeconomic Status

The level of education is correlated with economic status; a lower level of education is possibly the result of a lower socioeconomic status. For the Chesapeake Bay watermen, more than 8 years of education was found to be beneficial in protecting them from pterygium (OR, 0.42; 95% CI: 0.28-0.62).[49]

In the Barbados Eye Study,[37] logistic regression analyses indicated a positive association between pterygium and fewer years of education (12 years) (OR, 1.43; 95%CI: 1.01-2.03)[12]. In ZES[45] and HES,[46] it was found that fewer years of education (<3 years) had a positive effect on pterygium (OR, 1.6; 95%CI: 1.1-2.4) as did a low socioeconomic status (OR, 1.9; 95% CI: 1.5-2.4).

Dry Eye Symptoms and Signs

Studies found an association between pterygium and a shortened tear break-up time and Schirmer's test in the case-control studies.[42] A study[50] found the environmental factors associated with dry eye, such as ultraviolet light quantities and a dusty polluted environment, which have been implicated in pterygium formation.[42]

The HES[46] found pterygium was independently associated with Schirmer's test (5mm) (OR, 2.4; 95% CI:1.9-3.1), tear breakup time (10s) (OR, 2.3; 95%CI:1.8-2.9), and a positive association between dry eye symptoms and pterygium (OR, 1.9; 95%CI: 1.5-2.5).

Others

Studies have suggested that p53 and human papillomavirus may also be implicated in pterygium pathogenesis.[42] UV radiation can cause mutations in genes such as the p53 tumor suppressor gene, resulting in its abnormal expression in pterygial epithelium. These findings suggest that pterygium is not just a degenerative lesion, but could be a result of uncontrolled cell proliferation.

Risk factors for pterygium Site

The nasal part of the bulbar conjunctiva is more affected than the temporal part. Various explanations are given for its predilection for nasal side It is more exposed to direct irritation than the temporal conjunctiva.[48]

1. Light is reflected from the skin of the nose back on to the nasal limbus.

2. Transcameral light focusing on the nasal limbus may expose limbal basal stem cells to increased amounts of UVR and be associated with molecular genetic alterations to these cells, eventually leading to pterygium formation.[51]
3. Longer temporal eyelashes of the upper eyelid[52] and the greater downward bowing of the outer two thirds of the upper eyelid, shades and filter light falling on the temporal (compared with the nasal) conjunctiva and cornea.[53]
4. The normal flow of the tears is from temporal to nasal side towards the punctum and carries with it any dust particles entering the conjunctival sac and accumulates in lacus lacrimalis. This probably leads to more irritation of the nasal conjunctiva.
5. Greater curvature of nasal fibres of orbicularis oculi causing a greater squeezing effect upon nasal subconjunctival tissue.
6. Presence of two anterior ciliary arteries on the nasal side and only one on the temporal side. It is considered due to this fact that any irritant shall lead to greater hyperemia on nasal side and may play an important role in production of pterygia commonly on nasal side.

Pathophysiology

Early pathogenetic concepts.

The association between pterygium development and specific lifestyles, such as outdoors working or exposure to sunshine or dust led to the idea that

chronic ocular surface irritation by such environmental factors might be the cause of the condition.[51]

It was also proposed that pterygium arises from other sunshine-related conditions, such as the pingueculum, a hyalinized nodule appearing at the sclerocorneal limbus. Pingueculum has no growth potential *per se* but may become inflamed and can evolve into a true pterygium.[51]

The frequently observed conjunctival vascular congestion in the area of pterygium body has lead to the suggestion that medial rectus activity, which underlies the area of pterygium growth nasally, can cause blood flow disturbance potentially associated with pterygium growth.[51]

Early reports have even involved alterations in lacrimal composition or flow (pooling of tears) or the unspecified local effects of lactic acid secreted by periocular sweat glands.[51]

Concepts of inheritance.

Early reports mentioned the possibility of an autosomal dominant pattern of inheritance, based on cases with familial occurrence of pterygium. However, it could not be verified whether the pterygium itself is inherited, as an independent trait, or if the affected individuals shared an increased susceptibility to the oculodermal effects of solar light.[51]

The detection of potential tumor suppressor gene involvement in pterygium has raised the possibility of a 'two hit' mechanism (Knudson's theory) in its pathogenesis. According to this hypothesis, the 'first hit' in the process of a

tumor suppressor gene deactivation may be inherited whereas the 'second hit' may be inflicted by environmental factors, such as a viral infection or UVR.[51]

However, the fact that no specific genetic locus has so far been associated with pterygium development implies that further research in the area of genetic susceptibility for pterygium is required before safer conclusions on this issue are reached.[51]

The role of U.V. Radiations

The strong epidemiological correlation between pterygium development and exposure to sunshine has lead to the assumption that some parts of the solar radiation may have a direct pathogenic role. Early reports raised the possibility that solar light exposure acted in combination with exposure to dust or sand, thus leading to chronic ocular surface inflammation.[51]

However, the detection of high pterygium prevalence in sailors or fishermen, who lived in environments devoid of dust but instead were exposed to increased amounts of scattered light from reflective surfaces such as the sea surface, pointed towards an albedo involvement in pterygium formation. In fact, it was suggested that scattered light might follow alternative (transcameral) optical paths when entering the eye, thus hitting limbal stem cells from their inner surface.[51]

A study[54] observed a significantly high incidence of pterygia in welders who were exposed occupationally to excess ultraviolet radiation and found a close relationship between the incidence and the length of employment as a

welder.

Studies have even suggested that the nasal location of pterygium is an indication of the pathogenic role of solar light, since light may be reflected onto the nasal sclerocorneal limbus from the lateral nasal wall whereas the nasal bulbar conjunctival is more exposed to sunshine since brow hair is shorter nasally than temporally.[51]

The effects of UVR-A and UVR-B (290-400 nm) are considered particularly detrimental. At a molecular level, UVR is associated with the creation of active free radicals which attack and deactivate various macromolecules. Free radicals may in turn be deactivated by tear film proteins, including lactoferrin.[51]

The presence of Stocker's line along the head of pterygia lacking growth potential, may represent abnormal local iron metabolism along the advancing head of pterygium. Iron itself may be associated with increased free radical formation through biochemical (Fenton) reactions.[51]

Angiogenesis factor

It has been suggested that a pterygium angiogenesis factor may exist which develops following repeated irritation at the limbus. The presence of this factor produces vessel ingrowth and the formation of pterygium. It may be that prolonged ultraviolet exposure causes the biological changes in Bowman's membrane and that altered proteins so formed could then act as an angiogenic or 'pterygiogenic' factor.

It may be significant that corneal epithelial cells and not keratocytes are able to release a heat stable factor, which, in a dose dependent manner increases the proliferation of vascular endothelial cells.[48]

Ocular surface changes and pterygium.

Previous studies have reported an association between pterygium and dry eye changes, such as reduced tear-film break-up time (BUT).[55,56] Such findings indicated that pterygium may be a manifestation of a generalized ocular surface dysfunction, including a chronic inflammatory reaction.

In accordance with these reports, an up-regulation of the expression of human alpha- defensins and S100 A8 and A9 in tear fluids of pterygium patients provides additional indications for a connection between pterygium and chronic ocular surface inflammation.[51]

Another study[57] has reported the up-regulation of phospholipase D (PLD) types 2, 3 and 4 in pterygium, compared with normal conjunctiva. PLD are involved in various processes, including inflammation, cell differentiation, apoptosis and wound healing and the detection of PLD alterations in pterygium supports their potential role in pterygium pathogenesis.

Oxidative stress

Increased UVR-associated oxidative stress has been reported in pterygium, compared with normal conjunctiva, leading to the induction of proteins, such as survivin. The latter has been correlated with DNA oxidation and down-regulation of p53. Interestingly, it has been suggested that the presence of

iron deposits along the corneal head of pterygium may indicate oxidative stress affecting local epithelial cells and resulting in disturbed iron homeostasis.[51]

Molecular genetic alterations.

p53 levels have been reported increased in pterygia by several previous studies although other studies have not confirmed such findings.[58,59] The up-regulation of p53 expression in pterygia may merely reflect increased exposure to UVR, since the wild-type of p53 is known to increase in normal tissues in response to DNA damaging agents, such as UVR.[60]

Interestingly, the levels of p53 expression in pterygia have been found to differ between epithelial layers being higher in basal cells, compared to more superficial layers. This finding could reflect increased exposure to UVR according to the proposed theory of transcameral exposure of limbal basal (stem) cells to solar light.[51]

Recurrent pterygia also display reduced amounts or total lack of *p53* expression which may be an indication that the epithelial cells escape the *p53*-dependent cell cycle checkpoint. *p63* expression in pterygium resembles the patterns seen in normal limbus (expressed mainly at the basal epithelial layers) and differs from the pattern seen in normal cornea (almost total absence of *p63* expression), a finding supporting the possibility of limbal origin of pterygium.[51]

Many neoplasias and immortalized cell lines also display up-regulation of telomerase, a ribonucleoprotein participating in cell division by blocking

telomere shortening. Telomerase is not expressed in most adult human tissues, including normal conjuctiva.[51]

Telomerase is however expressed in pterygium, a finding attributed to neoplastic features of the lesion or, alternatively, to induction by UVR. Another interesting aspect of the molecular genetic profile of pterygium is the altered apoptotic potential of its epithelial cells.[51] Previous studies[61,62] have found that UVR induces apoptosis to normal corneal epithelium. However, epithelium in pterygium in possibly resistant to UVR-mediated apoptosis. It is likely that this finding is due to a disturbed balance between pro-apoptotic proteins (such as bax) and anti-apoptotic proteins (such as bcl-2) in the epithelium of pterygium, in favour of the latter. Differences in the apoptotic status between different epithelial cell layers have been detected with apoptosis remaining active at the basal epithelium of pterygium but not at more superficial epithelial layers.[51]

<u>The role of genetically altered limbal stem cells.</u>

A study[63] proposed that the initial biologic event in pterygium pathogenesis may be a genetic alteration of limbal stem cells, due to chronic UVR exposure. They postulated that a breakdown of the corneoscleral limbal barrier results in subsequent conjunctivalization of the cornea resulting in pterygium. They also suggested that the triangular (wing-like) shape of pterygium may in fact be explained by the limbal origin theory since a disrupted balance between the populations of epithelial cells in cornea and conjunctiva could, according to data from animal models, result in advancement of conjunctival epithelium on the corneal surface.

Further studies[64] in this area, employing immunohistochemistry, found that, in contrast to normal conjunctival, limbal, and corneal cells which immunostain primarily for matrix metalloproteinase-I (MMP-I), limbal basal epithelial cells (pterygium cells) immunostain for multiple types of MMPs (MMP-1, MMP-2, MMP-3, MMP-9, membrane type 1-MMP, and membrane type 2-MMP).

According to these results, the altered MMP expression of limbal basal epithelial cells (pterygium cells) enables them to invade and dissolute Bowman's layer leading to firm adhesion of the lesion on the corneal surface.[51]

Viral involvement.

Although early reports mentioned the possibility of an infectious origin of pterygium, evidence on this issue was not conclusive.[65] However, the advent of Polymerase chain reaction (PCR) as a research tool enabled the detailed investigation for viral DNA in samples of both pterygia and normal conjunctiva.[51]

The presence of viruses known to cause oculodermal infections, such as herpes simplex virus (HSV), and human papilloma virus (HPV), was examined. Results from several studies point towards the involvement of HPV in pterygium although large regional and racial differences have been reported.[51]

Growth factors and cytokines.

UVR-mediated genetic trauma may affect the expression of various cytokines, growth factors and growth factor receptors. Many such factors also

participate in normal corneal healing and their altered expression in pterygium may indicate a response to ocular surface damage inflicted by the lesion. UVR-inducible cytokines include the interleukin-1 (IL-1) system, acting in concert with tumor necrosis factor (TNF·) it leads corneal keratocytes to adopt a repair phenotype, the IL-6 (it promotes epithelial cell migration through the induction of integrin receptors) and IL-8 (displays mitogenic and angiogenetic activity).[51,64]

Growth factors involved in pterygium according to previous reports include the epidermal growth factor (EGF) and heparin-binding EGF, vascular endothelial growth factor (VEGF), basic fibroblast growth factor, platelet-derived growth factor, transforming growth factor-ß and insulin-like growth factor binding proteins.[64] VEGF has been detected in increased amounts in pterygium epithelium, compared with normal conjunctiva by studies employing immunohistochemistry. These results were confirmed by RT-PCR assays also revealing a correlation between VEGF expression and post-operative recurrence.[51]

Classification and morphology

Pterygium may be subdivided into four types based on clinical characteristics, pathology and suspected pathogenesis.[66]

1. True pterygium
2. Pseudo pterygium
3. Recurrent pterygium
4. Malignant pterygium

True pterygium

A true pterygium lies in the inter palpebral aperture and is firmly attached to the corneal stroma throughout its entire length.

Pseudo pterygium

It is a fibrovascular scar arising in the bulbar conjunctiva and extending onto the cornea. Unlike a true pterygium, it is the result of previous external ocular inflammation. Pseudopterygium formation is often seen after chemical burns, surgery, trauma, cicatrizing conjunctivitis and peripheral corneal ulceration.

It can be differentiated from the true pterygium by:

- Lying outside the palpebral aperture
- Its very loose or absent adherence to the corneal limbus such that a small muscle hook or canalicular probe may be passed under the body without resistance.

The degenerative elastoid histopathology may be present depending on the duration, anatomical location of the lesion and its chance for exposure to ultraviolet light.

Recurrent pterygium

A recurrent pterygium is secondary fibrovascular growth across the cornea from the corneo scleral defect of a previously excised pterygium.

Clinically, it appears as an elevated, growing, fibrovascular scar arising

from the excision site.

Recurrent pterygia are more aggressive in their growth characteristics and more difficult to treat. They are more common in younger patients with thick aggressive primary pterygia. With recurrence, there is a higher incidence of growth into the visual axis and of symblepharon formation.

Malignant pterygium

It is rare, seen as recurrent pterygium with restriction of ocular movement on the opposite side.

Pterygium can also be classified on the basis of fleshiness of the mass as progressive (fleshy) and stationary (Atrophic)

Progressive pterygium is thick, fleshy with marked vascularity. It is increasing in size and encroaches towards the centre of the cornea. Usually opaque infiltrative spot known as cap is present. Stocker's line is seen on the corneal epithelium in front of apex.

Atrophic (stationary) Pterygium is thick attenuated with poor vascularity. No opaque spot (cap) is absent.

Histological characteristics

Histologically and ultra structurally, pterygium, pinguecula and actinic degeneration of the skin are very similar.

A study[47] 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 fibres 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.

Signs and symptoms[66]

- Discomfort
- Foreign body sensation
- Congestion
- Irritation
- Dryness
- Tearing (Lacrimation)
- Occlusion of the visual axis (Decreased visual acuity).
- Diplopia on lateral gaze.
- Acquired irregular astigmatism.

- Painless area of elevated vascularized white tissue on the inner and out edge of the cornea.
- Impaired vision when growth extends into the papillary area of the cornea.

Treatment

Indications for Treatment of Pterygium [10]

1. Visual loss from proximity to visual axis
2. Threatening the visual axis
3. Visual loss from astigmatism
4. Eye movement restriction
5. Atypical appearance such as possible dysplasia
6. Observed growth by opthalmologist
7. Reported growth by patient
8. Symptoms of irritation etc
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.[9]

Surgical excision techniques

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 therapy25 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.[68] 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[69] began to be used in the 1950s and the use of Mitomycin C (MMC) as adjunct therapy[70] began in Japan in the 1960s.

Amniotic membrane to substitute the conjunctiva[71] was used as early as in 1946 but the idea was developed and popularized by Tseng[72] 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.[11]

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. The ‘bare sclera’ technique involved the removal of the lesion and peri-limbal conjunctiva with suturing of the remaining conjunctival rim onto the bare scleral surface at a variable distance from sclerocorneal limbus.[51]

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 trough 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 epithelialized 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 may range as high as 80%. This procedure is now regarded as unethical and is relegated to the history of treatment options for pterygium.[51]

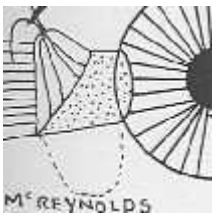
Simple conjunctival closure

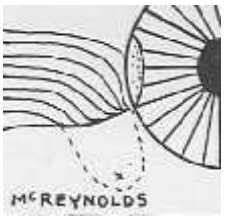
It generally involves the removal of the pterygium with minimal conjunctival excision and then closure of the conjunctiva with sutures leaving very little or no bare sclera. This is the simplest method and consists of extirpation of all the fibrovascular proliferation and suturing the upper and lower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

Transplantation of head of pterygium

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.

Mc Reynold 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 post operative cosmetic results.[73]

Conjunctival flap and autograft

Two reports[74,75] 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.[76]

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.[11]

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.[77]

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.[78]

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.[79]

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 haemostasis 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.[80]

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.[11]

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.[11] A study[81] 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.[11]

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.[11]

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.[82]

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.[51]

Amniotic membrane possesses antiscarring, antiangiogenic and anti-inflammatory properties, which may be useful for treating pterygium. A study[83] 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 epithelized cryopreserved human amniotic membrane, the efficacy of membranes that are alternatively prepared such as the de-epithelized 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.[11]

Three prospective studies[83-85] have compared amniotic membrane transplantation with other conventional treatment modalities. In a randomized

prospective study,[84] amniotic membrane transplant is associated with an unacceptably high recurrence rate compared with conjunctival autograft. This result is also supported by another study.[85]

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[86] demonstrated no significant difference in the recurrence rate compared with denuded amniotic membrane transplantation, operated eyes achieved almost immediate reepithelialization 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.[11]

It does not appear to offer any special advantage in preventing pterygium recurrence, with recurrence rates ranging from 6 to 100%.[11] As such this is not a favored 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.[11]

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 anti mitotic 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 (15 mg in 30 ml of Ringer's solution) is given every three hours in day time for 6 weeks.

Complications

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 epithelialization 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 depiginentation. The periorbital skin depigmentation has been cited, as the major reason thiotepa has not gained widespread acceptance in the post-operative treatment of pterygia.

Mitomycin-C (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 tumor cells.[51]

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.[51] Other agents include the alkylating agent 5-fluorouracil (5-FU), a pyrimidine analogue used either intraoperatively or as postoperative subconjunctival injections.[51]

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 the use of hyperbaric oxygen which induces hyperoxia, angiogenesis and episcleral fibroblast proliferation.[51]

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.[51]

With the introduction of a Strontium applicator for ophthalmological use in 1950, Strontium -90 has become the standard source of beta radiation. The ^{90}Sr 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.[51]

Recurrence rate is 3 - 11% However, its use is not innocuous and may be associated with serious complications, including vision threatening endophthalmitis.[51]

Complications

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

A study[87] reported delayed scleral necrosis and ulceration which led to pseudomonas endophthalmitis and evisceration.

Conjunctival autografts 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 beta-irradiation usage.[11]

A study[88] demonstrated that there was no statistically significant difference in the recurrence rates between conjunctival autografting and mitomycin C use. Compared with the use of mitomycin C and beta-irradiation, conjunctival autografting is more technically demanding and more time-consuming to perform.

Inter-surgeon variability in terms of surgical technique, skill and experience contributes to the wide variation in recurrence rates that have been reported. Once the surgical technique is mastered, however, conjunctival autografting is generally considered to be a better option than the other treatment modalities, because of its proven efficacy and its long safety record.

