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A Comparative Analysis of Outcomes of Pterygium Surgery with or without Collagen Matrix Implantation

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Abstract
Background*: Pterygium is a common disorder in many parts of the world, with reported prevalence rates ranging from 0.3 to 29%. Epidemiological studies have proposed an association with chronic exposure to sunlight and an increased geographical prevalence within a peri-equatorial 'pterygium belt' region (1).*
Pterygium excision is often combined with various adjunctive measures to prevent its recurrence, however recurrenece is still the most common post-surgical complication. Numerous techniques have been attempted to reduce localized fibrovascular activity and the overall rate of recurrence; these include, β-irradiation, conjunctival and limbal auto-grafting, antimitotic drugs and amniotic membrane transplantation (2). In recent years, a novel bioengineered product has been advocated for preventing recurrence and has shown promising outcomes in animal models This study was conducted to compare the effect of collagen matrix implant with conjunctival autograft following pterygium surgery (treatment group) with only conjunctival autograft following pterygium surgery (control group).
Methods: *Following informed consent, sixty eyes of 60 patients (females = 23, males =37, aged 23–67 years) were randomly allocated into two equal groups. Pterygia of all patients were excised and conjunctival autograft was done. However, for patients in the treatment group a 1×3 mm collagen matrix graft (Ologen) was implanted subconjunctivally under the graft. Patients were followed up for six months.*
The parameters studied were patient comfort, foreign body sensation, dellen formation, pterygium recurrence and time for absorption of the collagen matrix.
Results: *Results revealed that no eyes in the control group and one eye in the intervention group developed recurrence; dellen formation not was observed in any patient in both groups. Patient comfort and foreign body sensation did not differ significantly in both groups. Three eyes in treatment group developed a tenon's cyst. In 12 out of 30 eyes, the collagen matrix was not absorbed at six months post surgery.*
Conclusion: *In conclusion, the use of biodegradable collagen matrix implants (Ologen) following pterygium excision did not seem to be associated with a lower risk of recurrence. Moreover, tenon's cyst formation and persistence of the matrix subconjunctivally was observed. Further studies with adequate sample size are recommended for more comprehensive conclusion.*
Keywords: *Pterygium, Conjunctival autograft, Collagen Matrix, Subconjunctival placement*

I. Introduction

Pterygium is derived from the ancient Greek word pterygos for wing. It is a wing shaped, triangular, fibrovascular degenerative condition of subconjunctival tissue which proliferates as a vascularised granulation tissue to invade the cornea, destroying the superficial layers of the stroma and Bowman's membrane, the whole being covered by conjunctival epithelium. It is loosely adherent in its whole length to the underlying sclera, the area of adherence being always smaller than its breadth, so that there are folds at the upper and lower borders. Pterygia can vary from small, atrophic quiescent lesions to large aggressive, rapidly growing fibrovascular lesions that can distort the corneal topography and in advanced cases they can obscure the optical center of the cornea (3).

While there is currently no universal consensus for grading of pterygium, one of the current methods has graded pterygia as follows: stage 0: pinguecula posterior to the limbus; stage 1: pterygium restricted to the limbus; stage 2: pterygium only marginally invades the cornea; stage 3: pterygium is between the limbus and pupillary margin; and stage 4: pterygium is central to the pupillary margin (4).

Patients complain of no symptoms to significant symptoms of redness, swelling, itching, irritation and blurring of vision associated with elevated lesions of the conjunctiva and contiguous cornea in one or both eyes.

A pterygium is best left alone unless it is progressing towards the pupillary area, causing excessive astigmatism, restricting ocular motility or is disfiguring. There is no medical management of pterygium at present. Surgical removal is the accepted method of treatment. Various techniques have been tried in past from simple excision to use of adjunct therapies such as β irradiation, thiotepa, 5-FU, and mitomycin C. The prime challenge of pterygium surgery is prevention of recurrence. Reports of recurrence rates have varied from 25-45 % after simple excision of primary pterygium (5). Recurrence of pterygium is closely associated with corneo-limbal stem cell deficiency.

After excision of the pterygium, the defect in conjunctiva can be left as it is in bare sclera method or the defect can be covered by a variety of techniques. Spaeth *et al* introduced the surgical technique of using conjunctival auto graft for covering the bare sclera after pterygium excision. Conjunctival auto graft with limbal stem cell transplantation has shown promising results with low recurrence rates (6-8).