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.[51]

Such factors include Pegaptanib, an oligonucleotide aptamer that binds exclusively to the 165 amino acid isoform of VEGF, and recombinant monoclonal antibody Bevacizumab as well as its fragment Ranibizumab, both directed against VEGF.[51]

Previous studies have already evaluated the potential use of Bevacizumab in pterygium management.[89-90] 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.[51]

Fibrin glue: A tissue adhesive

Tissue adhesives have been used for closing and apposing wound edges quickly. Properties of ideal tissue adhesives include: postoperative comfort, cost-effectiveness, rapid setting time and transparency, high tensile strength by creating a strong bridge between wounded margins, easy application, biodegradability and biocompatibility.

Synthetic tissue adhesives, such as cyanoacrylate, induce sufficient fibrin cross-linking kinetics but are limited by direct tissue toxicity and barrier effects. Therefore, natural substances, such as fibrin, may have significant advantages.[22]

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.[91] Also it was in early forties that fibrin glue was introduced to ophthalmology to fixate penetrating corneal grafts in rabbits.[17]

In the last 10 years, fibrin adhesive has been used to successfully close cataract incisions, attach soft tissue in oculoplastic surgery, attach conjunctiva in

strabismus and in glaucoma surgery, treat leaking blebs, and close macular hole in retinal surgeries.[17]

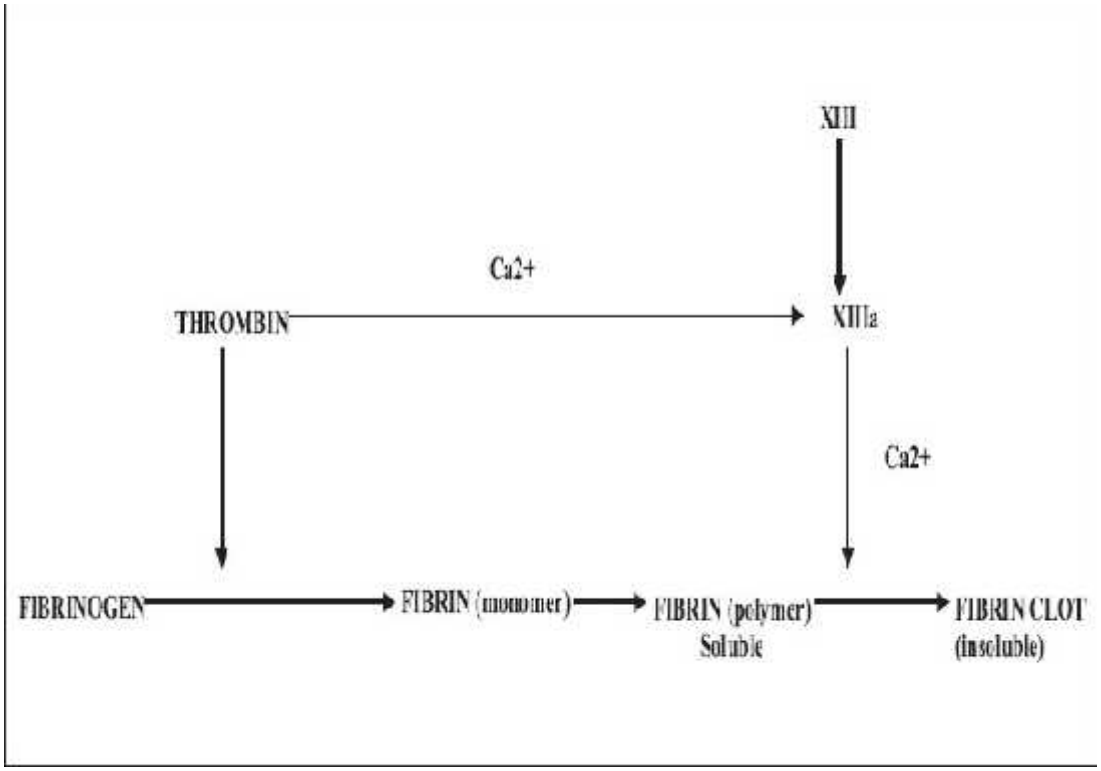
The sealer protein has two major components, fibrinogen and thrombin, and two coagulating factors, aprotinin (fibrinolysis inhibitor) and calcium chloride. The setting time of the mixture is usually dependent on the thrombin concentration. A fast-setting mixture sets within 30 s and a slow-setting mixture sets within 1—2 minutes.

Mechanism of action[17]

The final common pathway for both the extrinsic and intrinsic pathways of coagulation *in vivo* is mimicked by fibrin glue to induce tissue adhesion. Fibrin glue clot formation starts with the activation of Factor XIII by thrombin. The activated Factor XIII then hydrolyzes prothrombin to thrombin. Thrombin converts fibrinogen into fibrin. Fibrin self-assembles into fibers to form a 3-Dimensional matrix.

Thrombin also activates Factor XIIIa (present in the fibrinogen component of the glue), which stabilizes the clot by crosslinking fibrin fibers as well as inducing polymerization of the fibers in the presence of calcium ions.

The basis of the adhesion is the presence of the Factor XIII enzyme, which causes the fibrin to crosslink and form a coagulum with great cohesive strength.



The commercially available fibrin sealant kit contains the following in separate vials:

1. Freeze Dried Human Fibrinogen (40 mg/ml)
2. Freeze Dried Human Thrombin in (500 IU/ml)
3. No antimicrobial preservative is added in any of the components
4. Aprotinin solution (Bovine) as a sterile solution in a composition of 3000 kiu/ml
5. 1 x 5 ml ampoule of sterile water for injection
6. Applicator with two mixing chambers and one plunger guide

Storage

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

Advantages

Fibrin glue reduces the total surgical time because time required to place sutures is saved. The use of glue has been found to lower the risk of post-operative wound infection, contrary to conventional suturing. This can be attributed to accumulation of mucous and debris in sutures which may act as a nidus for infection.[17]

It is well tolerated, non-toxic 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. This reaction has been attributed to the presence of aprotinin in fibrin glue.[17]

Disadvantages

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 but 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.[17]

The commonly used method of viral inactivation is the solvent/detergent method which inactivates lipid coated viruses. Additional means of reducing viral transmission risk are a combination of γ-radiation, cryoprecipitation, adsorption, vapor heating, pasteurization and nanofiltration. Further insurance can be attained by testing viral markers from donors for 6 months to ensure sources are virus free.

Fibrin glue in pterygium surgery

Fibrin glue has been used as an alternative to sutures for securing conjunctival grafts. The use of fibrin glue shortens operating times significantly and is associated with less postoperative discomfort. 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.[11]

In a retrospective study,[9] authors demonstrated a pterygium recurrence rate of 5.3% with glue versus 13.5% with sutures. Another study,[22] showed that the use of fibrin glue was associated with a significantly shorter operative time and greater patient acceptance compared with using sutures.

Another study in 2008 evaluated the efficacy and safety of fibrin glue in conjunctival autograft fixation in primary pterygium compared with that of suturing.[92] They found that fibrin glue application takes significantly shorter operating time and associated with fewer post operative symptoms than a sutured graft, indicating the safety of the procedure.

Studies[93,94] have also demonstrated its efficacy for amniotic membrane graft fixation during pterygium surgery in terms of reduction of surgical time and post operative discomfort. A study reported that rubbing the eye can cause graft dehiscence following pterygium surgery with fibrin glue.[95]

Complications of pterygium treatment

Operative complications related to pterygium excision are uncommon, and are generally related to the surgical technique. This includes excessive bleeding, button hole of the conjunctiva graft, perforation of the globe with the suture needle, and injury to the medial rectus muscle. The main postoperative complication is recurrence. Other complications such as pyogenic granuloma, dellen, persistent epithelial defects are not uncommon, but these may be easily treated with no significant long-term sequelae.[51]

Complications of graft[66]

1. **Graft edema** may result secondary to inadequate debridement of the graft. All tenon's capsule remnants should be excised to avoid retraction and post operative edema. Edema usually subsided in the first week with topical steroid therapy.
2. **Graft Necrosis** is a rare complication occurring when the graft is misplaced with epithelial side down or if the recipient bed is avascular.
3. **Sclerocorneal dellen** occurs due to an oversized graft or persistent edema. Excessive use of the diamond burr or blade to resect the head of the pterygium produces a rough surface with poor lubrication and subsequent dellen formation.

4. **Epithelial Inclusion Cysts** are typically transparent and encapsulated. They appear 1 or 2 months post operatively and mat be produced by inclusion of epithelial debris beneath the conjunctival graft. Treatment includes excision of the involved conjunctiva and marsupalization of the cyst.
5. **Subconjunctival Haematomas** usually subside spontaneously without consequence, except for short term cosmetic appearance.
6. **Subconjunctival fibrosis** may occur at the donor site. The fibrosis is triggered by the abnormal exposure of Tenon's capsule and can cause problem that is usually cosmetic, although involvement of extra ocular muscle in the scar tissue may cause diplopia.
7. **Corneoscleral Thinning:-** It is more common in recurrent pterygia. Tendencies to use deep keratectomies to remove the head of the pterygium are the main cause of exaggerated scraping.

Other complications

Of greater concern is the potentially serious sight-threatening complications that have been associated with the use of adjunctive mitomycin C and beta-irradiation, such as scleral necrosis, infectious scleritis, severe secondary glaucoma, iritis, cataract, corneal edema, corneal perforation, and endophthalmitis. Complications arising from the use of beta irradiation have been reported in up to 13% of patients, with latency periods of up to 14.5 - 2.5 years.[51]

Chapter 4

Methodology

METHODOLOGY

The present study was conducted in the Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2011 to December 2011.

Study design

One year randomized controlled trial.

Place

This study was carried out at Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum a teaching hospital attached to Jawaharlal Nehru Medical College, Belgaum

Source of Data

Patients with primary pterygium attending Ophthalmology Out Patient Department at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Study Period

January 2011 to December 2011

Sample Size

A total of 44 patients divided into two groups of 22 each were studied.

Sampling procedure

The sample size was calculated based on the following formula.

$$n = \frac{2(z\alpha+z\beta)^2 \times p \times (100-p)}{(p_0-p_1)^2}$$

Where,

$Z\alpha$ = 1.96

$Z\beta$ = 0.84

p_0 = Efficacy in one group i.e. 50% patients having foreign body sensation

p_1 = Efficacy in 2nd group i.e. 20% patients having foreign body sensation

$p_0 - p_1$ = Effect size

p = $(p_0 - p_1) / 2$

By applying the above variables total sample size was calculated to be 44 that is;

- Group1; Suture group: n=22
- Group2; Fibrin glue group: n= 22

Randomization

Based on the computer generated randomization, patients were divided into two groups of 22 each.

Selection criteria

Inclusion criteria

- Patients with primary pterygium.

Exclusion criteria

- Subjects not giving consent for participation in the study.
- Any previous intra-ocular surgery.
- History of ocular trauma.
- Ocular surface infection.
- Patient on any anti-coagulant therapy.
- Known hypersensitivity to any component of fibrin glue.

Ethical clearance

Prior to the commencement, the study was approved by the Ethical and Research Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

All the patients fulfilling selection criteria were explained about the nature of the study and its implications and a written informed consent was obtained before enrollment (Annexure I).

Method of collection of data

After the enrollment, patients were interviewed for the demographic data such as age, sex, occupation. Patients were asked about the complaints and

detailed history was taken regarding the presenting illness. These findings were recorded on a predesigned and pretested proforma (Annexure II).

Ocular examination

Ocular examination included recording visual acuity with snellen's chart (in patients with visual acuity less than 6/60, acuity was recorded as counting fingers at particular distance or hand movements or perception of light or projection of rays).

Detailed anterior segment examination was done under slit lamp for the diagnosis of pterygium and characteristics such as grade, type and site were recorded. The grading of pterygium was done according to the classification as;[66]

- Grade 1 (atrophic) with episcleral vessels under the body of the pterygium not obscured and clearly distinguishable;
- Grade 2 (intermediate), with episcleral vessels under the body of the pterygium obscured partly and indistinguishable;
- Grade 3 (fleshy), episcleral vessels totally obscured;

Depending upon the progression, a thick fleshy and vascular pterygium with a few infiltrates in the cornea in front of the head of the pterygium were typed as progressive and thin, atrophic, attenuated with very little vascularity and no infiltrates in the cornea were typed as non-progressive. Further based on the location, the pterygium was labeled as nasal or temporal.

Pre-operative evaluation included keratometry, measurement of intra-ocular pressure and lacrimal sac patency test. Investigations such as random blood sugar, bleeding time and clotting time were performed.

Based on the randomization patients were allotted into the respective groups.

Surgical technique

The surgical procedures were standardized and were performed by an experienced single surgeon. The procedure was carried out under a peribulbar anaesthesia (Xylocaine 2% with 1:100,000 epinephrine). All procedures were performed using an operating microscope. Under aseptic conditions the universal wire lid speculum was inserted, a superior rectus bridle suture was inserted using 4-0 black silk suture material and was clipped to the drape. The body of the pterygium was marked using a sterile skin marker, and 0.1 ml of Xylocaine 2% with epinephrine was injected into the pterygium body. A No. 11 Bard Parker blade was used to excise the pterygium head from the cornea, and the body of the pterygium along with the underlying tenons was excised using Westcott scissors. Haemostasis of the scleral bed if required was done with a wet field cautery.

The area of the conjunctival defect was measured with a Castroviejo caliper, and a free conjunctival-limbal autograft measuring the same size as the conjunctival defect was obtained from the superotemporal quadrant of the bulbar conjunctiva. Westcott scissors were used to harvest the free conjunctival-limbal autograft. Meticulous dissection was performed to remove most of the tenons tissue in the autograft. The graft was moved over to the area of the conjunctival

defect, with care taken to maintain the limbus to limbus and stromal side down orientation. At this stage, depending on the group in which the patients were allocated to, the autograft was secured.

Reconstitution

The fibrin sealant is prepared according to the manufacturer's directions. Before use, the vials containing two components of fibrin glue, namely, thrombin and fibrinogen are taken out from the deep freeze and thawed to room temperature.

The first component that is the fibrinogen solution is prepared by mixing the fibrinogen powder with the aprotinin (bovine) solution.

The second component that is the thrombin solution is prepared by mixing the thrombin powder with water for injection provided in the kit.

Both the components are withdrawn in two separate syringes and are placed into the duploject injector. 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.

The reconstituted components in solution of fibrin sealant should be used by applying locally as soon as possible and not later than 4 hrs.

Group 1

The graft was placed on the cornea with the stromal side facing upwards. Three drops of the reconstituted fibrin glue mounted on two separate syringes on a Duploject injection system were then placed on the previously dried scleral bed, and the conjunctival graft was immediately flipped over the area of conjunctival defect. The graft was quickly smoothed out with a non-toothed forceps and the edges were opposed.

Group 2

Multiple interrupted 10-0 nylon sutures were used to attach the autograft to the underlying episcleral bed.

At the end of the procedure an antibiotic-steroid combination eye-drop was put in the conjuctival cul de sac and all the eyes were patched overnight.

Operating time was measured starting from insertion of lid speculum to its removal at the end of surgery.

Post operatively in both the groups an antibiotic-steroid combination eye-drop (Gatifloxacin 0.3% and dexamethasone 0.1%) were advised for six times a day for two weeks and then tapered off over next four weeks. Lubricating drops (Carboxy methyl cellulose sodium 0.5%) were advised four times a day for six weeks.

Follow-up

All patients were followed on post operative day one, one week, third week and sixth week. At every follow up visit patients were assessed for the outcome variables.

Outcome variables

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

The assessment of out variables 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.

The operated eye was evaluated for presence or absence of haemorrhage and displacement of graft. The overall appearance of the eye was assessed and graded as red or quiet. Further other complications such as graft oedema, graft extrusion, graft dehiscence, graft contraction, scleral thinning and granuloma formation were assessed and noted.

Statistical analysis

The data was coded and compiled on Microsoft Excel spreadsheet. Categorical data was expressed in terms of rates, ratios and percentages. Continuous variables were expressed as mean ± standard deviation (SD). The data was analysed by test of proportion and chi-square test. A probability value ('p' value) of < 0.05 was considered as statistically significant.

Chapter 5

Results

RESULTS

The present one year randomized controlled trial on 44 patients with primary pterygium attending Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum was conducted during the period of January 2011 to December 2011.

Based on the computer generated randomization, these patients were divided into two groups as below.

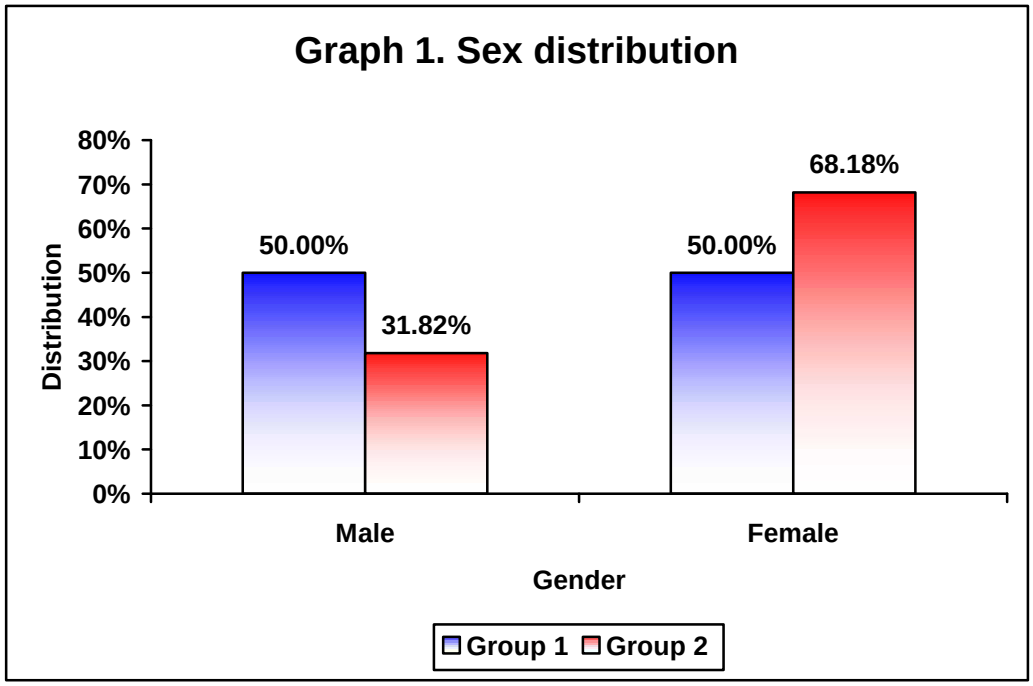
- Group1; Fibrin glue group: n= 22
- Group2; Suture group: n=22

The data was coded and compiled on Microsoft Excel spreadsheet. The data was analysed and results obtained are tabulated as below.

Table 1. Sex distribution

Sex Distribution	Group 1 (n=22)		Group 2 (n=22)	
	Number	**Percent**	**Number**	**Percent**
Male	11	50.00	7	31.82
Female	11	50.00	15	68.18
Total	**22**	**100.00**	**22**	**100.00**

x^2=1.50 **dF=1** **p=0.220**

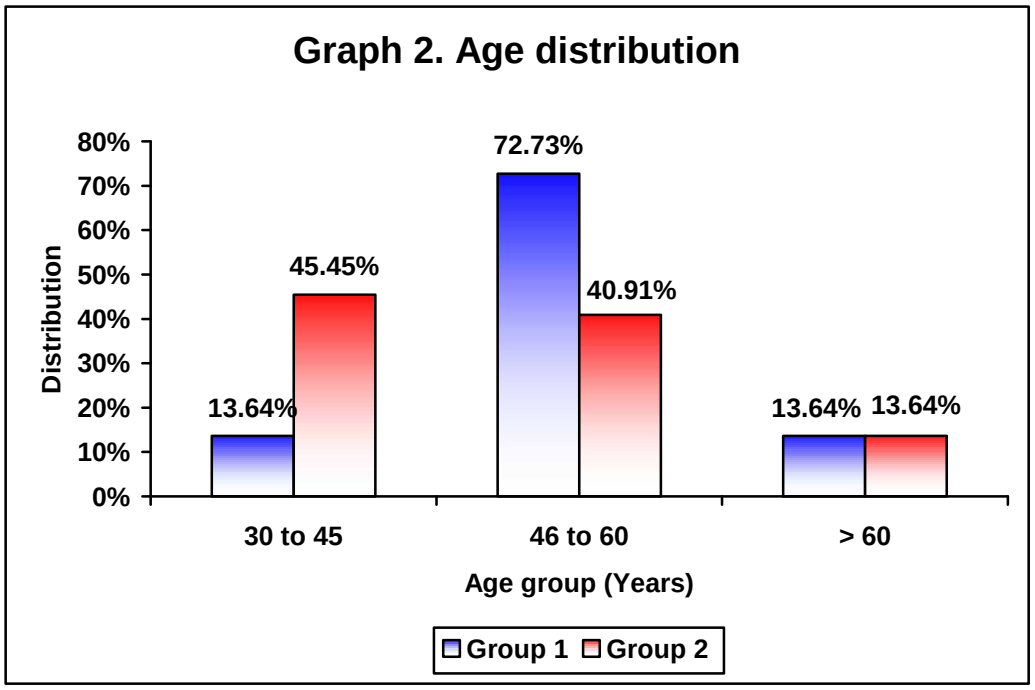


In the present study equal distribution of sex (50%) was seen in group 1 with male to female ratio of 1:1 and in group 2, female preponderance was seen with male to female ratio of 1:214. However, sex distribution in both the groups was comparable.

Table 2. Age distribution

Age group (Years)	Group 1 (n=22)		Group 2 (n=22)	
	Number	**Percent**	**Number**	**Percent**
30 to 45	3	13.64	10	45.45
46 to 60	16	72.73	9	40.91
> 60	3	13.64	3	13.64
Total	**22**	**100.00**	**22**	**100.00**

x^2=5.73 **dF=2** **p=0.057**

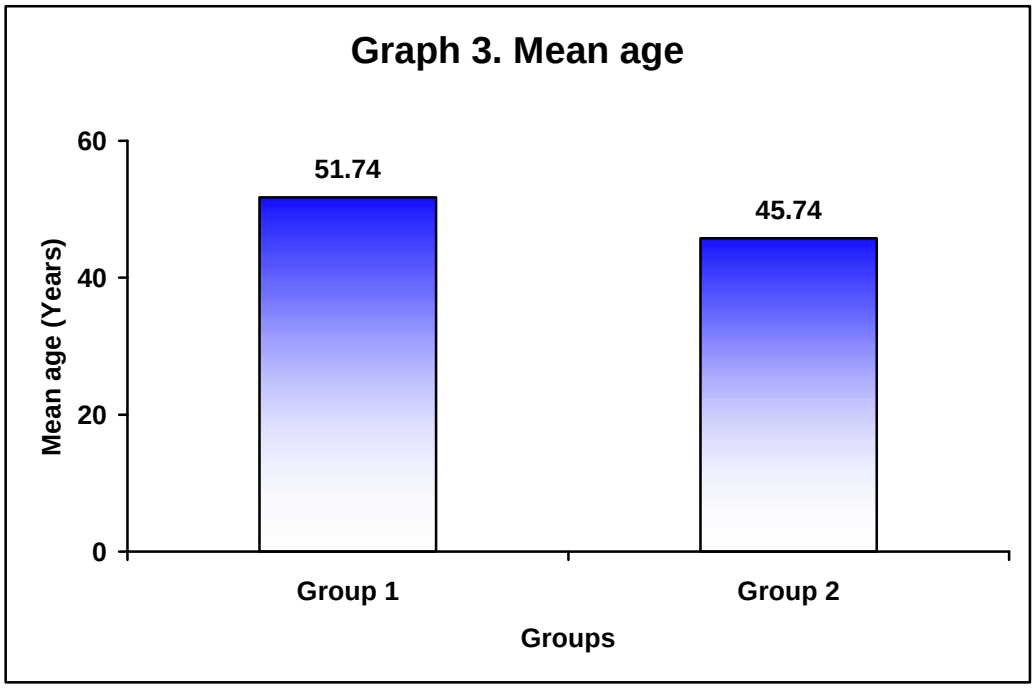


Of the 22 patients in group 1, 72.73% were aged between 46 to 60 years and in group 2, 45.45% patients were aged between 30 to 45 years. However this difference was statistically not significant.

Table 3. Mean age

Variables	Group 1 (n=22)	Group 2 (n=22)
Mean	51.74	45.74
SD	13.65	13.75
Median	54	47
Minimum	38	30
Maximum	73	68

t=1.4525 **dF=42** **p=0.1538**

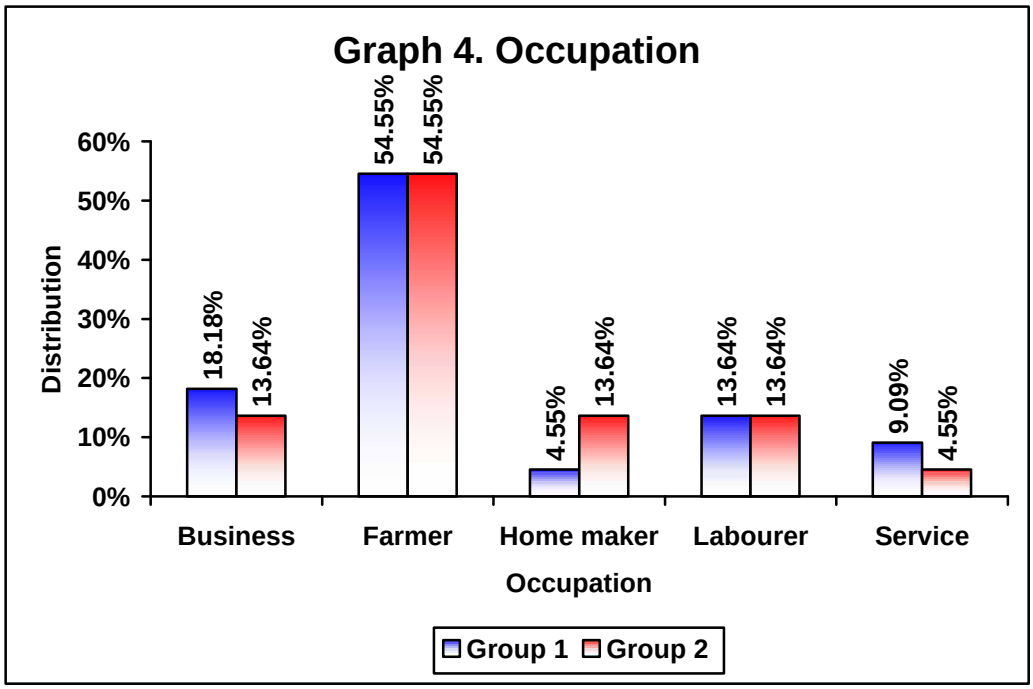


In the present study the mean age in group 1 was 51.74 ± 13.65 years and the median age was 54 years with range being 38 to 73. In group 2, the mean age was 45.74 ± 13.75 years and median age was 47 years with range being 30 to 68 years. Overall, the mean age in both the groups was comparable.

Table 4. Occupation

Occupation	Group 1 (n=22)		Group 2 (n=22)	
	Number	**Percent**	**Number**	**Percent**
Business	4	18.18	3	13.64
Farmer	12	54.55	12	54.55
Home maker	1	4.55	3	13.64
Labourer	3	13.64	3	13.64
Service	2	9.09	1	4.55
Total	**22**	**100.00**	**22**	**100.00**

x^2=1.48 **dF=4** **p=0.831**



The occupation of the patients in both the groups are as shown in table 4 and graph 4. The majority of them (54.55%) were farmers in both the groups. The occupation in both the groups was comparable.

Table 5. Laterality

Laterality	Group 1 (n=22)		Group 2 (n=22)	
	Number	**Percent**	**Number**	**Percent**
Unilateral	16	72.73	16	72.73
Bilateral	6	27.27	6	27.27
Total	**22**	**100.00**	**22**	**100.00**

x^2=0.00 dF=1 p=1.000

In this study 72.73% each patients in both the groups had unilateral pterygium and 27.27% each had bilateral pterygium.

Table 6. Chief complaints

Complaints	Group 1 (n=22)		Group 2 (n=22)	
	Number	**Percent**	**Number**	**Percent**
Fleshy mass	22	100.00	22	100.00
Vision diminution	6	27.27	9	40.91
Redness	10	45.45	10	45.45
Pain	0	0.00	0	0.00

Multiple features

In this study all the patients in both groups presented with fleshy mass. Vision diminution was noted in 27.27% of patients in group 1 and 40.91% in

group 2 and redness was present in 45.45% of patients in each group. However no patient complained about pain in both the groups.

Table 7. History

History	Group 1 (n=22)		Group 2 (n=22)	
	Number	**Percent**	**Number**	**Percent**
Watering	3	13.64	8	36.36
Discharge	0	0.00	0	0.00
Itching	7	31.82	15	68.18
Ocular irritation	9	40.91	14	63.64

Multiple features

In the present study among the patients with group 1, history of watering was recorded in 13.64%, itching was noted in 31.82% and ocular irritation was present in 40.91%. In group 2, 36.36% patients had watering, 68.18% had itching and 63.64% patients had ocular irritation.

Table 8. Past history

Past history	Group 1 (n=22)		Group 2 (n=22)	
	Number	**Percent**	**Number**	**Percent**
Intraocular surgery	0	0.00	0	0.00
Trauma	0	0.00	0	0.00
Other history	0	0.00	0	0.00
Associated medical conditions	1	4.55	1	4.55
Total	**1**	**4.55**	**1**	**4.55**

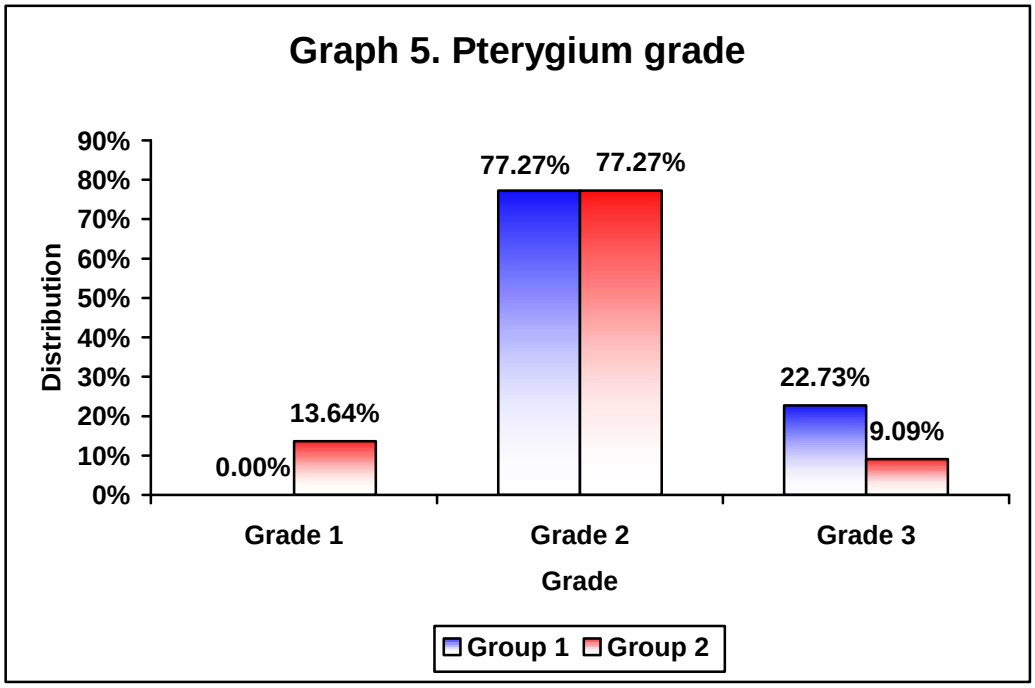
Multiple features

Past history of associated medical conditions in both the groups was noted among one (4.55%) patient each with coronary artery disease in group 1 and myasthenia gravis in group 2.

Table 9. Pterygium grade

Grade	Group 1 (n=22)		Group 2 (n=22)	
	Number	**Percent**	**Number**	**Percent**
Grade 1	0	0.00	3	13.64
Grade 2	17	77.27	17	77.27
Grade 3	5	22.73	2	9.09
Total	**22**	**100.00**	**22**	**100.00**

x^2=4.29 **dF=2** **p=0.117**

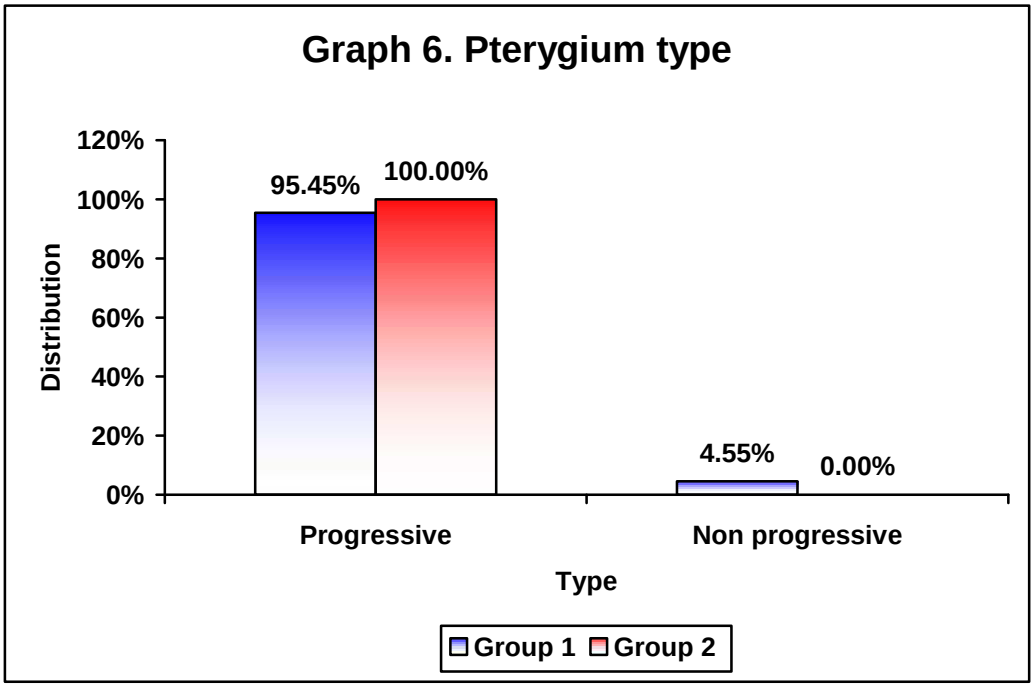


In this study most of the patients (77.27%) in both the groups had grade 2 pterygium. In group 1, 22.73% patients had grade 3 pterygium compared to 13.64% with grade 1 and 9.09% with grade 3 in group 2. However this difference was statistically not significant and both the groups were comparable.

Table 10. Pterygium type

Type	Group 1 (n=22)		Group 2 (n=22)	
	Number	**Percent**	**Number**	**Percent**
Progressive	21	95.45	22	100.00
Non progressive	1	4.55	0	0.00
Total	**22**	**100.00**	**22**	**100.00**

x^2=1.02 **dF=1** **p=0.312**

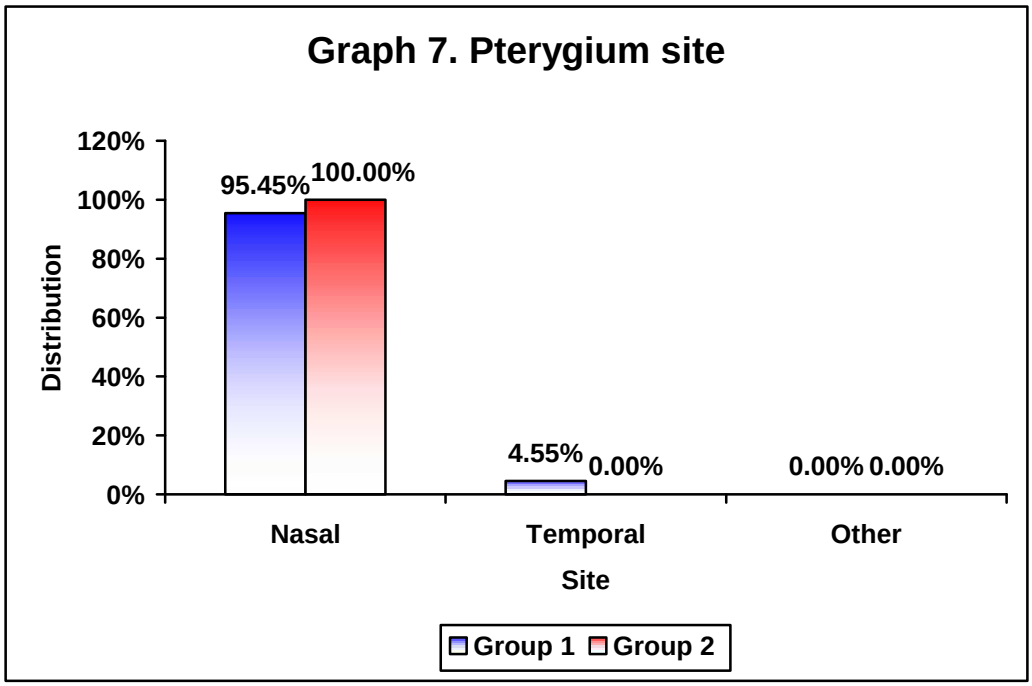


In this study majority of the patients (95.45% in group 1 and 100% in group 2) had progressive type of pterygium.

Table 11. Pterygium site

Site	Group 1 (n=22)		Group 2 (n=22)	
	Number	**Percent**	**Number**	**Percent**
Nasal	21	95.45	22	100.00
Temporal	1	4.55	0	0.00
Other	0	0.00	0	0.00
Total	**22**	**100.00**	**22**	**100.00**

x^2=1.02 **dF=1** **p=0.312**



In this study majority of the patient in both the groups had pterygium at nasal site. However one patient (4.55%) in group 1 had pterygium on temporal site.

Table 12. Operated side

Side	Group 1 (n=22)		Group 2 (n=22)	
	Number	**Percent**	**Number**	**Percent**
Right	12	54.55	10	45.45
Left	10	45.45	12	54.55
Total	**22**	**100.00**	**22**	**100.00**

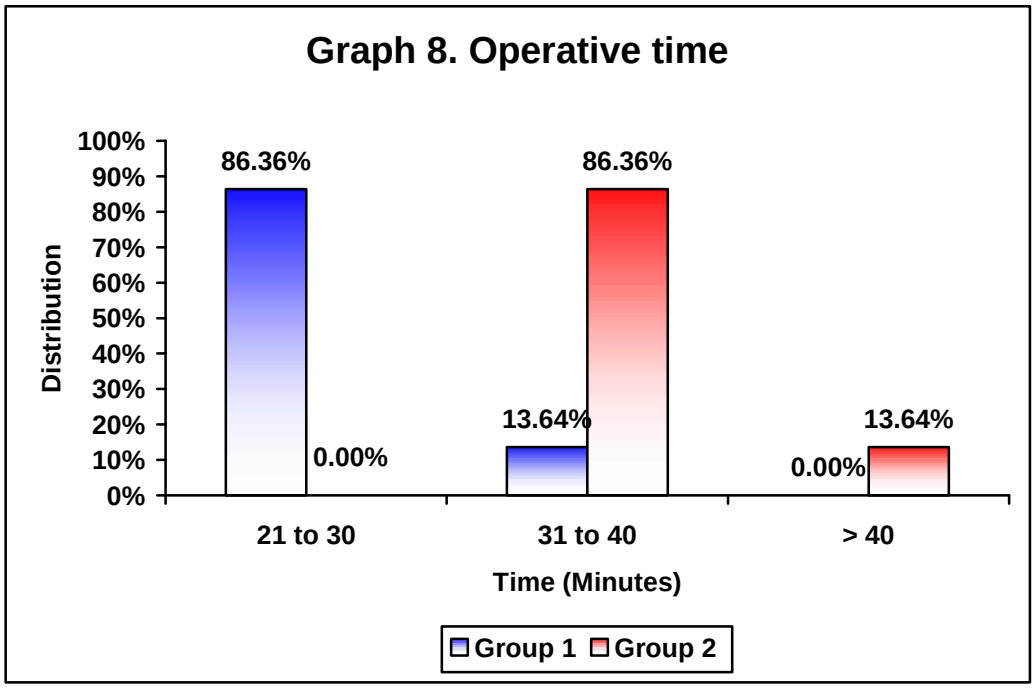
x^2=0.364 **dF=1** **p=0.546**

In this study, 54.55% patients in group 1 had surgery in the right eye and remaining (45.45%) patients underwent surgery in the left eye.