In recent years, a novel bioengineered product has been advocated for implantation and has shown promising outcomes in animal models Biodegradable collagen matrix implants (Ologen®) are porous scaffolds that can encourage a regenerative and non-scarring wound healing process without the use of medications. Ologen, a biodegradable, porous, porcine, collagen implant, was designed aiming to improve the long term success of trabeculectomy by decreasing the sub-conjunctival scarring but with less bleb-related complications (9). Its manufacturer has described its use not only for trabeculectomy, but also for other ophthalmic surgeries such as pterygium removal, oculoplastic surgery and veterinary surgery (12).

The principle of the collagen implant is to stimulate random growth of fibroblasts, which subsequently leads to normal wound healing. The scaffold's porous structure can work as a reservoir, a buffering system, and also as a controlled drainage solution. It randomizes the growth of myofibroblasts. It also prevents scar formation inside the wound by guiding fibroblasts to grow randomly throughout the matrix pores (10-11).

II. Methods

In this prospective study we studied 60 eyes of 60 patients with pterygium who had been referred to Ophthalmology Department of a tertiary care centre between Jan 2015 and Jun 2015. A comprehensive evaluation of patients was undertaken including patient's age, gender, medical and ocular history, visual acuity assessment, slit lamp examination and anterior segment photography

Patients were randomly assigned to either the intervention or control groups. Inclusion criteria were: pterygium encroaching the cornea at least 2mm, which was fleshy and vascular, decreased visual acuity due to involvement of visual axis or induced astigmatism and for cosmetic reasons.

Exclusion criteria included patients who had recurrent pterygium, pseudopterygium, evidence of systemic diseases like diabetes, HIV, hepatitis, past history of atopy and hypersensitivity, traumatic injury to the anterior segment of the eye.

All patients underwent complete history recording and ophthalmological examination before the surgical procedure. Photographs were taken preoperatively and postoperatively and informed consent was taken prior to surgery.

All patients underwent routine investigations and a pre-anaesthetic check up Pre-operative Ciprofloxacin eye drops (0.3%) 4 times a day was given to all patients one day prior to surgery.

III. Surgical procedure

After peribulbar block, the involved eye underwent standard ophthalmic sterile preparation and draping. Then eye was exposed for surgery using wire speculum. Lidocaine /epinephrine solution was injected sub conjunctivally under pterygium to make dissection easier and to act as a haemostatic. A no 11 blade was used to excise the pterygium head from the cornea. Blunt and sharp dissection was performed to separate the pterygium from underlying sclera and surrounding conjunctiva.

The area of conjunctival defect was measured with calipers and a free conjunctival limbal autograft measuring 1-2 mm larger than the defect was obtained from the superotemporal quadrant of the bulbar conjunctiva. Proper orientation was maintained, with the epithelium side up and limbal edge towards limbus.

In the intervention group, two anchoring sutures with 8/0 Vicryl were first applied superiorly and inferiorly and then Collagen matrix 3X1 mm was placed subconjunctivally below the conjunctival graft at least one mm behind the limbus. Rest of autograft margin was then attached with two or three interrupted sutures.

In second group only the conjunctival autograft was sutured as above but no collagen matrix was placed beneath it.Twenty-four hours following surgery all patients in both groups received treatment with drops of ciprofloxacin and dexamethasone four times a day and carboxymethylcellulose 0.5% three times a day for four weeks.

Follow-up visits for evaluation of patient comfort, foreign body sensation, complications or recurrence were on the first day, first week, first month, third month and sixth month postoperatively. The presence of dellen was considered as a complication, and recurrence was defined as at least 1 mm regrowth of the conjunctival fibrovascular tissue toward the cornea in both vertical and horizontal diameters during the follow-up.

The following variables were measured

Patients symptoms
Very painful, mild pain , no pain graded as 3, 2, 1
Foreign body sensation graded as 3, 2, 1
Lacrimation graded as 3, 2, 1
Recurrence graded as 2,1
Dellen Present/absent
Tenon's cyst Present/absent

IV. Results

Sixty eyes of 60 patients with unilateral or bilateral pterygium were enrolled (30 in treatment group and 30 in control group).

The mean age of the patients was 43.60 years in Conjunctival autograft group and 43.80 years in Ologen with conjunctival autograft group (Table 1).

Table 1 Comparison of age distribution of patients

Age in years	**Conjunctival autograft group**	**Ologen with conjunctival autograft group**
<=40	**7**	**9**
41-45	**10**	**4**
>45	**13**	**17**
Total	**30**	**30**

23 patients were female and 37 were male (Table 2).