Table 13. Operative time

Time (Minutes)	Group 1 (n=22)		Group 2 (n=22)	
	Number	**Percent**	**Number**	**Percent**
21 to 30	19	86.36	0	0.00
31 to 40	3	13.64	19	86.36
> 40	0	0.00	3	13.64
Total	**22**	**100.00**	**22**	**100.00**

x^2=38.00 **dF=2** **p<0.0001**

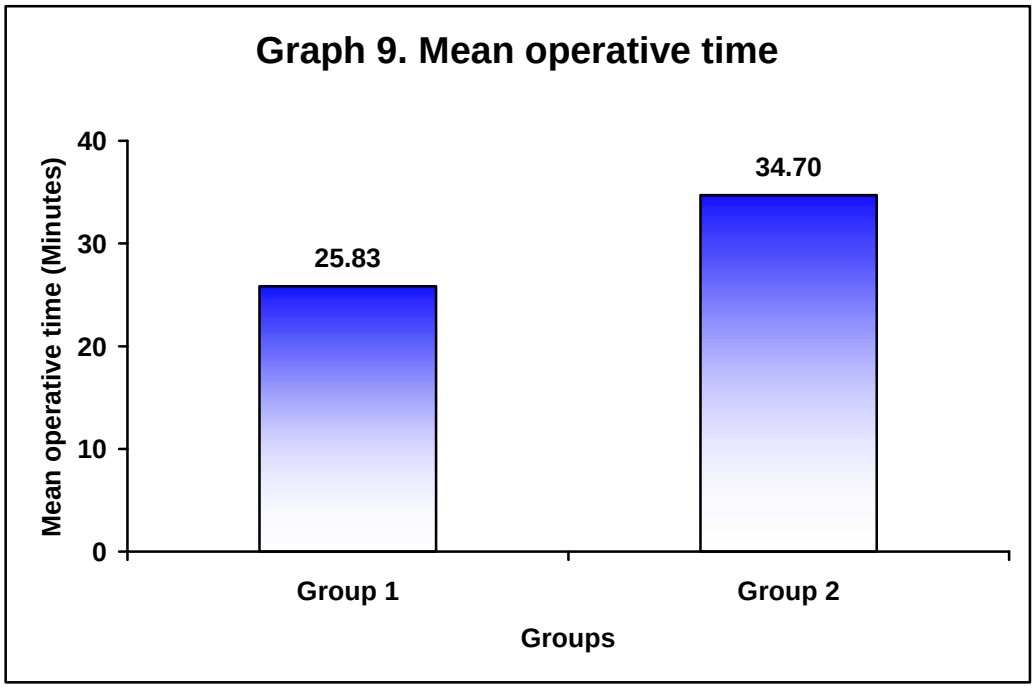


In this study among the majority of patients (86.36%) in group 1 the surgical time was significantly less (21 to 30 minutes) compared to group 2, where 86.36% required 31 to 40 minutes.

Table 14. Mean operative time

Variables	Group 1 (n=22)	Group 2 (n=22)
Mean	25.83	34.7
SD	6.23	7.96
Median	26	36
Minimum	22	31
Maximum	33	43

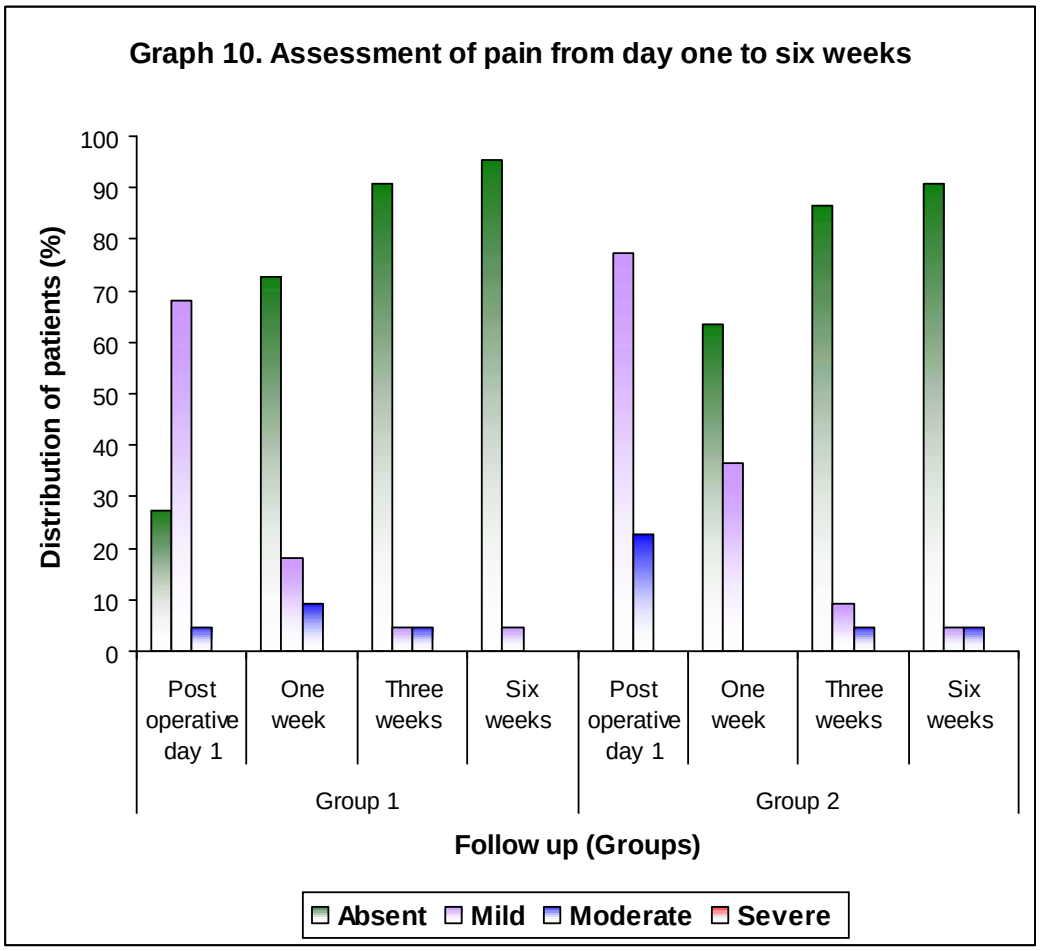
t=4.1159 **dF=42** **p=0.0002**



The mean surgical time in group 1 was significantly less compared to group 2 (25.83 ± 6.23 vs 34.70 ± 7.96 minutes). The median operative time in group 1 was 26 minutes with range being 22 to 33 and in group 2 it was 36 minutes with range being 31 to 43 minutes.

Table 15. Assessment of pain from day one to six weeks

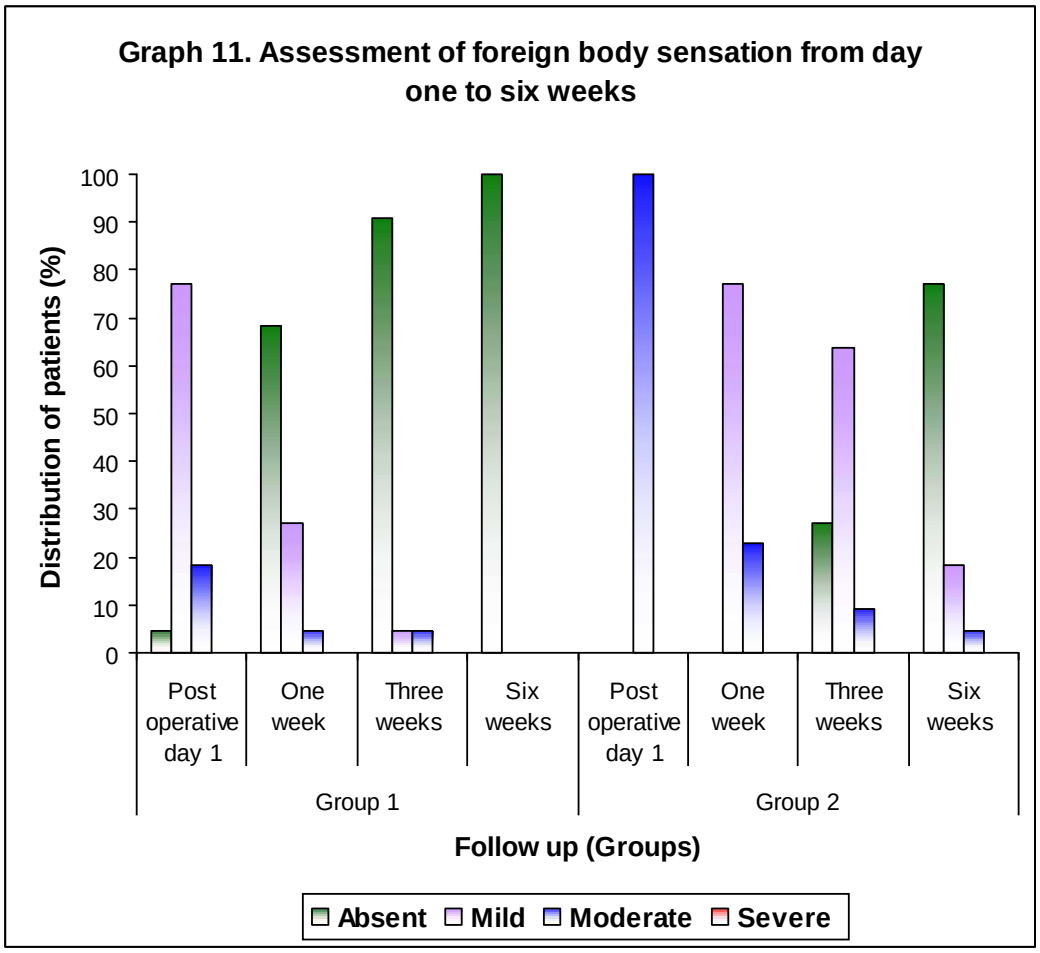
Follow up	Findings	Group 1 (n=22)		Group 2 (n=22)	
		Number	**Percent**	**Number**	**Percent**
Post operative	Absent	6	27.27	0	0.00
Day 1	Mild	15	68.18	17	77.27
	Moderate	1	4.55	5	22.73
	Severe	0	0.00	0	0.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=8.790		**dF=2**		**p=0.012**
One week	Absent	16	72.73	14	63.64
	Mild	4	18.18	8	36.36
	Moderate	2	9.09	0	0.00
	Severe	0	0.00	0	0.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=3.470		**dF=2**		**p=0.177**
Three weeks	Absent	20	90.91	19	86.36
	Mild	1	4.55	2	9.09
	Moderate	1	4.55	1	4.55
	Severe	0	0.00	0	0.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=0.359		**dF=2**		**p=0.836**
Six weeks	Absent	21	95.45	20	90.91
	Mild	1	4.55	1	4.55
	Moderate	0	0.00	1	4.55
	Severe	0	0.00	0	0.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=1.020		**dF=2**		**p=0.599**



In the present study on post operative day one, 68.18% patients in group 1 reported mild pain followed by 4.55% moderate and among 27.27% patients did not experience the pain. In group 2, majority (77.27%) experience mild pain and 22.73% had moderate pain. This difference between pain reported by patient was statistically significant (p=0.012). During the follow up at week one, three and six the pain reported by patients was similar in both the groups (p>0.05).

Table 16. Assessment of foreign body sensation from day one to six weeks

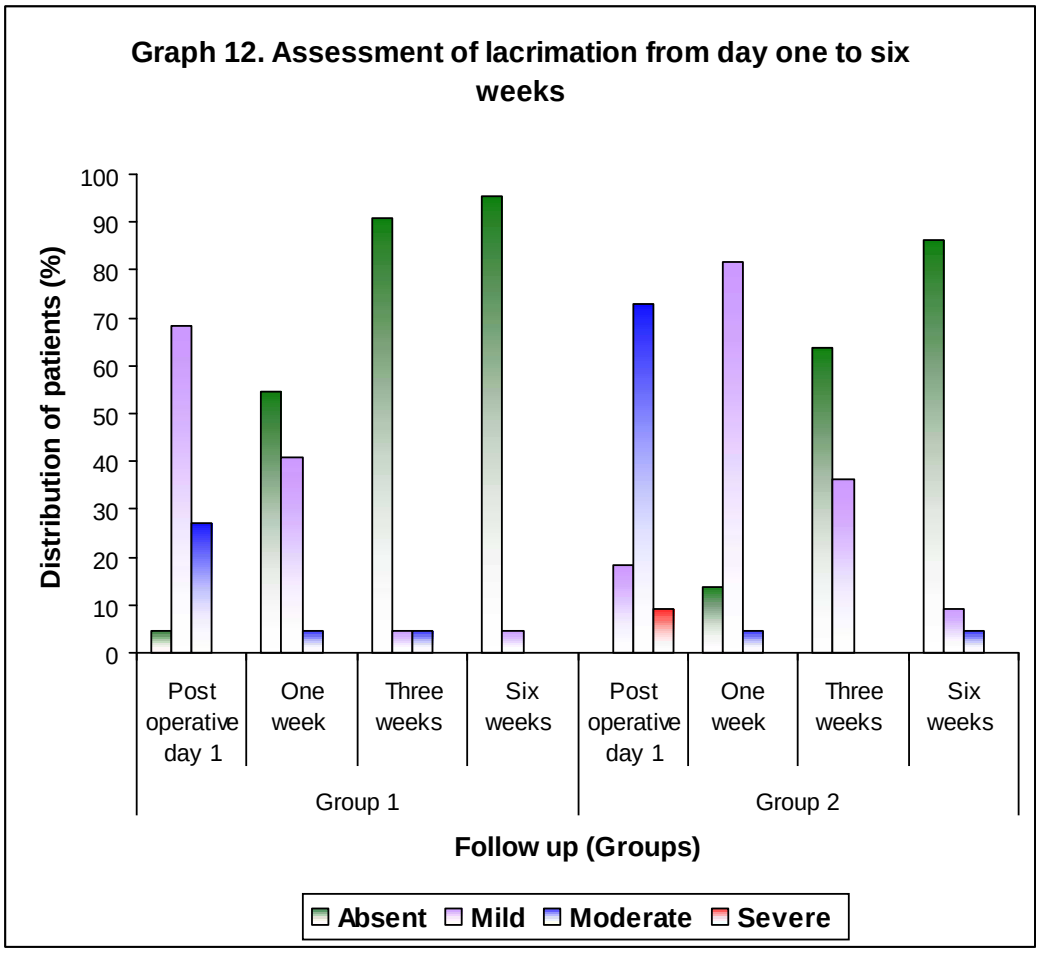
Follow up	Findings	Group 1 (n=22)		Group 2 (n=22)	
		Number	**Percent**	**Number**	**Percent**
Post operative	Absent	1	4.55	0	0.00
Day 1	Mild	17	77.27	0	0.00
	Moderate	4	18.18	22	100.00
	Severe	0	0.00	0	0.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=21.300		**dF=2**		**p<0.001**
One week	Absent	15	68.18	0	0.00
	Mild	6	27.27	17	77.27
	Moderate	1	4.55	5	22.73
	Severe	0	0.00	0	0.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=22.900		**dF=2**		**p<0.001**
Three weeks	Absent	20	90.91	6	27.27
	Mild	1	4.55	14	63.64
	Moderate	1	4.55	2	9.09
	Severe	0	0.00	0	0.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=19.100		**dF=2**		**p<0.001**
Six weeks	Absent	22	100.00	17	77.27
	Mild	0	0.00	4	18.18
	Moderate	0	0.00	1	4.55
	Severe	0	0.00	0	0.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=5.640		**dF=2**		**p=0.060**



In the present study, the foreign body sensation in group 1 was absent among 4.55% patients on day one, 68.18% during week one, 90.91% during week three and 100% at the end of the follow up whereas in group 2 all the patients (100%) complained about moderate foreign body sensation on day one which decreased among 77.27% to mild and persisted among 22.73% at week one. During week three and six, among 27.23% and 77.27% patients the sensation was absent respectively. This difference between foreign body sensation was statistically significant on day one, week one and week three follow ups ($p<0.001$) whereas at week six it was comparable in both the groups.

Table 17. Assessment of lacrimation from day one to six weeks

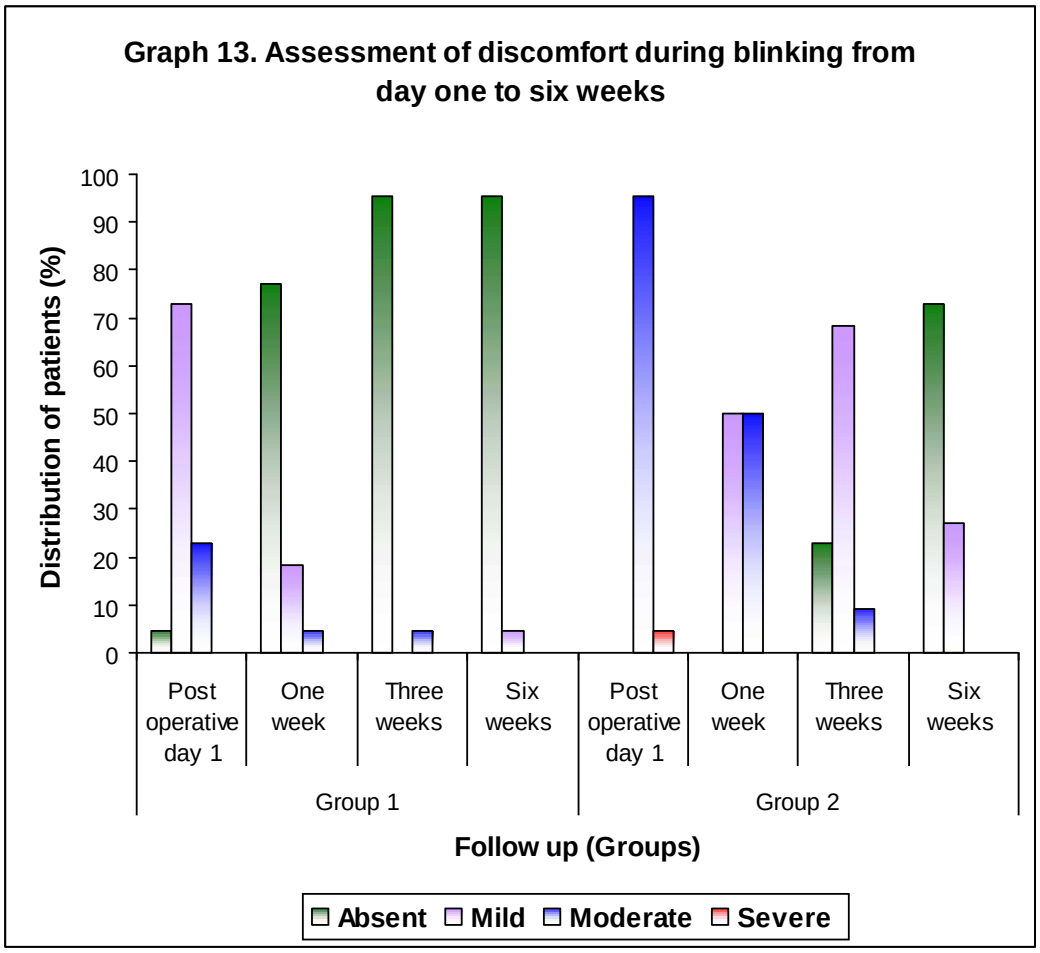
Follow up	Findings	Group 1 (n=22)		Group 2 (n=22)	
		Number	**Percent**	**Number**	**Percent**
Post operative	Absent	1	4.55	0	0.00
Day 1	Mild	15	68.18	4	18.18
	Moderate	6	27.27	16	72.73
	Severe	0	0.00	2	9.09
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=13.900		**dF=2**		**p=0.003**
One week	Absent	12	54.55	3	13.64
	Mild	9	40.91	18	81.82
	Moderate	1	4.55	1	4.55
	Severe	0	0.00	0	0.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=8.400		**dF=2**		**p=0.015**
Three weeks	Absent	20	90.91	14	63.64
	Mild	1	4.55	8	36.36
	Moderate	1	4.55	0	0.00
	Severe	0	0.00	0	0.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=7.500		**dF=2**		**p=0.023**
Six weeks	Absent	21	95.45	19	86.36
	Mild	1	4.55	2	9.09
	Moderate	0	0.00	1	4.55
	Severe	0	0.00	0	0.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=1.430		**dF=2**		**p=0.488**



In the present study the lacrimation was absent among 4.55%, 54.55%, 90.91% and 95.45% during post operative day one, week one, week three and six among the patients with group 1 respectively. In group 2, on day one all the patients complained about mild (18.18%) or moderate (72.73%) or severe lacrimation (9.09%). Among 13.64% patient at week one, 63.64% at week three and 86.36% lacrimation was not reported. These difference between lacrimation at day one, week one and three were statistically significant ($p<0.050$) whereas at week six no difference was observed between group 1 and 2.

Table 18. Assessment of discomfort during blinking from day one to six weeks

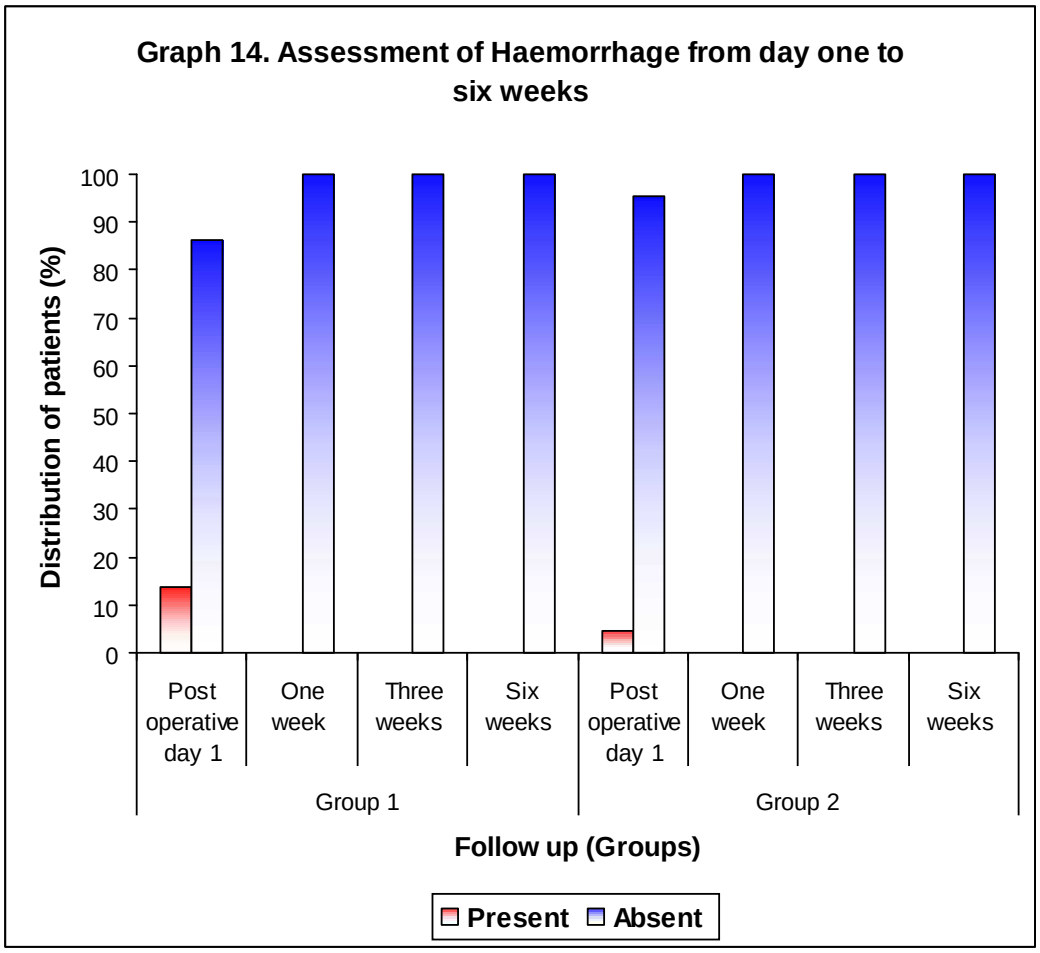
Follow up	Findings	Group 1 (n=22)		Group 2 (n=22)	
		Number	**Percent**	**Number**	**Percent**
Post operative	Absent	1	4.55	0	0.00
Day 1	Mild	16	72.73	0	0.00
	Moderate	5	22.73	21	95.45
	Severe	0	0.00	1	4.55
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=27.800		**dF=3**		**p<0.001**
One week	Absent	17	77.27	0	0.00
	Mild	4	18.18	11	50.00
	Moderate	1	4.55	11	50.00
	Severe	0	0.00	0	0.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=28.600		**dF=2**		**p<0.001**
Three weeks	Absent	21	95.45	5	22.73
	Mild	0	0.00	15	68.18
	Moderate	1	4.55	2	9.09
	Severe	0	0.00	0	0.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=25.200		**dF=2**		**p<0.001**
Six weeks	Absent	21	95.45	16	72.73
	Mild	1	4.55	6	27.27
	Moderate	0	0.00	0	0.00
	Severe	0	0.00	0	0.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=4.2500		**dF=1**		**p=0.039**



In group 1, the discomfort during blinking was not reported by 4.55% patient on day one. During week one 77.27% and week three and six 95.45% each did not report any discomfort. In group 2, all the patients reported discomfort during day one and week one. It was absent among 22.73% and 72.73% patients during week three and six respectively. This difference between the discomfort during blinking at all the four follow ups was statistically significant.

Table 19. Assessment of Haemorrhage from day one to six weeks

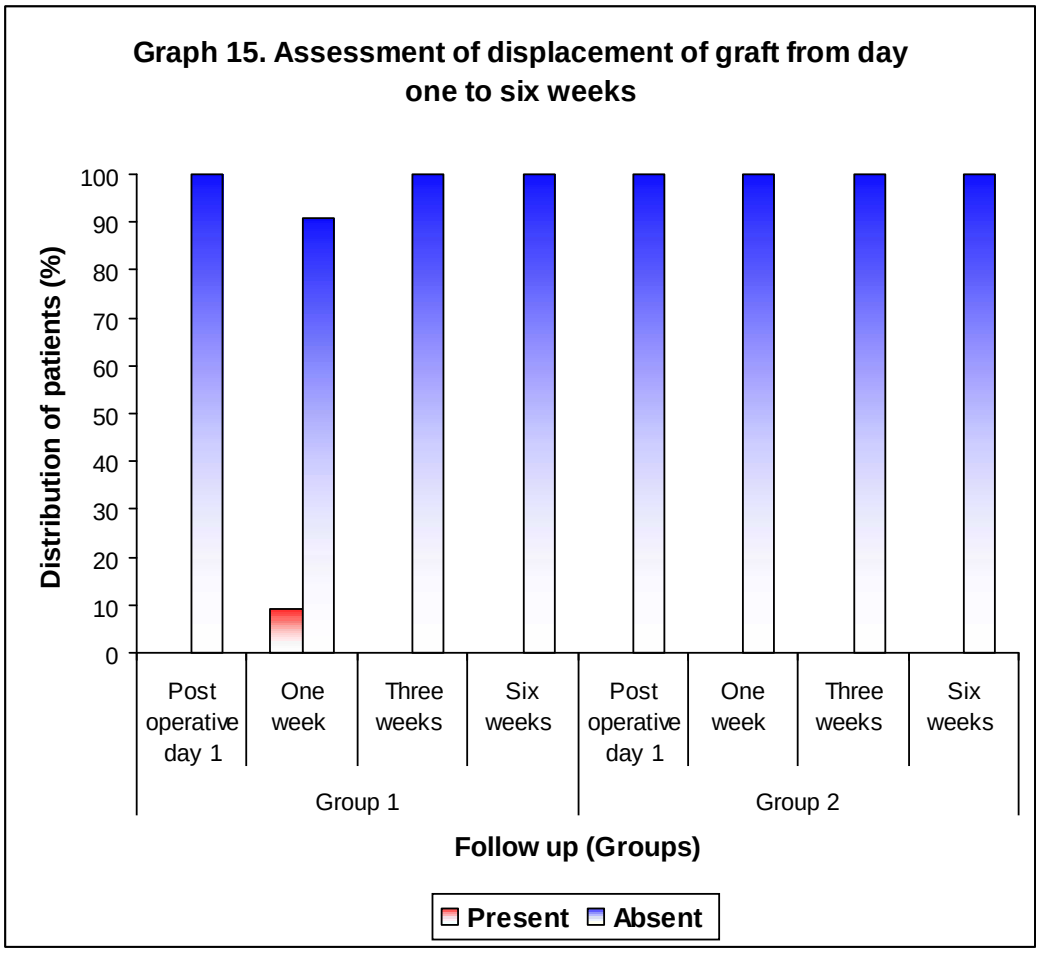
Follow up	Findings	Group 1 (n=22)		Group 2 (n=22)	
		Number	**Percent**	**Number**	**Percent**
Post operative	Present	3	13.64	1	4.55
Day 1	Absent	19	86.36	21	95.45
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=1.100		**dF=1**		**p=0.294**
One week	Present	0	0.00	0	0.00
	Absent	22	100.00	22	100.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=2.00		**dF=1**		**p=0.157**
Three weeks	Present	0	0.00	0	0.00
	Absent	22	100.00	22	100.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=0.000		**dF=1**		**p=1.000**
Six weeks	Present	0	0.00	0	0.00
	Absent	22	100.00	22	100.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=0.000		**dF=1**		**p=1.000**



The haemorrhage was observed in 13.64% patient in group 1 whereas in group 2 it was noted among 4.55% patients at post operative day one. However, this difference was statistically not significant ($p>0.050$).

Table 20. Assessment of displacement of graft from day one to six weeks

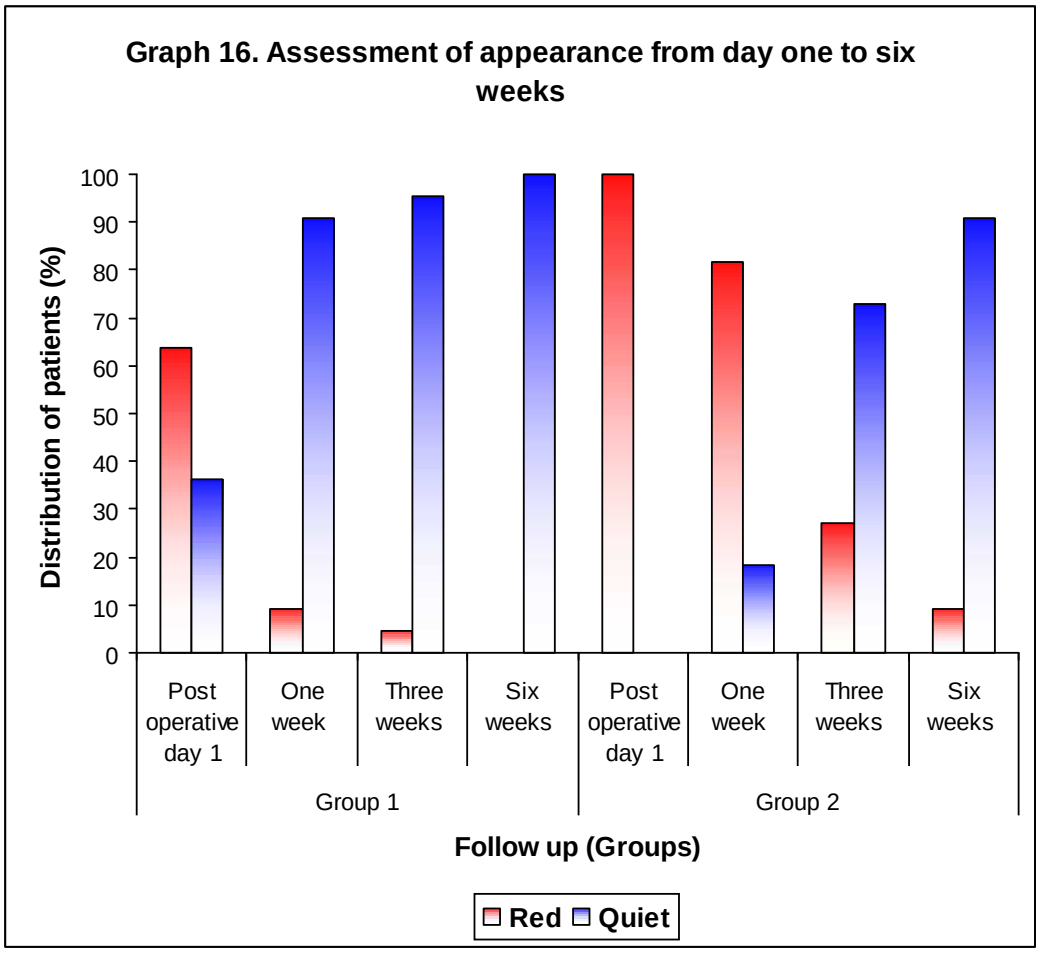
Follow up	Findings	Group 1 (n=22)		Group 2 (n=22)	
		Number	**Percent**	**Number**	**Percent**
Post operative	Present	0	0.00	0	0.00
Day 1	Absent	22	100.00	22	100.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=3.220		**dF=1**		**p=0.073**
One week	Present	2	9.09	0	0.00
	Absent	20	90.91	22	100.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=2.100		**dF=1**		**p=0.148**
Three weeks	Present	0	0.00	0	0.00
	Absent	22	100.00	22	100.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=2.100		**dF=1**		**p=0.148**
Six weeks	Present	0	0.00	0	0.00
	Absent	22	100.00	22	100.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=2.100		**dF=1**		**p=0.148**



The displacement of graft was noted among 13.64% patients in group 1 on day one and at week one, three and six 9.09% patients had displacement of graft whereas none of the patient at all the follow up presented with displacement. However, this difference was statically not significant.

Table 21. Assessment of appearance from day one to six weeks

Follow up	Findings	Group 1 (n=22)		Group 2 (n=22)	
		Number	**Percent**	**Number**	**Percent**
Post operative	Red	14	63.64	22	100.00
Day 1	Quiet	8	36.36	0	0.00
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=9.780		**dF=1**		**p=0.002**
One week	Red	2	9.09	18	81.82
	Quiet	20	90.91	4	18.18
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=23.500		**dF=1**		**p<0.001**
Three weeks	Red	1	4.55	6	27.27
	Quiet	21	95.45	16	72.73
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=4.250		**dF=1**		**p=0.039**
Six weeks	Red	0	0.00	2	9.09
	Quiet	22	100.00	20	90.91
	Total	**22**	**100.00**	**22**	**100.00**
	x^2=2.100		**dF=1**		**p=0.148**



The appearance of eye in group 1 was red among 63.64% patients on day one which reduced to 9.09% patients in week one and further to 4.55 in week three. All the patient at week six had quiet appearance at week six. In group 2, all the patient had red appearance during day one which reduced to 81.82% patients in week one, 27.27% in week three and at sixth week 9.09% patients had red appearance. This difference of appearance between the two groups was statistically significant at day one, week three and six.

Chapter 6

Discussion

DISCUSSION

A number of surgical adjunct therapies have been advocated for management of pterygium, But, an ideal procedure to minimize the postoperative inflammation and recurrence is not yet established. Conjunctival autograft is a simple and safe modality for the management of pterygium.[96]

Graft suturing has the disadvantage of a relatively long surgical time and sutures may not participate in wound healing thus causing additional trauma to graft tissue and risk of granuloma formation. Sutures might also act as nidus for inflammation hence allowing infectious agent to enter along the suture tract.

More recently use of conjunctival autograft with fibrin glue application is gaining its popularity with varied outcomes. Fibrin glue is safe and effective method for conjunctival autografting in primary pterygium excision. The use of fibrin glue to attach the autografts is not only as stable as those secured with sutures but also produce significantly less inflammation, better patient comfort, less operative time.[96]

Hence the present study was planned to assess the efficacy of fibrin glue versus suture in patients undergoing conjunctival autografting and also to compare operative time and post operative complications.

This one year randomized controlled trial on 44 patients with primary pterygium was conducted at Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2011 to December 2011. Based on the computer generated

randomization, these patients were divided into two groups namely, Group 1 (Fibrin glue group: n= 22) and Group 2 (Suture group: n=22).

In the present study equal distribution of sex (50%) was seen in group 1 (male to female ratio 1:1). In group 2, female preponderance (68.18%) was seen with male to female ratio of 1:2.14.

Similar pattern of sex distribution was reported in a study[77] at Turkey. A prospective, randomized, hospital based, comparative study[97] from India reported 22 females and 25 males out of 47 patients. Though the literature documents male preponderance, our study showed female preponderance in the second group and an equal prevalence in the first group which may be due to the fact that quite majority of patients come with cosmetic disfigurement and treatment. Also, as most of the women in our study came from rural areas and were exposed more to '*chullah*' smoke, it may point towards one of the etiological factors in development of pterygium.

In the present study among the patients in group 1, the most common age group was between 46 to 60 years (72.73%) and in group 2 it was 30 to 45 years (45.45%).

A study from Turkey[77] reported 44% patients below the age of 60 years and 56% with 60 years and older in fibrin glue group and in the suture group, 48% were from patients younger than 60 years and 52% were 60 years and above. A similar study[97] from India reported higher prevalence rate between the age group of 31 to 50 years which were comparable to the present study.

In the present study the mean age in group 1 was 51.74 ± 13.65 years and in group 2, it was 45.74 ± 13.75 years.

A study from Turkey[77] reported mean age of 53.4 ± 11.8 years in fibrin glue group and 58.8 ± 12.3 in suture group whereas a study from India[97] reported mean age of 43.40±11.91 and 48.53±13.1 years in fibrin glue and suture group respectively.

In the present study most of the patients (54.55%) were farmers in both the groups and no statistically significant difference was seen between both the groups suggesting the demographic characteristics were comparable in both the groups. There is scarcity of literature commenting about the role occupation while comparing the fibrin glue and sutures in attaching conjunctival autograft after pterygium excision. However, a population based study on 1888 participants found out that working outdoors increased the risk by 1.5-folds of developing pterygium.[37] The present study also shows a higher incidence in farmers.