Table 2 Gender distribution of patients

Gender	**Conjunctival autograft group**	**Ologen with conjunctival autograft group**
Male	19	18
Female	11	12
Total	30	30

In the first post operative week, both groups of patients complained of grade 1 pain. None of the patients in both groups complained of discomfort, pain, foreign body sensation or lacrimation after one week of the surgery.

Recurrence was graded as G1 (normal), G2 (fine episcleral vessels), G3 (conjunctival recurrence), or G4 (corneal recurrence) as described. As per this grading system, in the intervention group there was one patient who developed mild symptoms of recurrent inflammation, tearing, and foreign body sensation at the first month, which worsened in the third month with development of G4 recurrence. Table 3 (Fig 1 and Fig 2)

Table 3 Recurrence PO 3months

	Conjunctival autograft group	**Ologen with conjunctival autograft group**
No Recurrence	**30**	**30**
Recurrence	**00**	**01**

In the control group no patient developed recurrence. In our study, dellen formation was not observed in any patient in both the groups. Three patients in the ologen group developed tenon's cyst at one month postoperative period that did not resolve with topical steroids (Fig 3).

In our study 12 out of 30 patients in the intervention group still showed persistence of the Ologen implant subconjunctivally at six months following surgery (Fig 4).

V. Discussion

Pterygium is a common worldwide external eye disease affecting populations especially in tropical and subtropical areas. The primary management of pterygium is surgical. According to Rich et al, "to manage pterygium we can incise, excise, bury, transplant, graft, freeze, burn, cauterise, diathermies, divulse, evulse, chemically assault, irradiate or simply leave them to fate."

It is believed that surgical trauma and subsequent postoperative inflammation activate proliferation of subconjunctival fibroblasts and vascular cells, and deposition of proteins which in turn contributes to the pterygium recurrence. Simple excision of primary pterygia is associated with a high recurrence rate (33–45%) (13).

Several strategies have been advocated to curtail recurrence. The first emphasizes "thorough" removal of fibrovascular tissue, initially advocated by Barraquer (14) in 1980, stressed by Prabhasawat et al in 1997 (15), and reemphasized by Hirst(16). The second is to suppress the regrowth of fibrovascular tissue by intraoperative application of mitomycin C (6-7).The third is to cover the bare sclera with a conjunctival autograft , conjunctival limbal autograft or cryopreserved amniotic membrane. Intriguingly, despite these efforts, recurrence rates remain highly variable from 0% to 52.6% (17-19).

The factors influencing recurrence may include patient demographics, ethnic and environmental factors, pterygium morphological characteristics, different surgeons, and postoperative regimen (20).

The Ologen™ is an upgraded biodegradable, implantable scaffold collagen matrix consisting of lyophilized porcine atelocollagen (>90 %) and lyophilized porcine glycosaminoglycan (<10 %) with pore sizes of 10 to 300 μm. Atelocollagen is a highly purified pepsin-treated type I collagen. A collagen molecule has an amino acid sequence, a telopeptide, at both the N and C terminals, which confers most of the collagen's antigenicity. Atelocollagen obtained by pepsin treatment is low in immunogenicity, because it is free of telopeptide (21).

Ologen™ is available in various shapes and dimensions. When Ologen™ is placed in the subconjunctival space, the porous structure guides conjunctival fibroblasts and myoblasts to proliferate randomly and secrete connective tissue in the form of a loose matrix during the wound healing process. Therefore, it reduces scar formation and wound contraction. Due to this mechanism, Ologen™ is being used to enhance wound healing in ocular surface reconstruction with low immunogenicity. The implant leaves behind a loose alignment of collagen fibers inside scleral defects that is remarkably similar to normal tissue, with less scar formation than would otherwise have occurred (22). These findings suggest that Ologen™ provides a physiological structure for tissue repair, inducing a conjunctival wound to heal more in a physiological than a pathological manner.

In general, biodegradable collagen matrix implants have been used safely following trabeculectomy and they seem to be used as alternating treatments with antimitotic drugs; however, there are no reports of their efficacy in preventing pterygium recurrence vs conjunctival autografting.

In a non-randomized trial, Madrazo et al. deliberated the efficacy of a biodegradable collagen matrix implant following pterygium excision on 20 eyes, and followed up the patients for at least 3 months. They reported a pterygium recurrence rate of 5% without any complications or adverse effects (23).