In this study 72.73% each patients in both the groups had unilateral pterygium. All the patients in both groups presented with fleshy mass. Vision diminution was noted in 27.27% of patients in group 1 and 40.91% in group 2 and redness was present in 45.45% of patients in each group. However no patient complained about pain in both the groups. Among the patients with group 1, history of watering was recorded in 13.64%, itching was noted in 31.82% and ocular irritation was present in 40.91%. In group 2, 36.36% patients had watering, 68.18% had itching and 63.64% patients had ocular irritation.

The commonest signs and symptoms of pterygium include discomfort, foreign body sensation, redness, irritation, dryness, lacrimation and decreased visual acuity.[66]

In the present study most of the patients (77.27%) in both the groups had grade 2 pterygium. In group 1, 22.73% patients had grade 3 pterygium compared to 13.64% with grade 1 and 9.09% with grade 3 in group 2. In a study[98] from Malaysia done on 137 eyes of 113 patients reported 68% with grade 2 pterygium A similar study[21] from Philippines reported 55% of patients with grade 2 in suture group and 64% in fibrin glue group. Another study from Turkey[22] reported 48% patients with grade 2 pterygium in fibrin glue group compared to 52% in suture group.

Majority of the patients (95.45% in group 1 and 100% in group 2) had progressive type of pterygium. The commonest site in both the groups was nasal site. However one patient (4.55%) in group 1 had pterygium on temporal site. An epidemiological study[99] reported that, in the mono-ocular patients with one pterygium, 92.68% (38/41) were located on the nasal site. Despite this slight variation in pterygium characteristics there was no statistically significant difference between both the groups ($p>0.05$).

In this study, 54.55% patients in group 1 had surgery in the right eye and remaining (45.45%) patients underwent surgery in the left eye.

Among the majority of patients (86.36%) in group 1 the surgical time was significantly less (21 to 30 minutes) compared to group 2, where 86.36% required 31 to 40 minutes. The mean surgical time in group 1 was significantly less

compared to group 2 (25.83 ± 6.23 vs 34.70 ± 7.96 minutes). Longer operating time is considered to be closely associated with enhanced postoperative reaction and increased risk of infection and thus, reduction of operating time has important implications. A meta-analysis[100] of seven trials analyzed the duration of operation. Without exception, all the Randomized Controlled Trials clearly revealed statistically significant longer operating time for suture than for fibrin glue. Another study[97] done in India reported significantly less mean surgical time in fibrin glue group (22.72 ± 3.69 minutes vs 41.0 ± 3.53 minutes) compared to suture group. A similar Indian study[101] reported average surgical time as 21 minutes in the fibrin glue group as compared to 38 minutes in the suture group.

In the present study on post operative day one, significantly lower pain was reported by patients in group 1 (mild pain 68.18%; moderate 4.55%;) and among 27.27% patients did not experience the pain compared to group 2 wherein majority (77.27%) experienced mild and 22.73% had moderate pain (p=0.012). However, during the follow up at week one, three and six the pain reported by patients was similar in both the groups (p>0.05). A similar study[98] noted that on a 10-point numerical rating scale, both the fibrin adhesive and suture group had low median pain scores. However, the pain scores immediately post surgery and at 1 week post surgery were significantly lower in the fibrin adhesive group (P> 0.05). Another study from India[97] reported that, using fibrin glue instead of sutures when attaching the conjunctival autograft in pterygium excision causes significantly less pain. A study from Sweden[2] reported that the medians of the Visual Analogue Score values at each measurement occasion after adjusting for individual pain sensitivity found significantly lower pain levels in the glue group

both on day 0, and at each point of time during the first postoperative week and concluded that the use of a fibrin tissue adhesive when securing the autologous conjunctival graft in pterygium surgery causes significantly less pain than using sutures.

In the present study , the outcome with regard to foreign body sensation in group 1 was significantly better on day one, week one and week three follow ups that is, it was absent among 4.55% patients on day one, 68.18% during week one, 90.91% during week three and 100% at the end of the follow up compared to group 2 where all the patients (100%) complained about moderate foreign body sensation on day one which decreased to 77.27% to mild and persisted among 22.73% at week one. During week three and six, among 27.23% and 77.27% patients the sensation was absent respectively ($p<0.05$). At week six it was comparable in both the groups.

Similar study from India[98] 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 eyes respectively. At the end of 1 month, 90.91% patients 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 ($p<0.001$). Similar results were reported in a study from Israel[22] 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 ($p<0.001$).

A study[77] from Turkey found out that the intensity of the postoperative complaints including foreign-body sensation was significantly lower in patients

treated with fibrin glue than in those treated with sutures at both postoperative days 1 and 10 ($p<0.001$). Also, the intensity of itchy sensation at the first two postoperative visits was lower among patients in the fibrin glue group than in the suture group ($p<0.05$)

A study from Philippines[21] concluded that subjective symptoms of foreign body sensation were fewer and disappeared more rapidly in the fibrin glue group than the suture group. The intensity of symptoms was significantly lower in the fibrin glue group than the suture group on all follow-up days ($P>0.001$) and all patients treated with fibrin glue were asymptomatic after 2 weeks.

In the present study lacrimation was absent among 4.55%, 54.55%, 90.91% and 95.45% during post operative day one, week one, week three and six among the patients with group 1 respectively. In group 2, on day one all the patients complained about mild (18.18%) or moderate (72.73%) or severe lacrimation (9.09%). Among 13.64% patient at week one, 63.64% at week three and 86.36% lacrimation was not reported. Hence, the lacrimation was significantly less in group 1 at day one, week one and three compared to group 2 ($p<0.050$) whereas at week six no difference was observed between group 1 and 2.

A study from Philippines[21] concluded that subjective symptoms of lacrimation were fewer and disappeared more rapidly in the fibrin glue group than the suture group. Another study[77] from Turkey found out that lacrimation was significantly lower in patients treated with fibrin glue than in those treated with sutures at both postoperative days 1 and 10 ($p<0.001$). An Indian[98] study

reported significant symptomatic relief in lacrimation amongst the patients in fibrin glue group compared to suture group.

Another study[102] from Turkey also observed a lower score in post-operative patient's complaints of stinging, watering and pain.

In the present study, the discomfort during blinking was not reported by 4.55% patient on day one in group 1. During week one 77.27% and week three and six 95.45% each did not report any discomfort. In group 2, all the patients reported discomfort during day one and week one. It was absent among 22.73% and 72.73% patients during week three and six respectively. This difference between the discomfort during blinking at all the four follow ups was statistically significant ($p<0.05$).

In a study done in Philippines,[21] fibrin glue was used for attaching conjunctival autografts and resulted in less patient discomfort than did nylon sutures. Other two studies[22] compared the results of fibrin glue with sutures for conjunctival autografting. and their results confirmed the benefits of using fibrin glue over sutures with regard to postoperative discomfort.

A study from Turkey[103] observed that patient satisfaction with regard to subjective symptoms was significantly higher in the glue group than the suture group at all follow-up examinations, and the patients in the glue group experienced a more comfortable postoperative period.

In a meta-analysis[100] performed by it showed that total discomfort was considerably less in the fibrin group than in the suture group.

In the present study, the sub conjunctival haemorrhage was observed in 13.64% patient in group 1 whereas in group 2 it was noted among 4.55% patients at post operative day one which resolved spontaneously within one week in either groups (p>0.050).

A study done in Canada[78] found no significant difference in the degree of sub-conjunctival hemorrhage between the two groups at any point during the follow-up period**.** Another study[102] noticed hemorrhage under the graft in one case of group 1 on the second postoperative day. A meta-analysis[100] recorded no complication in both groups in 2 studies.

At postoperative day 7, partial conjunctival graft dehiscence was noted in two patients (9.09%) in the fibrin glue group. Grafts were reattached with fibrin glue under topical anaesthesia, and neither of the patients developed any complication in all the further follow ups. However, this difference was statically not significant (p>0.05). Graft dehiscence is a recognized complication of using tissue glue and has been previously reported in studies from Philippines[21] and Canada.[78] An Indian study[98] reported, in suture group all the patients had well placed graft on immediate post-operative day. Another study[101] observed 8.33% (1) patient out of 12 in the fibrin glue group with dislocation of the graft which then had to be sutured. Another study from Sweden[9] reported transplant loss as 1% patient out of 362 from fibrin glue group, 2% out of 156 from Vicryl suture group. Another study[104] from India showed all except 4% (1) autograft were taken up well. 4% (1) autograft was lost on the first post operative day.

In the present study two patients in the group 1 had graft retraction of 1.0 mm at the nasal site of the graft. The patients were closely followed, and reepithelialization of the conjunctival defect occurred within 2 weeks. A study[103] from Turkey documented a similar case in his study, comparing fibrin glue and sutures in attaching the autograft. Another similar study[20] from Spain also reported mild graft retraction which required no intervention for a complete secondary reepithelialization.

The appearance of eye in group 1 was red among 63.64% patients on day one which reduced to 9.09% patients in week one and further to 4.55 in week three. All the patient at week six had a quiet eye at week six. In group 2, all the patient had red appearance during day one which reduced to 81.82% patients in week one, 27.27% in week three and at sixth week 9.09% patients had red appearance. This difference of appearance between the two groups was statistically significant at day one, week three and six ($p<0.050$). A study[22] from Israel found out significantly less hyperemia and redness in the glue group. A study from India reported less number of cases with congestion in fibrin glue group vs suture group that is 26 vs 28 on day 1, 15 vs 25 on day 7, 3 vs 15 on day 15 and none on day 30, three months, six months in the fibrin glue group.

Graft edema was present in 4 (18.18%) patients in group 1 and in 3 (13.63%) patients in group 2, in all the patients the edema resolved spontaneously. A study[15] from Philippines reported that, postoperatively some amount of graft edema was present in all eyes, and it gradually subsided over time. Another study[103] from Turkey also had similar findings in his study. A

study from Spain[20] also reported 3 cases of graft edema which resolved spontaneously without any additional measures.

In the present study suture granuloma was noted in 2 cases in group 2, which was treated by removal of sutures and increased frequency of topical steroids. The granuloma resolved within 3 weeks. A study from Turkey[102] reported 7 out of 58 cases of suture granuloma, which were treated with suture removal and no recurrence of the granuloma was found in the subsequent follow ups. A randomized prospective study[105] from India reported one out of 30 cases of suture granuloma on 15th day post operative follow up in suture group where as no such complication was reported in fibrin glue group.

In the present study scleral thinning was found in 2 (9.09%) cases in group 2 whereas no such cases were reported in group 1. It is a well documented complication with the use of the anti metabolites such as mitomycin C,[106,107] but in our study intraoperative mitomycin C was not used in any of the cases. So the scleral thinning was attributed to the excessive cauterization of the scleral bed with the bi polar wet field cautery. Both the cases were treated with reducing the frequency of the topical antibiotic-steroid combination and increasing the frequency of lubricating tear drops instillation. Both the cases were healed over 1-2 weeks with complete reepithelization of the sclera.

Studies[108,109] from Taiwan and Egypt documented cases of scleral thinning in their studies and treated it with lubricating drops and topical antibiotics, and observed improvement in the condition over 1-3 weeks.

In the present study among the group 2, two cases were observed to have normal conjunctiva growing over the attached autograft which was suggestive of recurrence at the third follow up that is 3 weeks post-operative.

In the present study almost all the post-operative symptoms and signs of the conjunctival autografting were compared between the two groups, along with the analyses of the operative time and complications. This being a prospective, randomized clinical trial with a minimum of 6 week follow-up strengthens the credibility of the results.

The limitation of the study was a smaller sample size and a short follow up period to assess the recurrence rate of the pterygium. Another drawback was the lack of a cost-effectiveness analysis and also there are some concerns regarding the safety of fibrin glue use, including potential for anaphylactic reaction and disease transmission which was not considered in this study.

Long-term studies are needed to determine whether the rate of pterygium recurrence is affected by the use of fibrin glue instead of suture material.

Chapter 7

Conclusion

CONCLUSION

The present study showed better efficacy of fibrin glue in conjunctival autografting among the patients undergoing pterygium excision, in terms of pain, foreign body sensation, lacrimation and discomfort during blinking. Also, it significantly reduced the surgical time with fewer post operative complications.

Chapter 8

Summary

SUMMARY

Fibrin glues have been used in an array of ophthalmic procedures such as conjunctival closure in strabismus, vitreoretinal and glaucoma surgery. Because of its biological and biodegradable properties, fibrin-based adhesives may be used to attach the conjuctival autograft without inducing inflammation. The present study was undertaken to assess the efficacy of fibrin glue versus suture in patients undergoing conjunctival autografting and also to compare operative time and post operative complications.

This one year randomized controlled trial on 44 patients with primary pterygium was conducted at Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2011 to December 2011. Based on the computer generated randomization, these patients were divided into two groups namely, Group 1 (Fibrin glue group: n= 22) and Group 2 (Suture group: n=22).

In the present study equal distribution of sex (50%) was seen in group 1 and in group 2, female preponderance was seen with male to female ratio of 1:214. The mean age in group 1 was 51.74 ± 13.65 years and in group 2, it was 45.74 ± 13.75 years. All the patients in both groups presented with fleshy mass. Most of the patients (77.27%) in both the groups had grade 2. Majority of the patients (95.45% in group 1 and 100% in group 2) had progressive type of pterygium. Among the majority of patients (86.36%) in group 1 the surgical time was significantly less (21 to 30 minutes) compared to group 2, where 86.36%

required 31 to 40 minutes. The mean surgical time in group 1 was significantly less compared to group 2 (25.83 ± 6.23 vs 34.70 ± 7.96 minutes).

The present study showed better efficacy of fibrin glue in conjunctival autografting among the patients undergoing pterygium excision, in terms of pain, foreign body sensation, lacrimation and discomfort during blinking. Also, it significantly reduced the surgical time with fewer post operative complications.

Chapter 9

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Annexures

Annexure I

ANNEXURE I

I.D. NO. ☐☐☐

Mr/Mrs/Ms_____

You are invited to participate in our research study titled **"**The efficacy of Fibrin Glue vs Sutures for Attaching Conjunctival Autografts After Pterygium Excision – a randomized clinical trial**"** conducted by Dr. *** *****, Post Graduate student in M.S. Ophthalmology, under the guidance of Dr. **** ****, Associate Professor, Department of Ophthalmology, J N Medical College, Belgaum.

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

Purpose of the Study:

The purpose of research is to compare the efficacy of Fibrin Glue vs Sutures for Attaching Conjunctival Autografts After Pterygium Excision.

Procedure Involved

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

Risks and Benefits

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

Alternatives

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

Costs for participating in this research

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

Privacy and Confidentiality

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

Authorization to Publish Results

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

Compensation

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

Questions

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

1. Investigator, Dr. *** ******, Post Graduate student, Department of Ophthalmology, JNMC, Belgaum. Contact No. **** ******
2. Guide, Dr. **** *****, Associate Professor and Head, Department of Ophthalmology, JNMC, Belgaum. Contact No.***** ******
3. Principal, JNMC, Belgaum and Chairman, Institutional Ethics Committee. Contact No.**** *******

Consent for participation in research trial

I, Mr./Ms./Mrs _____ voluntarily agree for the participation as a subject of this study. By signing this consent form, I am not giving up any of my legal rights. I may withdraw from the study at anytime. I am signing the consent form after having read or been read for me in my own vernacular language, including the risks and the benefits and having all my questions answered.

Subject Name : _____

Signature or the Left Thumb Print of Subject : _____

Witness Name:_____

Signature of Witness:_____

Investigators Name: _____

Signature of Investigator: _____

Name of the guide: Dr. **** *******_____

Signature of the guide:_____

Date:

Place:

Annexures

Annexure II

ANNEXURE II – PROFORMA

I D No.

Name (in capital letters)

(First name) (Middle name) (Last name)

Age (in yrs)

Sex : (1=Male; 2=Female)

OP/I.P.No.

Address:

Telephone No.

Date of admission :

Date of surgery :

Date of discharge :

Provisional Diagnosis: Pterygium grade (1=1;2=2;3=3;) ☐

Pterygiumtype(1= progressive; 2= non progressive) ☐

Pterygiumsite(1= nasal; 2= temporal;3= other) ☐

Inclusion Criteria: (1=Met; 2=Not met) ☐

Informed consent: (1=Taken; 2=Not taken) ☐

Chief Complaints (1=Yes; 2=No)

Fleshy mass over cornea ☐

Diminution of vision ☐

Redness ☐

Pain ☐

History of present illness: (1= yes;2=no)	RE	LE
History of fleshy mass over cornea:		
History of pain : Mild	☐	☐
Moderate	☐	☐
Severe	☐	☐
History of redness:	☐	☐
History of watering:	☐	☐
History of discharge:	☐	☐
History of itching:	☐	☐
History of ocular irritation:	☐	☐
History of photophobia:	☐	☐
History of diplopia:	☐	☐
History of coloured halos:	☐	☐

Other complaints: (if present):

Past History (1=Yes; 2=No)

	RE	LE
Intra-ocular Surgery		
Trauma		
Other		

Other past history (if present):

Medical History (1=Yes; 2=No)

Diabetes	
Hypertension	
Bleeding disorders	
Others	

Other medical history (if present):

Family History ☐ (1=Significant; 2=Insignificant)

If 1, specify:

Personal History ☐ (1=Significant; 2=Insignificant)

If 1, specify:

General Physical Examination

Vitals

- Pulse (per min) ☐☐☐
- Blood Pressure (systolic/diastolic)(mm of hg) ☐☐☐/☐☐☐
- Temperature ☐ (1=Febrile; 2=Afebrile)

- Respiratory Rate (per min) | | | |

(1=Yes; 2=No)

Pallor		Clubbing	
Icterus		Lymphadenopathy	
Cyanosis		Oedema	

Systemic Examination (1=Normal; 2=Abnormal)

C V S If 2, specify	
R S If 2, specify	
C N S If 2, specify	
P / A If 2, specify	

Ocular Examination

- Head posture | | (1=Erect; 2=Tilted)
- Facial symmetry (1=Symmetrical; 2=Asymmetrical)
- Visual axes(1=Parallel, 2=Deviated)
- Extra-ocular movements (1=Normal; 2=Restricted)
    - Uniocular RE | | LE | |
    - Binocular | |

- Vision (1=6/6 - 6/12; 2=6/18 - 6/36; 3=< 6/36)

	RE	LE
Unaided		
Pin-hole		
Spectacles		

- Refraction

	RE				LE			
	Sphere	Cylinder	Axis	Vision	Sphere	Cylinder	Axis	Vision
Distance								
Near								

- Anterior segment examination

	RE	LE
Adnexa (1=Normal; 2=Abnormal) If 2, specify		
Conjunctiva Pterygium Present=1 Absent=2 If 1 Grade (1=i; 2=ii;3=iii)		
Location Nasal=1		

Temporal=2 Other=3		
Type (1=Progressive;2= non progressive)		
Cornea (1=Clear{other than conj. Mass}; 2=edematous; 3=other) If 3, specify		
Sclera (1=Normal; 2=Abnormal) If 2, specify		
Anterior chamber (1=Normal depth; 2=shallow; 3=deep)		
Iris (1=Normal; 2=Atrophic patches; 3=other) If 3, specify		
Pupil • Size (1=normal; 2=constricted; 3=dilated) • Reactions:		

o Direct o Indirect (1=present; 2=absent; 3=sluggish)		
Lens (1=Clear; 2=Cataract) (If 2: 1=immature; 2=mature; 3=hypermature)		

- Fundus

	RE	LE
Glow (1=Good; 2=Faint; 3=Absent)		
Media (1=Clear; 2=Hazy)		
Disc • Size (1=Normal; 2=small; 3=large) • Margins (1=Normal; 2=Abnormal) • VCDR (1=0.2; 2=0.3; 3=0.4; 4=0.5; 5=0.6; 6=0.7; 7=0.8; 8=0.9; 9=1.0) • NRR (1=Normal; 2=Thin)		

Blood vessels (1=Normal; 2=Abnormal)		
Background (1=Normal; 2=Tessellated; 3=Other)		
Macula (1=Normal; 2=Abnormal)		

Investigations

- Tonometry

	RE	LE
IOP (mm Hg)		

- Random blood sugar ☐☐☐

DIAGNOSIS:

SURGERY:

Autograft attached with (1= fibrin glue; 2= sutures) ☐

Operating time (1= <20mins;2= 21-30mins;3=31-40mins; ☐

4= 41-50mins;5=51-60mins; 6= >60mins)

FOLLOW UP

- Vision (1=6/6 - 6/12; 2=6/18 - 6/36; 3=< 6/36)

	RE	LE
Unaided		
Pin-hole		
Spectacles		

	1st op. day	**1st week**	**3rd week**	**6th week**
• Pain 1=absent; 2=mild; 3=moderate; 4=severe	☐	☐	☐	☐
• Foreign body sensation 1=absent; 2=mild; 3=moderate; 4=severe	☐	☐	☐	☐
• Lacrimation 1=absent; 2=mild; 3=moderate; 4=severe	☐	☐	☐	☐
• Discomfort during blinking 1=absent; 2=mild; 3=moderate; 4=severe	☐	☐	☐	☐

- Haemorrhage ☐ ☐ ☐ ☐

  1= present;

  2=absent

- Displacement of graft ☐ ☐ ☐ ☐

  1=present;

  2=absent

- Overall appearance of the eye ☐ ☐ ☐ ☐

  1=red;

  2=quiet

- Other findings(if any):

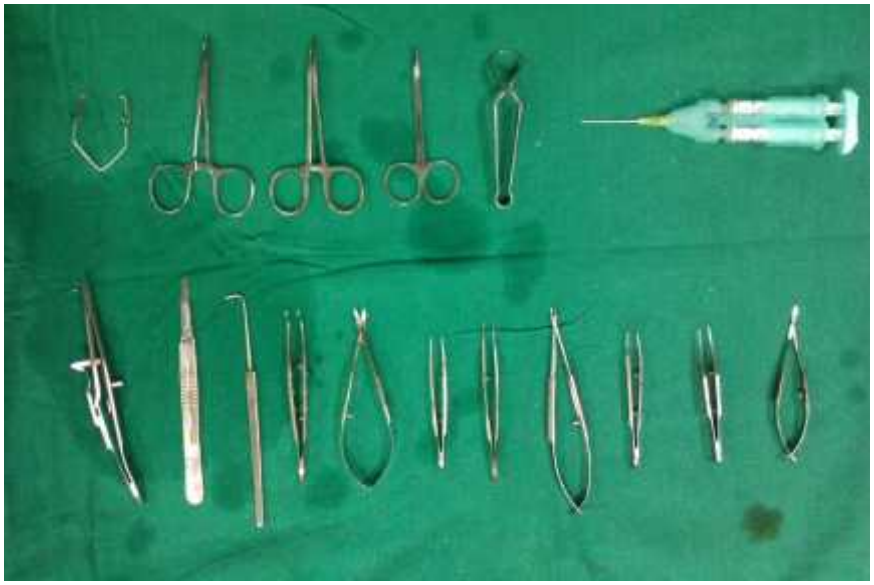
Annexures

Annexure III

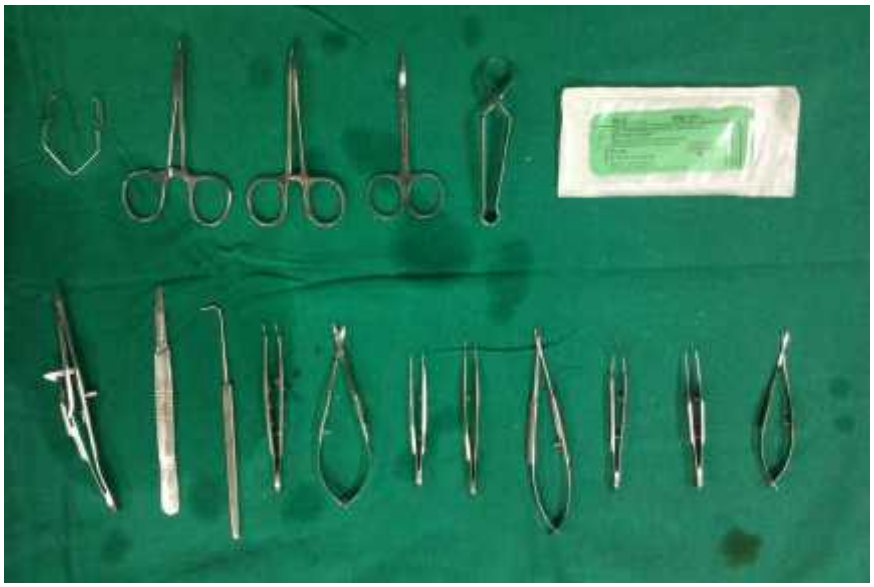
ANNEXURE III – PHOTOGRAPHS

Photograph 1. Fibrin glue

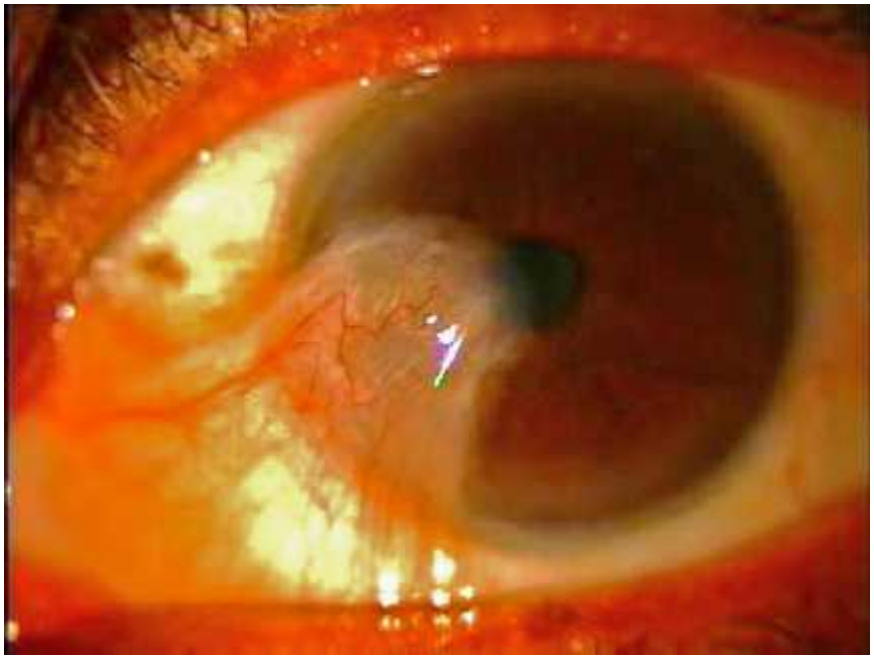
Photograph 2. Suture



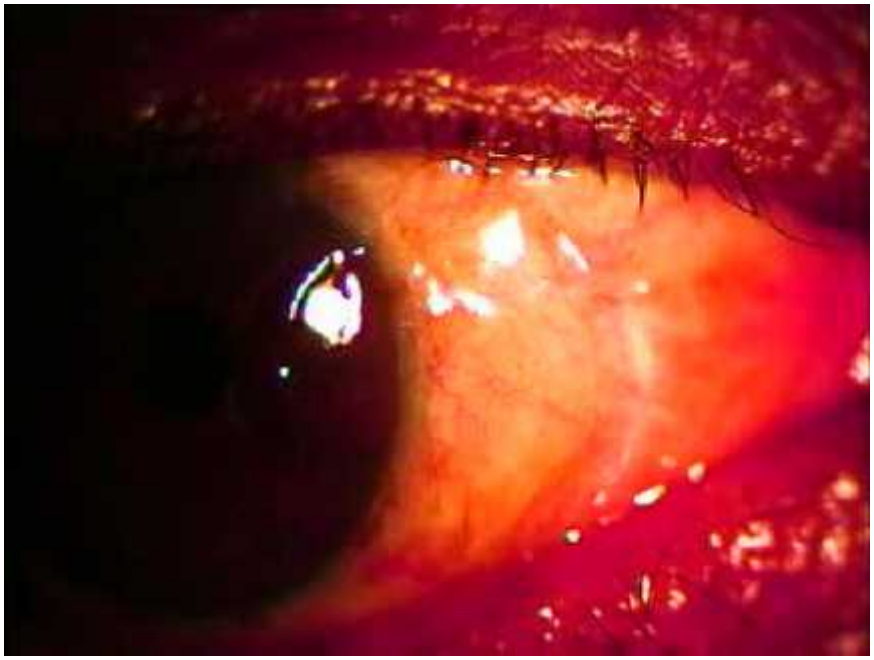
Photograph 3. Instrument set for fibrin glue group



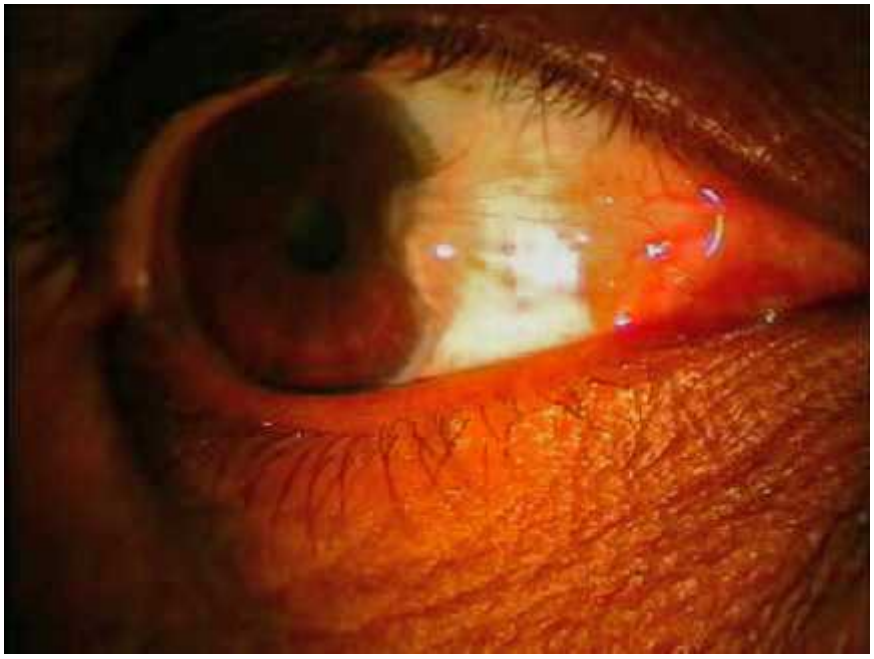
Photograph 4. Instrument for suture group



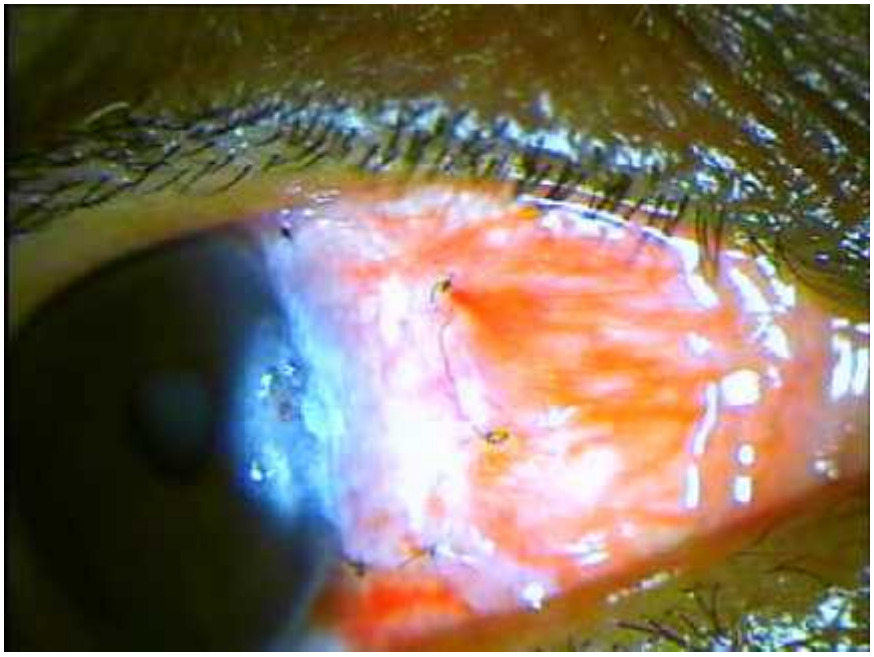
Photograph 5. Pre -operative grade 3 nasal pterygium



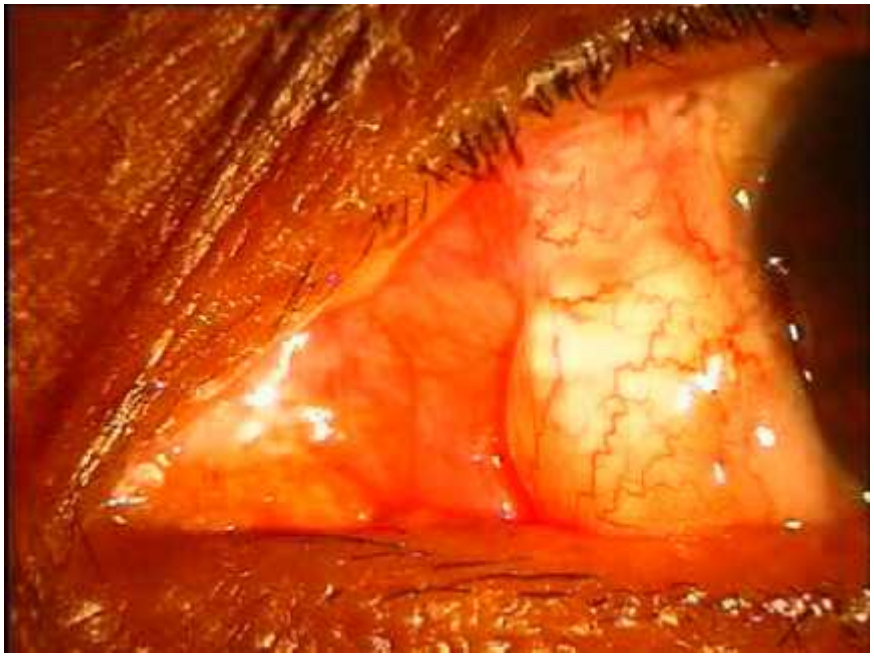
Photograph 6. Post operative with fibrin glue



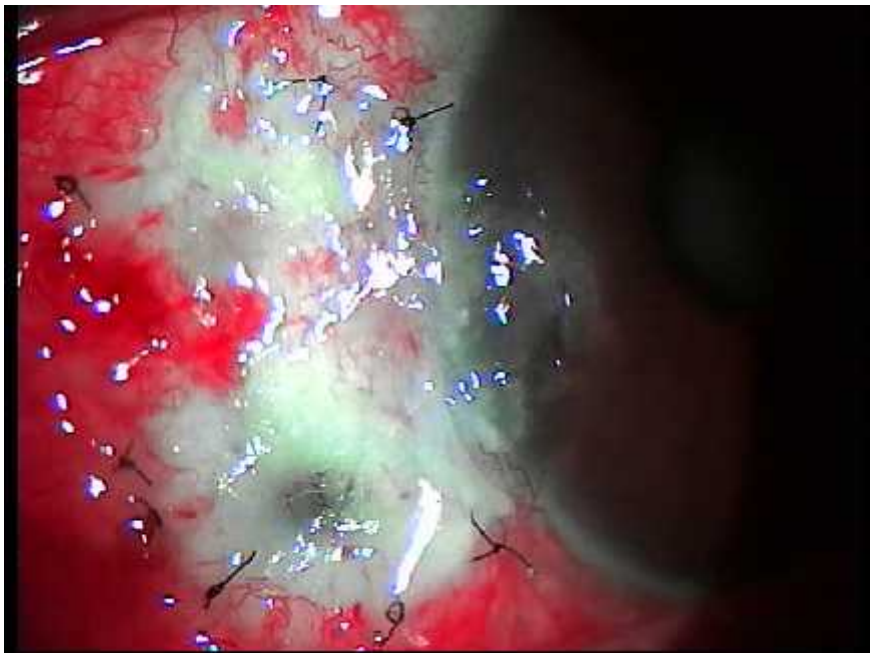
Photograph 7. Pre operative grade 2 nasal pterygium



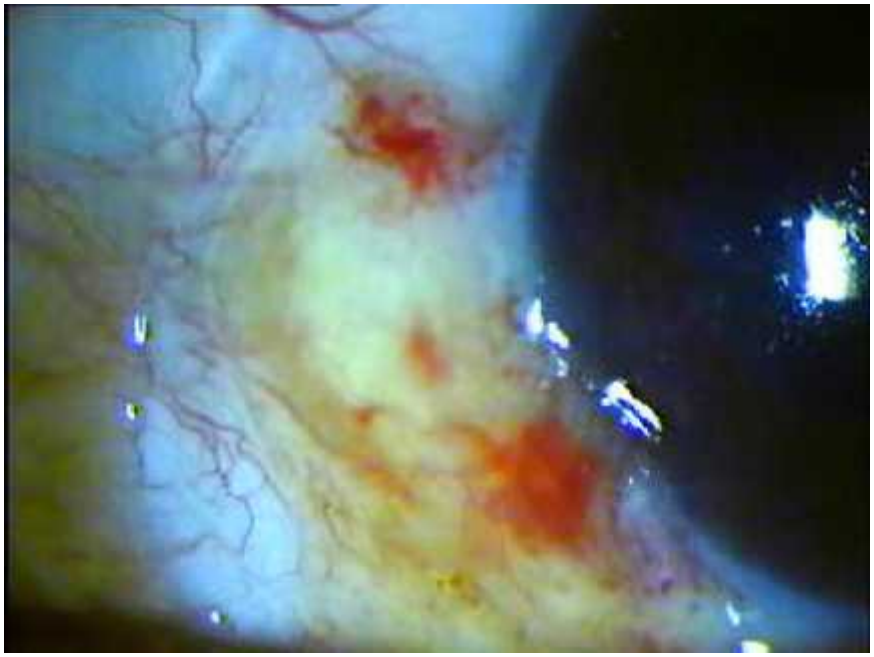
Photograph 8. Post operative with sutures