Arish M et al implanted collagen matrix in 20 eyes following pterygium surgery and found that it reduced the recurrence when compared with bare sclera excision. However, the limitation of this study was the bare sclera technique used for pterygium removal as this technique is less commonly used (24).

There is a theoretical risk of increased inflammation in eyes with Ologen implant as the implant is non-human (porcine) in origin. Reports in reconstructive surgery have shown an increased inflammation with signs

of foreign body reaction related to the porcine cross-linked collagen implants when used in the repair of incisional hernia (25). There are no such reports when used in ocular procedures.

Corneal dellen are small saucer-like excavations at the margin of the cornea. Scleral dellen result from local dehydration and thinning of the sclera tissues with exposure of the underlying uvea leading to their bluish color. Among the complications of pterygium surgery, corneoscleral dellen have been rarely reported, especially without the use of adjunctive therapy. In our study, dellen formation was not observed in any patient in both the groups.

Ologen is biodegraded by the body within 90~180 days from its implantation. However, we observed that 12 out of 30 patients in the implant /intervention group still showed persistence of ologen at six months following surgery.

VI. Conclusion

This study compared outcomes of collagen matrix implantation with conjunctival autograft following pterygium surgery with those of conjunctival autograft alone. The salient results in brief are:-

1. The use of ologen did not influence the incidence of foreign body sensation, watering and discomfort compared to conjunctival autograft,
2. Recurrence occurred in one patient with ologen implant and none in conjunctival autograft. The patient who developed recurrence was 35 years old. Young age has been observed as a factor determining recurrence in a number of studies (26), (27).
3. Three patients in ologen group developed a tenon's cyst at the site of implantation.
4. In twelve patients the ologen implant did not get reabsorbed at six months following surgery.
5. The collagen matrix implant did not appear to offer any substantial benefit over the current gold standard "conjunctival autograft".
6. However, more detailed studies are required to reach a definite conclusion.

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Fig 1 Pre op pterygium LE

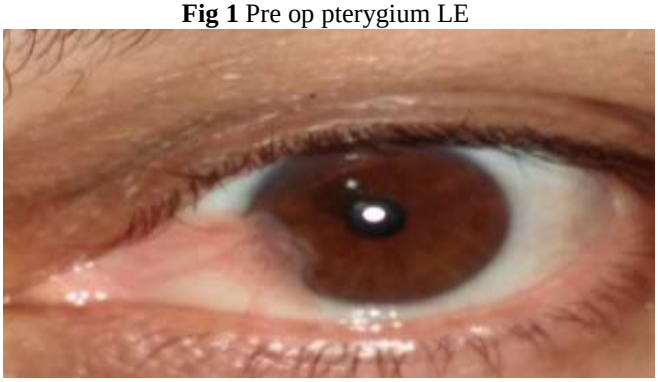

Fig 2 Post op left eye of same patient from intervention group at 3 months showing recurrence and persistence of collagen matrix

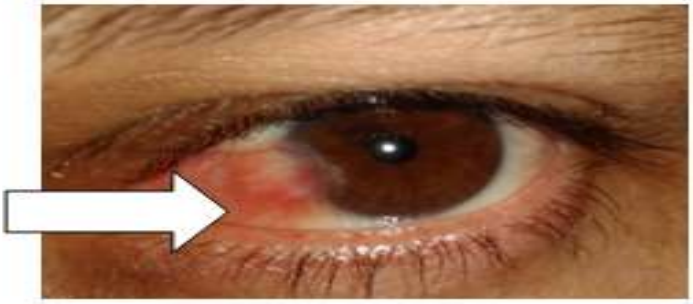

Fig 3 Tenon's cyst right eye following collagen matrix implantation

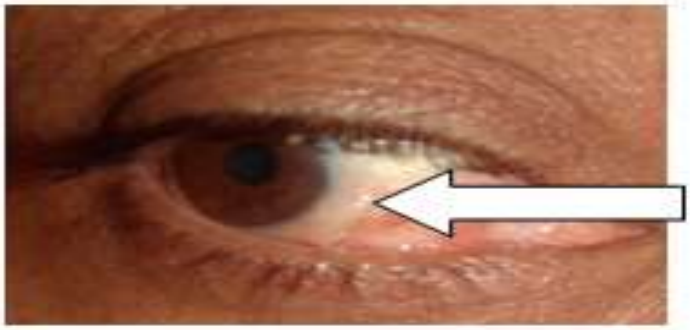

Fig 4 Post op at six months showing persistence of collagen matrix left eye