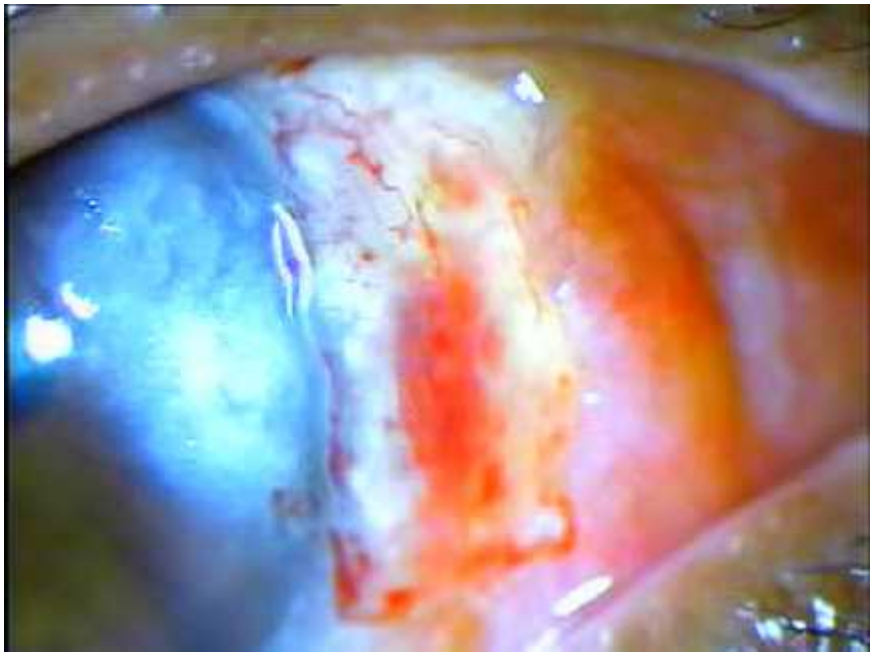
Photograph 9. Graft edema



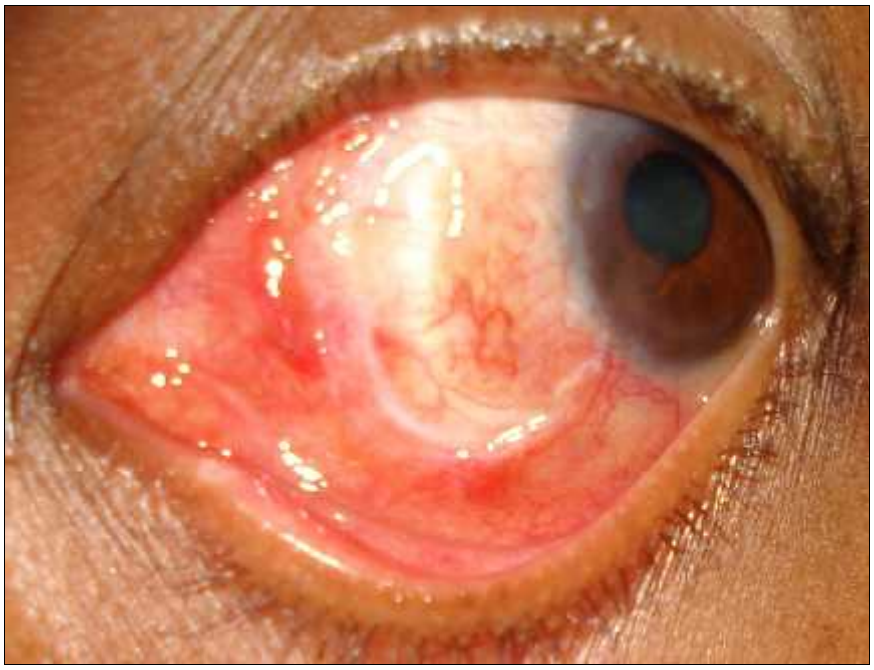
Photograph 10. Scleral thinning



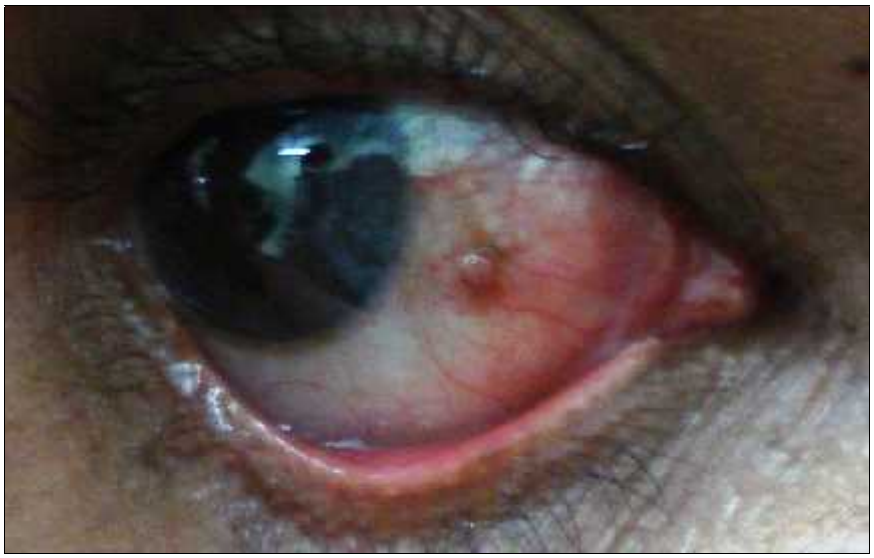
Photograph 11. Graft retraction



Photograph 12. Graft hemorrhage



Photograph 13. Graft retraction



Photograph 14. Suture granuloma

Annexures

Annexure IV

ANNEXURE IV – MASTER CHART

-	-	Negative
+	-	Positive
1	-	Absent
2	-	Mild
3	-	Moderate
4	-	Severe
Ab	-	Absent
B	-	Business
B/L	-	Bilateral
CG	-	Conjunctiva over graft
F	-	Farmer
GD	-	Graft dehiscence
GE	-	Graft edema
GF	-	Granuloma formation
GR	-	Graft retraction
H	-	Housewife
L	-	Labor
LE	-	Left eye
NCGG	-	Normal conjuntiva growing over the graft
NS	-	Nasal
P	-	Present
Post op	-	Post operative
PR	-	Progressive

Q	-	Qiet
RD	-	Red
RE	-	Right eye
S	-	Service
ST	-	Scleral thinning
St	-	Student
TP	-	Temporal
U/L	-	Unilateral

MASTER CHART - GROUP I (FIBRIN GLUE)

		Demography				Chief				History								Vision		Diagnosis							
														Past history						Grade		Type		Site			
Serial number	In/Out patient number	Sex	Age (Years)	Occupation	Laterality	Fleshy mass	Vision diminution	Redness	Pain	Watering	Discharge	Itching	Ocular irritation	Intraocular surgery	Trauma	Others	Medical history	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Operating side	Operating time
1	394935	1	73	F	U/L	+	-	-	-	-	-	-	-	-	-	-	-	6/18	6/18	2	-	PR	-	NS	-	RE	25
2	394925	1	47	L	B/L	+	-	+	-	-	-	-	-	-	-	-	-	6/9	6/9	2	2	PR	PR	NS	NS	LE	27
3	394934	2	65	F	U/L	+	+	-	-	-	-	-	-	-	-	-	-	6/18	6/18	-	2	-	PR	-	NS	LE	30
4	398692	1	49	B	U/L	+	-	-	-	-	-	-	-	-	-	-	-	6/6	6/6	-	2	-	2	-	TP	LE	28
5	398612	2	58	F	B/L	+	+	+	-	-	-	-	-	-	-	-	-	6/24	6/18	2	2	PR	PR	NS	NS	RE	25
6	398403	2	60	F	B/L	+	+	+	-	+	-	-	+	-	-	-	-	6/36	6/24	2	2	PR	PR	NS	NS	RE	22
7	402340	2	53	H	U/L	+	-	-	-	-	-	-	-	-	-	-	-	6/6	6/6	2	2	PR	PR	NS	NS	RE	30
8	402366	2	38	F	B/L	+	-	-	-	-	-	-	-	-	-	-	-	6/6	6/6	2	2	PR	PR	NS	NS	LE	26
9	407891	1	24	S	U/L	+	-	-	-	-	-	+	+	-	-	-	-	6/6	6/6	-	2	-	PR	-	NS	LE	24
10	407972	2	54	F	U/L	+	+	+	-	-	-	+	+	-	-	-	-	6/24	6/18	3	-	PR	-	NS	-	RE	32
11	409647	1	62	B	U/L	+	-	-	-	-	-	-	+	-	-	-	+	6/12	6/12	-	2	-	PR	-	NS	LE	28
12	409665	2	50	F	U/L	+	+	+	-	+	-	+	+	-	-	-	-	6/18	6/24	-	3	-	PR	-	NS	LE	25
13	417936	1	40	F	U/L	+	-	+	-	+	-	+	+	-	-	-	-	6/9	6/9	3	-	PR	-	NS	-	RE	23
14	417924	1	59	B	U/L	+	-	-	-	-	-	-	-	-	-	-	-	6/36	6/36	2	-	PR	-	NS	-	RE	32
15	418012	2	45	F	U/L	+	+	+	-	-	-	+	+	-	-	-	-	6/6	6/6	-	3	-	PR	-	NS	LE	27
16	418720	2	58	L	U/L	+	-	-	-	-	-	-	-	-	-	-	-	6/12	6/12	-	2	-	PR	-	NS	LE	28
17	418734	1	60	F	U/L	+	-	-	-	-	-	-	-	-	-	-	-	6/9	6/9	2	-	PR	-	NS	-	RE	30
18	421612	2	55	F	U/L	+	-	-	-	-	-	+	-	-	-	-	-	6/18	6/24	2	-	PR	-	NS	-	RE	24
19	421580	2	60	F	U/L	+	-	+	-	-	-	-	-	-	-	-	-	6/18	6/12	-	3	-	PR	-	NS	LE	25
20	1000731	1	17	St	B/L	+	-	-	-	-	-	-	+	-	-	-	-	6/6/	6/6/	2	1	PR	PR	NS	NS	RE	33
21	426835	1	52	B	B/L	+	-	+	-	-	-	+	-	-	-	-	-	6/18	6/18	2	2	PR	PR	NS	NS	RE	26
22	426878	1	50	L	U/L	+	-	+	-	-	-	-	+	-	-	-	-	6/12	6/9	2	-	PR	-	NS	-	RE	23

	Outcome																													
	Pain				Foreign body sensation				Lacrimation				Discomfort during blinking				Haemorrhage				Displacement of graft				Overall appearance				Other f	
Serial number	Post op Day 1	One week	Three weeks	Six weeks	Post op Day 1	One week	Three weeks	Six weeks	Post op Day 1	One week	Three weeks	Six weeks	Post op Day 1	One week	Three weeks	Six weeks	Post op Day 1	One week	Three weeks	Six weeks	Post op Day 1	One week	Three weeks	Six weeks	Post op Day 1	One week	Three weeks	Six weeks	Post op Day 1	One week
1	2	1	1	1	2	1	1	1	2	2	1	1	2	1	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	Q	Q	Q	-	GR
2	1	1	1	1	1	2	1	1	2	2	1	1	2	1	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	Q	Q	Q	-	-
3	2	2	1	1	2	2	1	1	2	2	1	1	2	2	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	Q	Q	Q	GE	-
4	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	Ab	Ab	Ab	Ab	Ab	P	Ab	Ab	Q	Q	Q	Q	-	-
5	2	2	1	1	2	1	1	1	2	1	1	1	2	1	1	1	P	P	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	Q	Q	-	-
6	3	3	2	1	2	2	2	1	2	2	2	1	2	1	1	1	P	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	Q	Q	Q	-	-
7	1	1	1	1	2	1	1	1	2	2	1	1	2	2	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Q	Q	Q	Q	-	GE
8	1	1	1	1	2	1	1	1	2	1	1	1	2	1	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Q	Q	Q	Q	-	-
9	2	3	3	2	2	3	3	1	2	3	3	2	2	3	3	2	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	RD	Q	GE	GE
10	1	1	1	1	2	2	1	1	3	2	1	1	2	2	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	Q	Q	Q	-	-
11	2	1	1	1	3	1	1	1	3	1	1	1	3	1	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	Q	Q	Q	-	-
12	2	1	1	1	2	1	1	1	2	1	1	1	3	1	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Q	Q	Q	Q	GR	-
13	1	1	1	1	3	2	1	1	2	1	1	1	3	1	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Q	Q	Q	Q	-	-
14	2	2	1	1	2	1	1	1	2	1	1	1	2	1	1	1	Ab	Ab	Ab	Ab	Ab	P	Ab	Ab	RD	Q	Q	Q	-	-
15	2	1	1	1	2	1	1	1	2	1	1	1	2	1	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	Q	Q	Q	-	-
16	2	1	1	1	2	1	1	1	3	2	1	1	3	1	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Q	Q	Q	Q	-	-
17	2	1	1	1	2	1	1	1	3	2	1	1	2	1	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	Q	Q	Q	-	-
18	2	1	1	1	2	1	1	1	2	1	1	1	3	1	1	1	P	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	Q	Q	Q	-	-
19	2	2	1	1	2	2	1	1	2	1	1	1	2	2	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Q	Q	Q	Q	-	-
20	2	1	1	1	3	1	1	1	3	1	1	1	2	1	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	Q	Q	Q	-	-
21	2	1	1	1	3	1	1	1	3	2	1	1	2	1	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	Q	Q	Q	GE	-
22	2	1	1	1	2	1	1	1	2	1	1	1	2	1	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Q	Q	Q	Q	-	-

MASTER CHART - GROUP I (FIBRIN GLUE)

indings	
Three weeks	Six weeks
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GE	-
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MASTER CHART - GROUP II (SUTURES)

Serial number	In/Out patient number	Demography			Laterality	Chief				History								Vision		Diagnosis						Operating side	Operating time	Outcome																															
														Past history						Grade		Type		Site				Pain				Foreign body sensation				Lacrimation				Discomfort during				Haemorrhage				Displacement of graft				Overall appearance				Other findings			
		Sex	Age (Years)	Occupation		Fleshy mass	Vision diminision	Redness	Pain	Watering	Discharge	Itching	Ocular irritation	Intraocular surgery	Trauma	Others	Medical history	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye			Post op Day 1	One week	Three weeks	Six weeks	Post op Day 1	One week	Three weeks	Six weeks	Post op Day 1	One week	Three weeks	Six weeks	Post op Day 1	One week	Three weeks	Six weeks	Post op Day 1	One week	Three weeks	Six weeks	Post op Day 1	One week	Three weeks	Six weeks	Post op Day 1	One week	Three weeks	Six weeks	Post op Day 1	One week	Three weeks	Six weeks
1	382699	2	30	F	U/L	+	-	+	-	-	-	-	-	-	-	-	-	6/6	6/6	1	-	PR	-	NS	-	RE	40	2	1	1	1	3	2	2	1	3	2	1	1	3	2	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	Q	Q	-	-	-	-
2	384193	2	60	F	B/L	+	-	+	-	-	-	-	-	-	-	-	-	6/12	6/18	1	1	PR	PR	NS	NS	LE	42	2	2	3	2	3	3	3	2	3	2	2	2	3	2	2	2	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	RD	Q	ST	ST	ST	-
3	399844	2	62	F	U/L	+	+	+	-	-	-	-	-	-	-	-	-	6/36	6/18	2	-	PR	-	NS	-	RE	38	2	1	2	1	3	2	3	2	3	2	2	2	3	2	3	2	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	RD	RD	-	-	GF	GD
4	402421	2	52	H	U/L	+	-	-	-	-	-	+	-	-	-	-	-	6/12	6/12	-	2	-	PR	-	NS	LE	38	2	1	1	1	3	3	2	1	3	2	1	1	3	3	2	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	Q	Q	-	-	-	-
5	403634	2	42	L	U/L	+	+	-	-	-	-	+	+	-	-	-	-	6/9	6/18	-	3	-	PR	-	NS	LE	41	2	1	1	1	3	2	1	1	3	2	1	1	3	2	2	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	Q	Q	-	-	-	-
6	405331	2	43	F	B/L	+	-	-	-	-	-	-	+	-	-	-	-	6/9	6/9	2	2	PR	PR	NS	NS	LE	37	2	2	1	1	3	2	2	1	2	2	1	1	3	3	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	Q	Q	Q	GE	-	-	-
7	413596	1	32	B	U/L	+	+	+	-	+	-	+	+	-	-	-	-	6/18	6/6	2	-	PR	-	NS	-	RE	36	3	2	2	1	3	2	2	1	4	2	2	1	4	3	2	1	P	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	Q	Q	-	-	-	-
8	414311	2	36	F	U/L	+	-	+	-	+	-	+	+	-	-	-	-	6/6/	6/6/	-	1	-	PR	-	NS	LE	34	2	1	1	1	3	2	2	1	3	2	2	1	3	3	3	2	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	Q	Q	-	-	-	-
9	415376	2	68	F	U/L	+	+	-	-	-	-	+	-	-	-	-	-	6/12	6/9	2	-	PR	-	NS	-	RE	35	2	1	1	1	3	2	2	1	3	2	2	1	3	3	2	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	Q	Q	GE	-	-	-
10	416328	1	43	F	U/L	+	-	+	-	+	-	+	+	-	-	-	-	6/9	6/9	-	2	-	PR	-	NS	LE	32	2	1	1	1	3	2	1	1	3	2	1	1	3	2	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	Q	Q	-	-	-	-
11	424612	2	65	H	U/L	+	-	-	-	-	-	+	+	-	-	-	-	6/18	6/24	-	2	-	PR	-	NS	LE	33	2	2	1	1	3	3	2	2	3	3	2	1	3	3	2	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	RD	Q	NCGG	-	-	-
12	424638	2	45	L	U/L	+	-	-	-	+	-	+	+	-	-	-	-	6/12	6/18	-	2	-	PR	-	NS	LE	37	3	2	1	1	3	3	2	2	3	2	2	1	3	3	2	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	RD	RD	GD	GF	-	-
13	428365	1	38	SR	B/L	+	+	+	-	+	-	+	+	-	-	-	-	6/18	CF3n	2	3	PR	PR	NS	NS	LE	33	2	1	1	1	3	2	1	1	4	2	1	1	3	2	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	Q	Q	-	-	-	-
14	429141	2	42	F	U/L	+	-	-	-	-	-	+	-	-	-	-	-	6/12	6/9	2	-	PR	-	NS	-	RE	31	2	1	1	1	3	2	2	1	3	2	1	1	3	2	2	2	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	RD	Q	GR	-	-	-
15	443853	1	47	B	B/L	+	-	-	-	-	-	+	+	-	-	-	-	6/12	6/9	2	2	PR	PR	NS	NS	RE	35	2	2	1	1	3	2	1	1	3	2	1	1	3	2	2	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	Q	Q	Q	CG	-	-	-
16	444205	2	40	F	U/L	+	-	-	-	-	-	-	-	-	-	-	-	6/9	6/9	2	-	PR	-	NS	-	LE	31	3	1	1	1	3	2	1	1	2	2	1	1	3	3	2	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	Q	Q	Q	-	-	-	-
17	445285	1	55	L	U/L	+	+	+	-	+	-	+	+	-	-	-	-	6/18	6/24	2	-	PR	-	NS	-	RE	43	3	2	1	1	3	2	2	1	3	2	1	1	3	2	2	2	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	Q	Q	ST	-	-	-
18	446184	2	53	F	B/L	+	+	+	-	+	-	+	+	-	-	-	-	6/60	IMC	3	3	PR	PR	NS	NS	RE	40	2	1	1	3	3	2	1	3	3	2	1	3	3	2	1	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	RD	Q	-	-	-	-
19	451249	2	48	F	U/L	+	+	-	-	-	-	+	-	-	-	-	-	6/18	6/24	-	2	-	PR	-	NS	LE	38	2	1	1	1	3	2	2	1	2	1	1	1	3	3	2	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	Q	Q	Q	-	-	-	-
20	451285	2	50	H	U/L	+	-	-	-	-	-	-	+	-	-	-	-	6/12	6/12	2	-	PR	-	NS	-	RE	34	2	1	1	1	3	3	2	1	2	1	1	1	3	2	2	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	Q	Q	-	-	-	-
21	452511	1	52	B	U/L	+	-	-	-	+	-	-	+	-	-	-	-	6/9	6/9	-	2	-	PR	-	NS	LE	37	2	1	1	1	3	2	2	1	3	2	2	1	3	3	2	1	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	Q	Q	-	-	-	-
22	454151	1	47	F	B/L	+	+	+	-	-	-	+	+	-	-	-	rasth	6/9	6/9	2	2	PR	PR	NS	NS	RE	31	3	2	1	1	3	2	2	1	3	1	1	1	3	3	2	2	Ab	Ab	Ab	Ab	Ab	Ab	Ab	Ab	RD	RD	Q	Q	GE	-	-	-